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Intergenerational transmission of the effects of maternal exposure to childhood maltreatment on offspring obesity risk: a fetal programming perspective

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Abstract

Childhood obesity constitutes a major global public health challenge. A substantial body of evidence suggests that conditions and states experienced by the embryo/fetus *in utero* can result in structural and functional changes in cells, tissues, organ systems and homeostatic set points related to obesity. Furthermore, growing evidence suggests that maternal conditions and states experienced prior to conception, such as stress, obesity and metabolic dysfunction, may spill over into pregnancy and influence those key aspects of gestational biology that program offspring obesity risk. In this narrative review, we advance a novel hypothesis and life-span framework to propose that maternal exposure to childhood maltreatment may constitute an important and as-yet-underappreciated risk factor implicated in developmental programming of offspring obesity risk via the long-term psychological, biological and behavioral sequelae of childhood maltreatment exposure. In this context, our framework considers the key role of maternal-placental-fetal endocrine, immune and metabolic pathways and also other processes including epigenetics, oocyte

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mitochondrial biology, and the maternal and infant microbiomes. Finally, our paper discusses future research directions required to elucidate the nature and mechanisms of the intergenerational transmission of the effects of maternal childhood maltreatment on offspring obesity risk.

Keywords

Childhood obesity; childhood maltreatment; intergenerational transmission; fetal programming; pregnancy; gestational biology

1. Introduction

Childhood obesity represents a major, global public health challenge. Its etiology is multifactorial, and currently identified risk factors account for only a moderate proportion of its prevalence (Robinson et al., 2017; van der Klaauw & Farooqi, 2015; Willyard, 2014). Furthermore, once established, obesity is extremely difficult to reverse (Schwartz, 2017), underscoring the critical importance of primary prevention (Ghoorah et al., 2014). Thus, the elucidation of additional risk factors remains a key priority. In this perspectives paper, we advance the concept that an additional determinant of an individual's risk for childhood obesity may arise from her or his mother's physiological and emotional states prior to conception. ***Specifically, we hypothesize that maternal exposure to maltreatment during the period of her own childhood may constitute an important and novel risk factor for increased susceptibility in her offspring for the development of obesity and metabolic dysfunction***.

The extent of an individual's exposure to obesogenic factors clearly is an important determinant of her or his likelihood of developing obesity. However, it also is evident that individuals vary widely in terms of the effects of obesogenic exposures on obesity risk (*i.e.*, exhibit considerable variation in their susceptibility) (Albuquerque et al., 2017). Thus, primary prevention of obesity necessitates not only addressing the obesogenic exposure part of the equation, but also and critically importantly a better understanding of the determinants of individual differences in *susceptibility* to the effects of obesogenic factors (Bluher, 2019).

In this regard, growing evidence suggests developmental processes during intrauterine life play a key role in determining susceptibility to childhood obesity (*i.e.*, the concept of fetal programming) (Entringer et al., 2015; Friedman, 2018). Furthermore, over and beyond effects of events during pregnancy, the importance of maternal preconceptional conditions is becoming increasingly evident (Haire-Joshu & Tabak, 2016), as some of their long-term effects carry forward and spill over into pregnancy to impact key gestational biology-related endocrine, immune and metabolic processes implicated in fetal programming of childhood obesity risk. In light of these considerations, we submit that *maternal exposure to childhood maltreatment (CM)* may constitute a novel, important, and as-yet-underappreciated and understudied condition of interest. We have previously published a perspective paper that describes our conceptual formulation by which maternal CM exposure may contribute to fetal programming of offspring brain development (Buss et al., 2017). While the current paper shares many commonalities and arguments within the context of the broader

framework of CT exposure and fetal programming, we focus here on the different and equally important outcome of offspring obesity risk.

This perspectives paper begins with an overview of the problem of childhood obesity and the evidence for preconception and prenatal exposures and conditions that may influence susceptibility to development of obesity via the process of fetal programming of health and disease risk. Next, we address the issue of childhood maltreatment, with a brief overview of its prevalence and long-term health consequences. We then summarize findings that suggest the long-term effects of CM may not be restricted to the life span of the exposed individual alone, but also may be transmitted across generations to influence the development and health of their offspring, including offspring obesity risk. We then present our conceptual framework to describe the three key elements which may plausibly explain an intergenerational transmission of the effects of maternal CM on childhood obesity risk; i) spillover of the adverse behavioral, psychological and physiological sequelae of maternal CM from the preconceptional to prenatal life stage; ii) the impact of these sequelae on various gestational biological pathways that may program the developing fetus for an increased susceptibility towards obesity in childhood; iii) the potential interaction of prenatal and postnatal states and conditions related to maternal CM exposure, which could further explain the risk for obesity development in the child. We also present recommendations for future directions to advance this field of research and lastly, highlight the public health significance of this framework.

2. The problem of childhood obesity.

Obesity represents one of the most urgent national and global health challenges because of its high prevalence and adverse health, economic and societal consequences (Kelly et al., 2013; McPherson, 2014; Schwartz, 2017). Childhood obesity is a particularly grave concern because children with obesity are substantially more likely to be affected by obesity in adulthood (Serdula et al., 1993; Whitaker et al., 1997) and to develop obesity-related disorders at younger ages (Dabelea & Harrod, 2013; Freedman et al., 2001) and of greater severity (Dietz, 1998; Fagot-Campagna et al., 2001; Freedman et al., 2007). The ramifications are alarming: Owing to the increase in obesity, life expectancy in developed countries is projected to decrease for the first time in recent history (Olshansky et al., 2005).

2.1 Susceptibility

The extent of any given individual's exposure to obesogenic factors clearly is an important determinant of her or his likelihood of developing obesity. However, it also is evident that individuals vary widely in terms of the *magnitude of effects* of obesogenic exposures on obesity risk. In other words, they exhibit differences in their susceptibility for developing obesity (Albuquerque et al., 2017). Thus, primary prevention of obesity may necessitate not only addressing the obesogenic exposure part of the equation, but also and critically importantly, the determinants of individual differences in *susceptibility* to the effects of obesogenic factors.

What, then, determines individual differences in susceptibility? The conventional paradigm proposes that an individual's genetic makeup (reflected in DNA sequence variation) is the

primary determinant of her or his susceptibility. However, based on findings from genome wide association and other studies, it is increasingly apparent that genetic makeup alone (*i.e.*, independently) accounts for only a modest proportion of the observed variance in obesity risk (Robinson et al., 2017; Sluyter et al., 2013; van der Klaauw & Farooqi, 2015; Willyard, 2014). Even among carriers of genetic loci most strongly associated with obesity risk (*e.g.*, polymorphisms of the FTO gene (Albuquerque et al., 2013; Deliard et al., 2013; Leon-Mimila et al., 2013)), it appears that factors such as early developmental processes may *moderate* this susceptibility. For example, among carriers of the FTO risk alleles, infants with a lower body mass index (BMI) are at increased risk of developing childhood obesity (Sovio et al., 2011). Thus, it is the phenotypic specification of the initial settings or *set-points* of central and peripheral systems implicated in *energy balance homeostasis* that appears to play a major role in determining susceptibility for future obesity (adiposity) risk (Schwartz, 2017). We note that the U.S. Endocrine Society recently published a scientific position statement arguing that based on the convergence of evidence, *obesity should now be conceptualized as a disorder of the energy homeostasis system*, rather than simply arising from the accumulation of excess weight. Moreover, they emphasized the need to elucidate underlying mechanisms, with a major focus on developmental influences (Schwartz, 2017).

2.2 Role of developmental processes.

A growing and converging body of epidemiological, clinical and experimental evidence in humans and animals now supports the concept that phenotypic specification of complex traits (such as the initial setting of the energy balance homeostasis system) is an *emergent property* of developmental processes in early life, particularly during the intrauterine period (*i.e.*, the process of fetal programming of health and disease risk) (Langley-Evans, 2006; Padmanabhan et al., 2016). In this regard, it also is evident, firstly, that the *proximate* mechanism by which gestational conditions impact phenotypic specification is ultimately biological in nature (Catalano & Shankar, 2017); secondly, that *stress-related* maternal-placental-fetal endocrine, immune/inflammatory, oxidative and metabolic pathways may play a particularly prominent role in this process (Entringer et al., 2015); and thirdly, that a constellation of *upstream* maternal biophysical, behavioral, psychological and clinical states exert a major influence on gestational biology (Keenan et al., 2018; Stephenson et al., 2018). Thus, primary prevention (of the establishment of increased susceptibility for obesity) implies not only the identification of relevant modifiable risk factors, but also and importantly, the critical time period(s) for intervention.

With the exception of new and controversial germline gene-editing approaches (Ormond et al.,2017), the prenatal period may represent one of the earliest possible windows for deploying primary prevention strategies to target potentially modifiable risk factors that influence gestational biology, in order to influence the individual's susceptibility for developing obesity. Furthermore, developmental trajectory models suggest that complex phenotypes emerge through a series of interactions or conditional probabilities. That is, the likelihood of acquiring any given phenotype is shaped by events and environments at earlier, critical stages of development (Barker, 2002). For example, the effects of genes on fetal growth and birth outcomes are conditioned by the intrauterine and fetal environment; the

effects of birth outcomes on infant growth and health status are conditioned by events and environments during the early infancy period, and so forth.

2.3 Role of maternal preconceptional state.

It is clear that maternal exposures and experiences during pregnancy can potentially impact embryonic/fetal development, in part, *via* their effects on gestational biology. But what of exposures and experiences that may have occurred earlier, *prior* to conception? Could some of these, when a woman becomes pregnant, also impact gestational biology (which in turn may affect offspring phenotypes such as energy balance homeostasis set points and risk for obesity and metabolic dysfunction)? Growing evidence suggests that certain maternal pre-conceptional states and conditions do exert a substantial influence on gestational biology (Lewis et al., 2015; Moussa et al., 2016) and fetal development. Indeed, there is increasing recognition that the time window for potential intervention on the process of fetal programming of obesity risk and associated comorbidities should be extended to the maternal pre-conception period (Haire-Joshu & Tabak, 2016; Mumford et al., 2014).

With respect to maternal pre-conceptional factors that may promote fetal programming of obesity risk, high maternal BMI and associated comorbid states (*e.g.* diabetes, metabolic syndrome) and unhealthy lifestyle behaviors (*e.g.* poor diet and sedentariness) have received considerable attention to date (Drake & Reynolds, 2010; Lane et al., 2015). However, other exposures over a woman's life course, and particularly exposure to adversity during the early life period, may also exert long term effects on physiology and health. Upon becoming pregnant, these long-term effects may spill-over into the gestational period to influence aspects of maternal-placental-fetal biology that are implicated in the process of fetal programming of obesity risk.

3. The problem of childhood maltreatment exposure.

3.1 Prevalence and Long-term Health Consequences of CM Exposure.

The detrimental effects of stress exposure on health and disease risk are well established. They are particularly pronounced when stress occurs during critical developmental periods (Heim & Binder, 2012). Although stress is a ubiquitous feature of modern life, certain stressors stand out in terms of their salience and consequences. *Childhood maltreatment – physical, sexual or emotional abuse, or physical or emotional neglect – likely represents one of the most pervasive and pernicious stressors in society in terms of its widespread prevalence and devastating long-term consequences*. Estimates from the Centers for Disease Control and Prevention and others suggest a majority of children are exposed to one or more traumatic events in their lifetimes (CDC, 2010; Hussey et al., 2006), and that 30–40% of adult women have experienced at least one, and 15–25% more than one type of CM (Scher et al., 2004). CM produces a suite of adverse and long-lasting biological, biophysical, behavioral and psychological sequelae including depression, post-traumatic stress disorder, substance abuse, unhealthy dietary practices, risky sexual behavior, obesity, premature menarche, and dysregulated neural, endocrine, immune and metabolic function that may result in chronic inflammation and elevated cardiometabolic disease risk factors (Afifi et al., 2009; Anda et al., 2006; Dong et al., 2004; Felitti et al., 1998; Heim et al., 2010; Jakubowski

et al., 2018; Min et al., 2013; Rasmussen et al., 2019). In the context of pregnancy and fetal development, it is apparent that many of these adverse sequelae of CM, singly and collectively, represent the very same constellation of maternal risk factors that have been implicated in the process of fetal programming of obesity risk.

3.2 Intergenerational Transmission of the Adverse Sequelae of CM Exposure.

Emerging evidence now suggests that among women, the long shadow cast by childhood maltreatment may not be restricted to their lifespan, but also may be transmitted to their children. Indeed, children of CM-exposed mothers, in the absence of CM exposure to themselves, exhibit alterations in stress physiology systems (Bierer et al., 2014; Brand et al., 2010; Jovanovic et al., 2011), behavioral disorders (conduct problems, internalizing and externalizing behavior), autism spectrum disorder (Collishaw et al., 2007; Plant et al., 2013; Roberts et al., 2013), and obesity (Leonard et al., 2017; Roberts et al., 2014). The time windows, mechanisms and pathways are not well understood, and their elucidation is an area of considerable scientific and public health interest and importance.

In this context, the prevailing paradigm posits that the child's brain represents the primary outcome of interest (Buss et al., 2017; Everaerd et al., 2015; McLaughlin et al., 2014). However, we submit that another child outcome of at least equal importance and public health significance may also be implicated – that of childhood obesity risk. Direct evidence comes from two recent large cohort studies. In a study of 16,774 mother-child dyads, Roberts *et al.* reported an approximately 50% increased incidence of obesity among children (aged 9–14 yrs) of CM-exposed mothers, with the most pronounced effect in children whose mothers were most severely abused (Roberts et al., 2014). Also, in another study of 6,718 mother-child dyads, Leonard *et al.* reported a 21% increased risk of obesity among children (aged 2–5 yrs) whose mothers were physically abused in childhood (Leonard et al., 2017). Indirect evidence comes from the convergence of a large body of epidemiological, clinical and experimental findings in humans and animals that suggest *all* the above-described maternal states that, on one hand, constitute the adverse sequelae of CM exposure, also are, on the other hand, associated with increased risk of obesity in their offspring (Midei et al., 2010; Midei et al., 2013; Rikknen et al., 2002; Tamayo et al., 2010).

4. Conceptual framework: intergenerational transmission of the effects of maternal exposure to CM on offspring obesity risk

We articulate here a trans-disciplinary, lifespan framework for the intergenerational, mother-to-child transmission of the effects of maternal exposure to CM on offspring obesity risk. This framework is based on principles from evolutionary and developmental biology, and it integrates the concepts of *biological embedding of life experiences* and *fetal origins of health and disease risk* (see Figure 1). Its major elements are as follow: ***1***) When women who had been exposed to maltreatment in their childhood become pregnant, many or all of the long-term biological, biophysical, behavioral and psychological sequelae of CM exposure (*e.g.*, endocrine, immune and metabolic dysfunction, obesity, unhealthy diet (over- or under nutrition), substance abuse, depression, stress hyper-responsiveness) may carry forward and spill over into their gestational state (Barrios et al., 2015; Hollingsworth et al.,

2012; Moog et al., 2012; Nagl et al., 2015; Slopen et al., 2015). ***2***) Next, through the process of fetal programming, the CM experience of one generation (mother) may influence the health of the subsequent generation (child), thereby creating an intergenerational cycle. Intergenerational transmission *in utero* is largely determined by the degree to which the developing placental-fetal unit receives and transduces biological signals indicative of maternal state (in this case, of maternal CM-related alterations in her systemic physiology), and by the extent to which such signals participate in offspring phenotypic specification. Additional pathways of inter-generational transmission of maternal CM's sequelae may include effects of CM exposure on germ line epigenetic characteristics, oocyte cytoplasm/follicular fluid biology, and infant microbiome acquisition. ***3***) Our model recognizes that the prenatal and postnatal effects of maternal CM sequelae on childhood obesity risk may not be mutually exclusive, and thus, also considers the mediating or moderating effects of CM-related postnatal factors such as breast feeding and the quality of mother-child attachment. However, we submit it is important to ascertain whether such intergenerational effects start *in utero*, as elucidation of the earliest transmission windows and mechanisms is necessary to develop efficacious strategies for primary prevention. The plausibility of each component of our model is supported by empirical evidence in not only the general population (Entringer et al., 2012a; Godfrey & Barker, 2001; Wadhwa, 2005; Wadhwa et al., 2011), but also more specifically by findings among offspring of CM exposed women (Leonard et al., 2017; Roberts et al., 2014).

We also note here that the concept of intergenerational transmission of the adverse sequelae of maternal CM exposure is not new. Indeed, previous research has established the existence of such effects, but with a primary focus on child neurodevelopmental/behavioral phenotypes as the principal outcome of interest; on the child's postnatal period of life as the primary transmission window; and on the quality of maternal parenting behavior as the primary transmission pathway. What is novel about our hypothesis is the formulation that childhood obesity risk may represent an additional and at least equally important outcome of interest and public health significance; that the process of intergenerational transmission may start as early as during the child's intrauterine period of life; and that stress-related maternal-placental-fetal gestational biology may represent a key transmission pathway. We also note that while maternal obesity (which is one of the long-term consequences of CM exposure (Hollingsworth et al., 2012; Midei et al., 2010)) represents an example of a condition that may mediate the link between maternal CM and offspring obesity risk, the intergenerational effects of maternal CM likely include but may not be restricted to this pathway alone. In this paper we discuss several other equally plausible candidate pathways.

5. Relevance of the fetal programming approach.

Development is a plastic process, wherein a range of different phenotypes can be expressed from a given genotype. The concept of fetal programming describes the journey across the multi-contoured landscape from genotype to phenotype, whereby the embryo/fetus *seeks*, *receives*, and *responds* to the intrauterine environment during sensitive periods of proliferation, differentiation and maturation, resulting in structural and functional changes in cells, tissues, organ systems and homeostatic set points. These changes, independently or through interactions with subsequent processes and environments, may confer critical long-

term consequences for future health and disease susceptibility (Entringer et al., 2012a; Gluckman & Hanson, 2004a; Hanson et al., 2011).

5.1 From the perspective of childhood obesity risk.

As discussed earlier, the magnitude of cumulative exposure to obesogenic conditions only partially accounts for obesity risk (Sluyter et al., 2013; Willyard, 2014). There are large individual differences in susceptibility for weight gain and fat mass accretion upon exposure to an identical degree of excess energy intake (Brehm et al., 2005; Warwick & Schiffman, 1992). Furthermore, currently-identified genetic variants account for less than 5% of variation in BMI (Locke et al., 2015; Speliotes et al., 2010). Growing evidence supports the concept that the *origins of obesity can be traced to the intrauterine period of life* (Entringer et al., 2012b; Oken & Gillman, 2003), at which time the developing fetus responds to suboptimal conditions by producing structural and functional changes in cells, tissues and organ systems (Barker, 2002; Gluckman & Hanson, 2004b). Many of these changes, such as altered set points in hypothalamic circuits that regulate appetite and satiety (Cripps et al., 2005), reduced pancreatic β-cell mass (Portha et al., 2011), impaired adipocyte (PPAR-ɣ) function (Desai & Ross, 2011), and reduced insulin sensitivity (Catalano et al., 2009) have important long-term consequences for the *propensity* for developing obesity and associated disorders through one or both of two processes: they may influence magnitude and choice of dietary intake, and they may influence the biological fate of energy intake. It is important to note that these intrauterine effects set the stage, but by no means negate the importance of postnatal influences such as infant nutrition and feeding practices. In fact, the effects of fetal programming may interact additively or multiplicatively with such postnatal effects. Thus, we suggest that incorporation of the life course perspective to the fetal programming paradigm provides the optimal framework for elucidating key pathways underlying the intergenerational transmission during gestation of maternal CM experience on newborn and infant adiposity.

5.2 From the perspective of intergenerational effects of maternal CM exposure.

To date, the literature on the intergenerational effects of maternal CM exposure has focused on the child's early postnatal period of life as the primary transmission window. However, the application of the fetal programming paradigm may shed new light on the potential for transmission to begin at an earlier time period (during the highly sensitive period of gestation and *in utero* development). The concept that a woman's pre-conceptional state may have important implications for her child's intrauterine development is supported by the key tenets of evolutionary and life history theory (Kermack et al., 1934). CM experience represents a critical cue of extrinsic morbidity and unpredictability that may change life history strategies and alter morphological, physiological and behavioral traits (Braendle et al., 2011) that, in turn, impact the state in which a woman enters pregnancy. The plausibility of our hypothesis that the adverse effects of maternal CM on child obesity risk may start during the intrauterine period comes from *a*) studies we have recently published demonstrating the first *direct* links between maternal CM exposure and *i*) *placental-fetal stress biology* via production and trajectory of placental corticotrophin-releasing hormone (CRH) (Moog et al., 2016), a key regulator of fetal growth, parturition, and childhood obesity risk (Gillman et al., 2006; Wadhwa et al., 2004); *ii*) increased susceptibility for

maternal hypothyroidism during pregnancy (Moog et al., 2017a); *iii*) altered fetal brain development during gestation, characterized by a lower cortical gray matter volume in the newborn (Moog, et al., 2017b); and *b*) observations that the above-described CM sequelae are associated with biological alterations during pregnancy that, in turn, may directly or indirectly be linked to childhood obesity risk (Donahue et al., 2011; Donnelly et al., 2015; Gademan et al., 2014; Gillman et al., 2006; Hellmuth et al., 2016; Josefson et al., 2014; Moon et al., 2013; Much et al., 2013; Schaefer-Graf et al., 2011; Stirrat et al., 2014; Teague et al., 2015).

6. Mechanisms for the intergenerational transmission of the effects of maternal CM on offspring obesity

The biological pathway by which maternal states impact intrauterine development is a longitudinal process, beginning before conception and extending into the postnatal period, and which may involve several mechanisms including; *i)* transduction and reception of biological signals across the placental-fetal unit that participate in fetal development and phenotypic specification (including, but not limited to the establishment of *de novo* epigenetic alterations in the embryo/fetus/child), *ii)* preconceptional effects on (maternal) oocytes and follicular fluid composition, *iii*) the composition and activity of the maternal microbiome prior to and during gestation, and *iv)* postnatal processes including feeding practices, mother-child attachment, and infant microbiome acquisition.

6.1 Maternal and fetal gestational biology

A crucial component of our formulation is the question of whether maternal CM sequelae can influence those specific aspects of gestational biology that participate in fetal programming of child obesity risk. In this regard, we propose that maternal and fetal endocrine, immune/inflammatory, metabolic and lipid biology collectively constitute an attractive candidate mechanism. Firstly, these systems are responsive to *all* classes of intrauterine perturbations linked to maternal CM sequelae (sensors); secondly, they extensively mediate communication between maternal and fetal compartments (transducers); and thirdly, they play an essential, obligatory role in orchestrating and producing variation in key events underlying cellular growth, replication and differentiation in the brain (regions and circuitry underlying energy balance homeostasis) and peripheral tissues (adipocytes, pancreas, liver, muscle) related to obesity and metabolic dysfunction-related phenotypes (effectors) (Fowden et al., 2006; Matthews, 2000; Thompson & Al-Hasan, 2012).

6.1.1 Role as sensors of the adverse sequelae of maternal CM exposure.—

Substantial evidence in non-pregnant women demonstrates the persistent, life-long impact of CM on endocrine, metabolic, and inflammatory pathways, suggesting that in the context of pregnancy and fetal development these biological systems may act as sensors of a constellation of unfavorable external environmental conditions related to maternal CM exposure. For instance, CM induces endocrine dysregulation *via* dysregulated cortisol response and hypothalamic-pituitary-adrenal (HPA)-axis reactivity (Carpenter et al., 2009; Klaassens et al., 2009), promotes chronic inflammation *via* elevated pro-inflammatory cytokines (Friedman et al., 2015; Matthews et al., 2014), and is associated with adverse

metabolic and lipid profiles *via* increased risk of type 2 diabetes mellitus (Rich-Edwards et al., 2010; Thomas et al., 2008) and the metabolic syndrome (Midei et al., 2013). Previous research and our own published and preliminary studies suggest there is a continuity and spill-over effect from the pre-conceptional to the gestational state of many of the conditions that are CM sequelae, such as maternal depression (Barrios et al., 2015), inflammation (Slopen et al., 2015), HPA axis hypersensitivity (Moog et al., 2012), and obesity (Hollingsworth et al., 2012; Nagl et al., 2015). Moreover, the pre-preconception and/or prenatal presence of several of the same states and conditions that happen to be CM sequelae has been shown to impact gestational biology. These include psychological (depression, PTSD), dysregulated HPA-axis activity (Christian, 2014; Christian et al., 2010), metabolic (chronic inflammation, elevated lipids, insulin resistance) (Heerwagen et al., 2013; Winzer et al., 2004), biophysical (obesity, elevated fat mass) (Friedman, 2015; Stirrat et al., 2016), and behavioral (smoking, drug abuse) (Collier et al., 2015; Somm et al., 2008; Xia et al., 2014) factors. In many instances, the biological effects of maternal exposure to CM or adult preconceptional abuse have also been documented in fetal (cord) blood (Moog et al., 2012; Sternthal et al., 2009).

6.1.2 Role as transducers between the maternal and fetal compartments of the sequelae of maternal CM.—Current evidence links the above-mentioned biological pathways and specific biomarkers across the maternal and fetal compartments, supporting the plausibility that information about the existence of unfavorable external environmental conditions, which have been “sensed” by maternal biology, also utilize these same biological systems as a pathway for the mother-to-fetus transmission of this information. For example, prenatal stress induction in animals elevates maternal and fetal cortisol, with a high correlation between their respective concentrations (Rakers et al., 2015). Levels of the pro-inflammatory cytokine Interleukin (*IL*)-6 are similarly correlated in maternal and cord blood among pregnancies delivered by elective Cesarean section (*i.e.*, in the context of absence of the acute physiological stress of labor) (Vega-Sanchez et al., 2010). Maternal metabolic dysregulation such as poor glycemic control is reflected in elevated cord blood C-Peptide, a biomarker of fetal insulin secretion (Josefson et al., 2014; Scholtens et al., 2014; Walsh et al., 2014). Maternal and fetal leptin also are highly correlated (Josefson et al., 2014; Luo et al., 2013; Walsh et al., 2014), while plasma free fatty acids are correlated between maternal and fetal compartments in normoglycemic as well as pregnancies affected by gestational diabetes mellitus (Schaefer-Graf et al., 2008; Schaefer-Graf et al., 2011).

6.1.3 Role as effectors of fetal programming of newborn and childhood obesity risk.—Substantial human and animal literature suggests that dysregulation of the gestational biological systems mentioned above is associated with increased childhood adiposity and obesity risk, thereby suggesting that these same biological ligands act on targets within the fetal compartment to causally produce phenotypic effects that underlie the outcomes of interest (in this case, offspring obesity/adiposity). For example, cortisol and corticotrophin releasing hormone (CRH) in gestation predict macrosomia (Stirrat et al., 2014) and early childhood central adiposity (Gillman et al., 2006). IL-6 has been identified as among the strongest prenatal predictors of child adiposity (Radaelli et al., 2006), while other inflammatory markers have also been implicated (Mestan et al., 2010). Biomarkers of

maternal and fetal metabolic dysregulation such as poor maternal glycemic control and insulin resistance (Schaefer-Graf et al., 2011; Scholtens et al., 2014), elevated cord blood C-peptide (Hou et al., 2014; Regnault et al., 2011), and elevated maternal/fetal leptin (Donnelly et al., 2015; Josefson et al., 2014; Walsh et al., 2014), *all* have been linked to child adiposity. Triglycerides in maternal and cord blood also are strongly associated with adiposity at birth (Nayak et al., 2013; Schaefer-Graf et al., 2008; Scholtens et al., 2014) and in childhood (Gademan et al., 2014). Prenatal fatty acid profiles are emerging as predictors of childhood obesity risk (Schaefer-Graf et al., 2008; Scholtens et al., 2014) and are reported to exert an even larger effect than triglycerides and lipoproteins on offspring BMI, body fat percentage, and waist-to-height ratio (Gademan et al., 2014). Maternal omega-6 fatty acid status is associated with birth weight (Much et al., 2013) and percent body fat at 4 years of age (Moon et al., 2013), while a raised omega-6/omega-3 ratio in cord blood demonstrated a strong positive association with child adiposity at age 3 years (Donahue et al., 2011).

6.2 Epigenetic characteristics

Several epigenetic states/characteristics are *prospectively* associated with adiposity and metabolic dysfunction (Godfrey et al., 2011; Lin et al., 2017), and growing evidence supports a role for certain environmental exposures/conditions in the production of some of these epigenetic characteristics (Bays & Scinta, 2015; Godfrey et al., 2011). From the developmental perspective, epigenetic inter-generational transmission of obesity risk may occur *via* one or both of two possible routes; *i*) inheritance of maternally-derived epigenetic alterations in the germ line (oocytes), and *ii*) *de novo* production of epigenetic marks in the offspring *via* exposure to maternal conditions during intrauterine life. There is currently very limited evidence (and only among animal studies) to suggest that some epigenetic marks can survive the erasure and re-establishment of epigenetic characteristics that occurs shortly after fertilization. Animal models of early life stress have demonstrated that some epigenetic inheritance may be possible through the paternal germ line (Gapp et al., 2014; Soubry et al., 2014), as environmental conditions can influence the miRNA composition of sperm. In this way, it is plausible that paternal CM exposure also may contribute to the intergenerational transmission of CM effects on offspring health, but thus far this concept has only been studied in the context of paternal stress and offspring brain development (Yeshurun & Hannan, 2019). Furthermore, epigenetic inheritance has not yet been demonstrated through the maternal germ line, which would be required to support the inter- and trans-generational transmission of effects of early life exposures, including that of CM (Daxinger & Whitelaw, 2012). However, it is plausible that *de novo* production of epigenetic alterations in the developing fetus, via the sequelae of maternal CM exposure (Palma-Gudiel et al., 2015), may contribute to the developmental programming of childhood obesity (Heerwagen et al., 2010; Laker et al., 2013). For example, several animal studies have demonstrated that maternal obesity and in utero exposure to excess maternal lipids can impact gene pathways of metabolic importance for the developing fetus, including those for lipid oxidation (Bruce et al., 2009), insulin resistance (Yan et al., 2010), cellular differentiation (Kirchner et al., 2010; Zhu et al., 2008), adipogenesis (Muhlhausler et al., 2007), and brain circuitry affecting appetite regulation and feeding behavior (Chang et al., 2008). In a longitudinal human cohort study, unbalanced maternal diet in pregnancy was associated with alterations in DNA methylation in the adult offspring within genes for 11-betahydroxysteroid dehydrogenase

type 2 (cortisol regulation), glucocorticoid receptor, and insulin-like growth factor-2, which were positively associated with increased adiposity and blood pressure (Drake et al., 2012). However, maternal obesity and poor diet are only two sequelae associated with exposure to CM. The potential effects of maternal stress and other behavioral, psychological and physiological sequelae of CM on epigenetic alterations during fetal development require significantly more research in longitudinal human studies.

6.3 Oocyte cytoplasm and mitochondrial function

The cytoplasm of the oocyte and follicular fluid constitutes the very first environmental exposure for a fertilized egg (in humans it takes about 24–36 hrs post fertilization for the newly-conceived individual's full DNA complement to be assembled from maternal and paternal chromosomes). The quality of the oocyte cytoplasm is known to impact many outcomes including early embryonic survival, establishment and maintenance of pregnancy, fetal development, and even adult disease risk (Krisher, 2004). The structure and function of mitochondria, cellular proteins, and RNA molecules contained in the oocyte cytoplasm are central to these processes (Van Blerkom, 2011), and these may be altered by preconception states and conditions during the process of oocyte growth and maturation. For example, maternal obesity prior to conception, a common sequelae of CM exposure, is associated with altered oocyte endoplasmic reticulum (ER) stress signaling (Latham, 2015), resulting in reduced mitochondrial membrane potential and increased autophagy (Wu et al., 2015). As such, oocyte mitochondrial dysfunction may contribute to the intergenerational transmission of obesity (Turner & Robker, 2015). Studies of women undergoing *in vitro* fertilization also indicate that psychosocial stress (An et al., 2013; Turner et al., 2013) and heightened physiological reactivity to stress (Facchinetti et al., 1997) is associated with reduced oocyte competence and failure to conceive. Although alterations in oocyte cytoplasm have not yet been studied in relation to maternal CM exposure, it is plausible that the adverse lifelong sequelae of CM (*i.e.*, stress in this context) could affect oocyte quality and mitochondrial function across all stages of oocyte development and maturation, thereby influencing aspects of fetal development that are associated with increased susceptibility for excess adiposity via inherited cellular metabolic dysfunctions. While this mechanism has not yet been studied in humans, there is supporting evidence from animal studies (Turner & Robker, 2015). Luzzo et al. demonstrated that blastocysts from female mice with obesity, after transfer to females without obesity for gestation, resulted in low birth weight phenotype offspring at risk of subsequent increased adiposity and glucose intolerance (Luzzo et al., 2012).

6.4 Maternal and Infant Microbiome

A rapidly growing and convergent body of literature has linked characteristics of the infant gut microbiome with the subsequent development of offspring disorders, including obesity (Luoto et al., 2013). The composition of the infant microbiome is determined by not only perinatal and early postnatal exposures (such as mode of delivery, infant feeding practices, antibiotic use) but also directly and indirectly by the composition and activity of the maternal microbiome during pregnancy (Soderborg et al., 2016). Recent evidence indicates the presence of microbial DNA in the placenta, amniotic fluid, meconium and umbilical cord blood from healthy pregnancies without intrauterine infection (Funkhouser & Bordenstein, 2013), suggesting some mechanism(s) for direct microbial transfer between the

maternal and fetal compartments in utero, which may subsequently shape the composition of the infant microbiome. While research in this area is currently in its infancy, one hypothesized mechanism is that maternal microbes reach the placenta via the bloodstream after translocation across the gut epithelium (Jenmalm, 2017; Soderborg et al., 2016). Maternal gut and cervicovaginal microbes may indirectly influence obesity risk in the child via alterations to systemic maternal biology (e.g., enhanced inflammation, increased availability of metabolic fuels) (Basu et al., 2011), facilitating fetal programming of brain and peripheral tissues with predisposition for greater adiposity during in utero development and early childhood. Furthermore, the maternal microbiome composition and activity may influence the development of the fetal immune system (Jenmalm, 2017), which then would be expected to play a role in the establishment of the newborn and infant microbiome.

Thus, an increasing body of empirical and experimental evidence suggests that the determinants of the maternal microbiome composition before and during pregnancy may contribute to the intergenerational transfer of obesity risk. Maternal overweight, obesity and unhealthy periconceptional diet are currently the primary exposures under study in this regard, and have each been associated with an altered microbiome during pregnancy (Collado et al., 2008; Gohir et al., 2015a; Santacruz et al., 2010), which in turn affects the infant microbiota acquisition, composition and activity (Collado et al., 2010; Gohir et al., 2015b). Additional factors which are also known sequelae of CM exposure, such as psychological stress (Gur & Bailey, 2016), depression (Daniels et al., 2017), substance abuse (Engen et al., 2015; Volpe et al., 2014) and socioeconomic disadvantage (Miller et al., 2016), have also been associated with alterations in microbiome composition in non-pregnancy studies. Empirical evidence suggests that early life trauma may impact the process of microbial colonization, or may have differential effects based on how the microbiota influence the HPA axis in early life development (Daniels et al., 2017).

6.5 Postnatal factors

Our model recognizes that maternal CM exposure may exert independent postnatal effects on child obesity risk, and furthermore, that prenatal and postnatal effects may interact in programming susceptibility for obesity. An important and potentially modifiable early postnatal factor contributing to childhood obesity is infant diet/feeding practices, particularly breastfeeding and its duration (Hunsberger et al., 2013; Oddy et al., 2014), which may also mitigate the impact of earlier adverse prenatal exposures (Gibbs & Forste, 2014). A study from a large Norwegian cohort (N=53,934) reported that women with CM-exposure had a 41% increased risk of ceasing breastfeeding before 4 months postnatal (Sorbo et al., 2015), and similar findings have been reported in a smaller Canadian cohort (Boston, 2012). Moreover, it is evident that many sequelae of CM, including depression (Ahlqvist-Bjorkroth et al., 2016), anxiety (Arifunhera et al., 2015), abuse exposure in adulthood (Silverman et al., 2006), and obesity (Wojcicki, 2011), are associated with reduced breastfeeding initiation and/or duration.

Another early-life factor that is significantly associated with offspring obesity risk is poor quality maternal-child attachment (Anderson & Whitaker, 2011), which may also be affected by maternal CM exposure and psychological state (Mogi et al., 2011). While the mechanism

underlying this link is uncertain, poor quality maternal-child attachment may affect the development of children's emotion regulation and stress response systems, with subsequent effects on appetite, sleep and activity (Anderson et al., 2012). Furthermore, maternal psychosocial states in pregnancy such as anxiety and depression, which are also CM sequelae, have been associated with 'fussy' child temperament (Austin et al., 2005), a characteristic linked to shorter breastfeeding duration (Niegel et al., 2008), early introduction of solid foods (Wasser et al., 2011), and altered parental sensitivity/attachment (Planalp & Braungart-Rieker, 2013). Thus, there is evidence for interaction effects between CM sequelae and postnatal factors that are strongly implicated in the development of childhood adiposity.

As discussed in the previous section, the infant microbiome is another postnatal factor believed to play an important role in the development of childhood obesity. While we have outlined how the effects of maternal CM exposure and its sequelae may influence the infant microbiome acquisition, composition and activity via the maternal microbiome, we hypothesize that these effects are likely to persist throughout the postnatal period (e.g. altered microbial and immune composition of breastmilk, suboptimal feeding practices), potentially augmenting the adverse effects of prenatal programming mechanisms. However, we are not currently aware of any studies describing the association of maternal CM exposure with infant microbiome composition, neither from the perspective of fetal programming or postnatal acquisition.

7. Identifying vulnerable population groups and informing public health measures

The long-term burden of the development of obesity-related comorbidities in childhood and adult life cannot be ignored, and ongoing, effective early-life intervention strategies for obesity prevention are required (Institute of Medicine, 2011; Lakshman et al., 2012). While the majority of national public health policies currently target school-aged children and adolescents, the growing body of evidence for prenatal programming of susceptibility to childhood obesity has been repeatedly highlighted as a critical window of intervention (Lakshman et al., 2012; Nader et al., 2012; Wojcicki & Heyman, 2010). Indeed, prenatal interventions have targeted gestational weight gain, diet, and exercise in pregnancy, however, these measures have demonstrated limited success in influencing birth weight and offspring adiposity (Dodd et al., 2014; Poston et al., 2015; Walsh et al., 2012). We suggest that a greater emphasis on improving preconception health may be required to ameliorate the intergenerational transmission of obesity (Haire-Joshu & Tabak, 2016; Mumford et al., 2014). Thus, adopting a fetal programming approach to investigate the intergenerational transmission of the effects of maternal CM on offspring obesity risk offers the potential and new opportunity to identify a vulnerable target population, and specific behavioral, biological and/or psychological pathways amenable to intervention that may help tackle the growing burden of childhood obesity.

The multitude of adverse health sequelae experienced by individuals exposed to CM highlights their increased healthcare requirements across their lifespan (Arnow, 2004;

Hulme, 2000). Moreover, the American College of Obstetricians and Gynecologists report that female survivors of sexual abuse may be less likely to seek appropriate prenatal care services compared to non-exposed women (American College of Obstetricians and Gynecologists, 2011), thus increasing the likelihood for adverse pregnancy and neonatal outcomes. Therefore, our perspective highlights the urgency for public health policies and practices to identify, engage with and treat women with CM exposure, in order to address their own health requirements and possibly reduce the risk of adverse health consequences for their unborn children.

Another important factor to consider in identifying vulnerable population groups is maternal socioeconomic status (SES). A bidirectional relationship may exist between SES and CM, such that the incidence of CM is higher among families of lower SES (Lefebvre et al., 2017; Walsh et al., 2019), and exposure to CM is subsequently associated with lower SES in adulthood, even after adjusting for childhood SES (Zielinski, 2009). Furthermore, lower SES is associated with a higher likelihood of developing obesity in childhood and across the life-course (Andrea et al., 2017; Newton et al., 2017). Thus, SES may lie on the causal pathway between maternal CM exposure and intergenerational transmission of its effects on offspring obesity risk, highlighting the need to develop efficacious public health strategies to improve the health and wellbeing of socially disadvantaged women, with potential impact on health outcomes for subsequent generations.

8. Research Directions

It is evident from the review of literature presented in this paper that there is a strong scientific premise underlying each component of the proposed model for intergenerational transmission of the effects of maternal CM on offspring obesity risk. However, longitudinal studies across intrauterine life and extending into the postnatal period are required to verify our hypotheses, and to investigate the proposed fetal programming mechanisms. While animal studies have provided an initial platform to investigate the gestational biological effects of preconception or prenatal stress and subsequent influence on offspring obesity, there are no appropriate animal models for CM exposure. Thus, human studies are warranted that systematically characterize the gestational environment in which offspring of mothers with CM-exposure develop.

While observational, longitudinal studies of this nature may provide important insight to the intergenerational effects of CM exposure on offspring obesity, we acknowledge that this study design suffers several limitations, particularly with respect to causal inference. Knowledge gleaned from observational studies regarding the most vulnerable population groups and mechanisms of transmission of CM effects should, therefore, be targeted in future intervention studies. Given the multitude of adverse effects of CM exposure on the mother, future interventions should consider integrating behavioral, psychological and pharmacological modalities in an attempt to mitigate the effects of the sequelae of maternal CM on fetal programming pathways related to susceptibility to offspring obesity. Ideally, such interventions should target the preconception period in an effort to improve the embryonic/fetal environment from the time of conception.

New approaches to identify and interpret information from placental and fetal exosomes in the maternal compartment may advance our understanding of which biological factors in the fetal compartment play key roles in obesity-related phenotypic specification in the offspring. There is also much scope for further animal and human studies to investigate the impact of maternal CM exposure on *de novo* epigenetic alterations, oocyte biology, the composition and activity of the maternal microbiome and acquisition and establishment of the infant microbiome. For example, longitudinal case-control studies among women undergoing *in vitro* fertilization could reveal whether maternal CM exposure is associated with alterations in oocyte cytoplasm or mitochondrial function, and whether such alterations predict downstream adiposity and cardiometabolic outcomes in the offspring. Similarly, comparing the microbiome composition and activity of CM and non-CM exposed women before and during pregnancy, and follow-up with the infant microbiome, growth and adiposity, could provide insight as to whether microbial composition and colonization plays a role in transmitting the effects of maternal CM on offspring obesity risk. Furthermore, future studies examining the transmission of the effects of CM exposure must carefully consider the moderating effects of prenatal conditions and exposures on postnatal factors in the intergenerational transfer of obesity risk among this vulnerable population.

9. Conclusions

In summary, childhood abuse and neglect represent one of the most pervasive, persistent and pernicious stressors in our society. Emerging evidence now suggests the adverse consequences of CM may not be restricted to the exposed women alone, but may also be transmitted to their children. The perspective outlined in this article proposes that the intergenerational transmission of the adverse effects of maternal CM may start as early as the child's intrauterine period of life, via a culmination of gestational biological pathways, in order to increase the propensity for obesity in the offspring. Longitudinal prospective studies are required to test this hypothesis, and to elucidate intrauterine biological processes that may be amenable to intervention. Ultimately, the aim would be to break the vicious cycle of the enduring consequences of early life stress passed down from a vulnerable population of abused women, to the even more vulnerable population of their unborn children.

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References

American College of Obstetricians and Gynecologists, 2011 Committee Opinion No. 498: Adult Manifestations of Childhood Sexual Abuse. Obstetrics & Gynecology, 118(2, Part 1), 392–395. doi:10.1097/AOG.0b013e31822c994d [PubMed: 21775872]

Afifi TO, Boman J, Fleisher W, & Sareen J, 2009 The relationship between child abuse, parental divorce, and lifetime mental disorders and suicidality in a nationally representative adult sample. Child Abuse Negl, 33(3), 139–147. [PubMed: 19327835]

Ahlqvist-Bjorkroth S, Vaarno J, Junttila N, Pajulo M, Raiha H, Niinikoski H, et al., 2016 Initiation and exclusivity of breastfeeding: association with mothers' and fathers' prenatal and postnatal depression and marital distress. Acta Obstet Gynecol Scand. doi:10.1111/aogs.12857

Albuquerque D, Nobrega C, & Manco L, 2013 Association of FTO polymorphisms with obesity and obesity-related outcomes in Portuguese children. PLoS One, 8(1), e54370. doi:10.1371/journal.pone.0054370 [PubMed: 23342142]

Albuquerque D, Nobrega C, Manco L, & Padez C, 2017 The contribution of genetics and environment to obesity. Br Med Bull, 123(1), 159–173. doi:10.1093/bmb/ldx022 [PubMed: 28910990]

An Y, Sun Z, Li L, Zhang Y, & Ji H, 2013 Relationship between psychological stress and reproductive outcome in women undergoing in vitro fertilization treatment: Psychological and neurohormonal assessment. Journal of Assisted Reproduction and Genetics, 30(1), 35–41. doi:10.1007/s10815-012-9904-x [PubMed: 23212833]

Anda RF, Felitti VJ, Bremner JD, Walker JD, Whitfield C, Perry BD, et al., 2006 The enduring effects of abuse and related adverse experiences in childhood. A convergence of evidence from neurobiology and epidemiology. Eur Arch Psychiatry Clin Neurosci, 256(3), 174–186. doi:10.1007/s00406-005-0624-4 [PubMed: 16311898]

Anderson SE, Gooze RA, Lemeshow S, & Whitaker RC, 2012 Quality of early maternal-child relationship and risk of adolescent obesity. Pediatrics, 129(1), 132–140. doi:10.1542/peds.2011-0972 [PubMed: 22201144]

Anderson SE, & Whitaker RC, 2011 Attachment security and obesity in US preschool-aged children. Arch Pediatr Adolesc Med, 165(3), 235–242. doi:10.1001/archpediatrics.2010.292 [PubMed: 21383273]

Andrea SB, Hooker ER, Messer LC, Tandy T, & Boone-Heinonen J, 2017 Does the association between early life growth and later obesity differ by race/ethnicity or socioeconomic status? A systematic review. Annals of epidemiology, 27(9), 583–592.e585. doi:10.1016/j.annepidem.2017.08.019 [PubMed: 28911983]

Arifunhera JH, Srinivasaraghavan R, Sarkar S, Kattimani S, Adhisivam B, & Vishnu Bhat B, 2015 Is maternal anxiety a barrier to exclusive breastfeeding? J Matern Fetal Neonatal Med, 1–4. doi:10.3109/14767058.2015.1104662

Arnow BA, 2004 Relationships between childhood maltreatment, adult health and psychiatric outcomes, and medical utilization. Journal of Clinical Psychiatry, 65, 10–15.

Austin M-P, Hadzi-Pavlovic D, Leader L, Saint K, & Parker G, 2005 Maternal trait anxiety, depression and life event stress in pregnancy: relationships with infant temperament. Early Human Development, 81(2), 183–190. doi:10.1016/j.earlhumdev.2004.07.001 [PubMed: 15748973]

Barker DJ, 2002 Fetal programming of coronary heart disease. Trends Endocrinol Metab, 13(9), 364–368. [PubMed: 12367816]

Barrios YV, Gelaye B, Zhong Q, Nicolaidis C, Rondon MB, Garcia PJ, et al., 2015 Association of childhood physical and sexual abuse with intimate partner violence, poor general health and depressive symptoms among pregnant women. PLoS One, 10(1), e0116609. doi:10.1371/journal.pone.0116609 [PubMed: 25635902]

Basu S, Haghiac M, Surace P, Challier JC, Guerre-Millo M, Singh K, et al., 2011 Pregravid obesity associates with increased maternal endotoxemia and metabolic inflammation. Obesity (Silver Spring), 19(3), 476–482. doi:10.1038/oby.2010.215 [PubMed: 20930711]

Bays H, & Scinta W, 2015 Adiposopathy and epigenetics: an introduction to obesity as a transgenerational disease. Curr Med Res Opin, 31(11), 2059–2069. doi:10.1185/03007995.2015.1087983 [PubMed: 26331354]

Bierer LM, Bader HN, Daskalakis NP, Lehrner AL, Makotkine I, Seckl JR, et al., 2014 Elevation of 11β-hydroxysteroid dehydrogenase type 2 activity in Holocaust survivor offspring: Evidence for an intergenerational effect of maternal trauma exposure. Psychoneuroendocrinology, 48, 1–10. doi:10.1016/j.psyneuen.2014.06.001 [PubMed: 24971590]

Bluher M, 2019 Obesity: global epidemiology and pathogenesis. Nat Rev Endocrinol, 15(5), 288–298. doi:10.1038/s41574-019-0176-8 [PubMed: 30814686]

Boston N (2012). The association between childhood trauma and breastfeeding for a sample of women from Hamilton, Ontario, Canada (MSc), Emory university.

Braendle C, Heyland F, & Flatt T (2011). Integrating mechanistic and evolutionary analysis on life history variation In Flatt T & Heyland F (Eds.), Mechanisms of life history evolution. The genetics and physiology of life history traits and trade-offs (pp. 3–10): Oxford University Press.

Brand SR, Brennan PA, Newport DJ, Smith AK, Weiss T, & Stowe ZN, 2010 The impact of maternal childhood abuse on maternal and infant HPA axis function in the postpartum period. Psychoneuroendocrinology, 35(5), 686–693. doi:10.1016/j.psyneuen.2009.10.009 [PubMed: 19931984]

Brehm BJ, Spang SE, Lattin BL, Seeley RJ, Daniels SR, & D'Alessio DA, 2005 The role of energy expenditure in the differential weight loss in obese women on low-fat and low-carbohydrate diets. Journal of Clinical Endocrinology & Metabolism, 90(3), 1475–1482. [PubMed: 15598683]

Bruce KD, Cagampang FR, Argenton M, Zhang J, Ethirajan PL, Burdge GC, et al., 2009 Maternal high-fat feeding primes steatohepatitis in adult mice offspring, involving mitochondrial dysfunction and altered lipogenesis gene expression. Hepatology, 50(6), 1796–1808. doi:10.1002/hep.23205 [PubMed: 19816994]

Buss C, Entringer S, Moog NK, Toepfer P, Fair DA, Simhan HN, et al., 2017 Intergenerational Transmission of Maternal Childhood Maltreatment Exposure: Implications for Fetal Brain Development. J Am Acad Child Adolesc Psychiatry, 56(5), 373–382. doi:10.1016/j.jaac.2017.03.001 [PubMed: 28433086]

Carpenter LL, Tyrka AR, Ross NS, Khoury L, Anderson GM, & Price LH, 2009 Effect of childhood emotional abuse and age on cortisol responsivity in adulthood. Biol Psychiatry, 66(1), 69–75. doi:10.1016/j.biopsych.2009.02.030 [PubMed: 19375070]

Catalano PM, Presley L, Minium J, & Hauguel-de Mouzon S, 2009 Fetuses of obese mothers develop insulin resistance in utero. Diabetes Care, 32(6), 1076–1080. doi:dc08–2077[pii]10.2337/dc08-2077 [PubMed: 19460915]

Catalano PM, & Shankar K, 2017 Obesity and pregnancy: mechanisms of short term and long term adverse consequences for mother and child. Bmj, 356, j1–j1. doi:10.1136/bmj.j1 [PubMed: 28179267]

CDC. 2010 Adverse childhood experiences reported by adults --- five states, 2009. MMWR Morb Mortal Wkly Rep, 59(49), 1609–1613. [PubMed: 21160456]

Chang GQ, Gaysinskaya V, Karatayev O, & Leibowitz SF, 2008 Maternal high-fat diet and fetal programming: increased proliferation of hypothalamic peptide-producing neurons that increase risk for overeating and obesity. J Neurosci, 28(46), 12107–12119. doi:10.1523/jneurosci.2642-08.2008 [PubMed: 19005075]

Christian LM, 2014 Effects of stress and depression on inflammatory immune parameters in pregnancy. American Journal of Obstetrics & Gynecology, 211(3), 275–277. doi:10.1016/j.ajog.2014.06.042 [PubMed: 24956551]

Christian LM, Franco A, Iams JD, Sheridan J, & Glaser R, 2010 Depressive symptoms predict exaggerated inflammatory responses to an in vivo immune challenge among pregnant women. Brain Behav Immun, 24(1), 49–53. doi:10.1016/j.bbi.2009.05.055 [PubMed: 19464358]

Collado MC, Isolauri E, Laitinen K, & Salminen S, 2008 Distinct composition of gut microbiota during pregnancy in overweight and normal-weight women. Am J Clin Nutr, 88(4), 894–899. [PubMed: 18842773]

Collado MC, Isolauri E, Laitinen K, & Salminen S, 2010 Effect of mother's weight on infant's microbiota acquisition, composition, and activity during early infancy: a prospective follow-up study initiated in early pregnancy. Am J Clin Nutr, 92(5), 1023–1030. doi:10.3945/ajcn.2010.29877 [PubMed: 20844065]

Collier AC, Sato BL, Milam KA, & Wright TE, 2015 Methamphetamine, smoking, and gestational hypertension affect norepinephrine levels in umbilical cord tissues. Clin Exp Obstet Gynecol, 42(5), 580–585. [PubMed: 26524802]

Collishaw S, Dunn J, O'Connor TG, & Golding J, 2007 Maternal childhood abuse and offspring adjustment over time. Dev Psychopathol, 19(2), 367–383. doi:10.1017/S0954579407070186 [PubMed: 17459175]

Cripps RL, Martin-Gronert MS, & Ozanne SE, 2005 Fetal and perinatal programming of appetite. Clin Sci (Lond), 109(1), 1–11. [PubMed: 15966867]

Dabelea D, & Harrod CS, 2013 Role of developmental overnutrition in pediatric obesity and type 2 diabetes. Nutr Rev, 71(S1), S62–S67. [PubMed: 24147926]

Daniels JK, Koopman M, & Aidy SE, 2017 Depressed gut? The microbiota-diet-inflammation trialogue in depression. Curr Opin Psychiatry. doi:10.1097/yco.0000000000000350

Daxinger L, & Whitelaw E, 2012 Understanding transgenerational epigenetic inheritance via the gametes in mammals. Nat Rev Genet, 13(3), 153–162. doi:10.1038/nrg3188 [PubMed: 22290458]

Deliard S, Panossian S, Mentch FD, Kim CE, Hou C, Frackelton EC, et al., 2013 The missense variation landscape of FTO, MC4R, and TMEM18 in obese children of African Ancestry. Obesity, 21(1), 159–163. doi:10.1002/oby.20147 [PubMed: 23505181]

Desai M, & Ross MG (2011). Fetal programming of adipose tissue: effects of intrauterine growth restriction and maternal obesity/high-fat diet. Paper presented at the Seminars in reproductive medicine.

Dietz WH, 1998 Health consequences of obesity in youth: childhood predictors of adult disease. Pediatrics, 101(3 Pt 2), 518–525. [PubMed: 12224658]

Dodd JM, Turnbull D, McPhee AJ, Deussen AR, Grivell RM, Yelland LN, et al., 2014 Antenatal lifestyle advice for women who are overweight or obese: LIMIT randomised trial. Bmj, 348, g1285. doi:10.1136/bmj.g1285 [PubMed: 24513442]

Donahue SM, Rifas-Shiman SL, Gold DR, Jouni ZE, Gillman MW, & Oken E, 2011 Prenatal fatty acid status and child adiposity at age 3 y: results from a US pregnancy cohort. Am J Clin Nutr, 93(4), 780–788. doi:10.3945/ajcn.110.005801 [PubMed: 21310834]

Dong M, Giles WH, Felitti VJ, Dube SR, Williams JE, Chapman DP, et al., 2004 Insights into causal pathways for ischemic heart disease: adverse childhood experiences study. Circulation, 110(13), 1761–1766. doi:10.1161/01.CIR.0000143074.54995.7F [PubMed: 15381652]

Donnelly JM, Lindsay KL, Walsh JM, Horan M, Molloy EJ, & McAuliffe FM, 2015 Fetal metabolic influences of neonatal anthropometry and adiposity. BMC Pediatr, 15, 175. doi:10.1186/s12887-015-0499-0 [PubMed: 26555879]

Drake AJ, McPherson RC, Godfrey KM, Cooper C, Lillycrop KA, Hanson MA, et al., 2012 An unbalanced maternal diet in pregnancy associates with offspring epigenetic changes in genes controlling glucocorticoid action and foetal growth. Clin Endocrinol (Oxf), 77(6), 808–815. doi:10.1111/j.1365-2265.2012.04453.x [PubMed: 22642564]

Drake AJ, & Reynolds RM, 2010 Impact of maternal obesity on offspring obesity and cardiometabolic disease risk. Reproduction, 140(3), 387–398. doi:10.1530/rep-10-0077 [PubMed: 20562299]

Engen PA, Green SJ, Voigt RM, Forsyth CB, & Keshavarzian A, 2015 The Gastrointestinal Microbiome: Alcohol Effects on the Composition of Intestinal Microbiota. Alcohol Research : Current Reviews, 37(2), 223–236. [PubMed: 26695747]

Entringer S, Buss C, Swanson JM, Cooper DM, Wing DA, Waffarn F, et al., 2012a Fetal programming of body composition, obesity, and metabolic function: the role of intrauterine stress and stress biology. J Nutr Metab, 2012, Article ID 632548, 632516 pages.

Entringer S, Buss C, Swanson JM, Cooper DM, Wing DA, Waffarn F, et al., 2012b Fetal programming of body composition, obesity, and metabolic function: the role of intrauterine stress and stress biology. J Nutr Metab, 2012, 632548. doi:10.1155/2012/632548 [PubMed: 22655178]

Entringer S, Buss C, & Wadhwa PD, 2015 Prenatal stress, development, health and disease risk: a psychobiological perspective – 2015 Curt Richter Award Winner. Psychoneuroendocrinology, 62, 366–375. doi:10.1016/j.psyneuen.2015.08.019 [PubMed: 26372770]

Everaerd D, Klumpers F, Zwiers M, Guadalupe T, Franke B, van Oostrom I, et al., 2015 Childhood Abuse and Deprivation are Associated with Distinct Sex-Dependent Differences in Brain Morphology. Neuropsychopharmacology. doi:10.1038/npp.2015.344

Facchinetti F, Volpe A, Matteo ML, Genazzani AR, & Artini GP, 1997 An increased vulnerability to stress is associated with a poor outcome of in vitro fertilization-embryo transfer treatment. Fertil Steril, 67(2), 309–314. doi:10.1016/S0015-0282(97)81916-4 [PubMed: 9022608]

Fagot-Campagna A, Narayan KM, & Imperatore G, 2001 Type 2 diabetes in children. BMJ, 322(7283), 377–378. [PubMed: 11179142]

Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al., 1998 Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med, 14(4), 245–258. [PubMed: 9635069]

Fowden AL, Giussani DA, & Forhead AJ, 2006 Intrauterine Programming of Physiological Systems: Causes and Consequences. Physiology, 21(1), 29–37. doi:10.1152/physiol.00050.2005 [PubMed: 16443820]

Freedman DS, Khan LK, Dietz WH, Srinivasan SR, & Berenson GS, 2001 Relationship of childhood obesity to coronary heart disease risk factors in adulthood: the Bogalusa Heart Study. Pediatrics, 108(3), 712–718. [PubMed: 11533341]

Freedman DS, Mei Z, Srinivasan SR, Berenson GS, & Dietz WH, 2007 Cardiovascular risk factors and excess adiposity among overweight children and adolescents: the Bogalusa Heart Study. J Pediatr, 150(1), 12–17 e12. [PubMed: 17188605]

Friedman EM, Karlamangla AS, Gruenewald TL, Koretz B, & Seeman TE, 2015 Early life adversity and adult biological risk profiles. Psychosom Med, 77(2), 176–185. doi:10.1097/psy.0000000000000147 [PubMed: 25650548]

Friedman JE, 2015 Obesity and Gestational Diabetes Mellitus Pathways for Programming in Mouse, Monkey, and Man-Where Do We Go Next? The 2014 Norbert Freinkel Award Lecture. Diabetes Care, 38(8), 1402–1411. doi:10.2337/dc15-0628 [PubMed: 26207051]

Friedman JE, 2018 Developmental Programming of Obesity and Diabetes in Mouse, Monkey, and Man in 2018: Where Are We Headed? Diabetes, 67(11), 2137–2151. doi:10.2337/dbi17-0011 [PubMed: 30348820]

Funkhouser LJ, & Bordenstein SR, 2013 Mom Knows Best: The Universality of Maternal Microbial Transmission. PLOS Biology, 11(8), e1001631. doi:10.1371/journal.pbio.1001631 [PubMed: 23976878]

Gademan MG, Vermeulen M, Oostvogels AJ, Roseboom TJ, Visscher TL, van Eijsden M, et al., 2014 Maternal prepregancy BMI and lipid profile during early pregnancy are independently associated with offspring's body composition at age 5–6 years: the ABCD study. PLoS One, 9(4), e94594. doi:10.1371/journal.pone.0094594 [PubMed: 24740157]

Gapp K, Jawaid A, Sarkies P, Bohacek J, Pelczar P, Prados J, et al., 2014 Implication of sperm RNAs in transgenerational inheritance of the effects of early trauma in mice. Nat Neurosci, 17(5), 667–669. doi:10.1038/nn.3695 [PubMed: 24728267]

Ghoorah K, Campbell P, Kent A, Maznyczka A, & Kunadian V, 2014 Obesity and cardiovascular outcomes: a review. European Heart Journal: Acute Cardiovascular Care(Epub ahead of print), doi: 2048872614523349.

Gibbs BG, & Forste R, 2014 Socioeconomic status, infant feeding practices and early childhood obesity. Pediatr Obes, 9(2), 135–146. doi:10.1111/j.2047-6310.2013.00155.x [PubMed: 23554385]

Gillman MW, Rich-Edwards JW, Huh S, Majzoub JA, Oken E, Taveras EM, et al., 2006 Maternal corticotropin-releasing hormone levels during pregnancy and offspring adiposity. Obesity (Silver Spring), 14(9), 1647–1653. doi:10.1038/oby.2006.189 [PubMed: 17030976]

Gluckman PD, & Hanson MA, 2004a Living with the past: evolution, development, and patterns of disease. Science, 305(5691), 1733–1736. [PubMed: 15375258]

Gluckman PD, & Hanson MA, 2004b Living with the past: evolution, development, and patterns of disease. Science, 305(5691), 1733–1736. [PubMed: 15375258]

Godfrey KM, & Barker DJ, 2001 Fetal programming and adult health. Public health nutrition, 4(2B; SPI), 611–624. [PubMed: 11683554]

Godfrey KM, Sheppard A, Gluckman PD, Lillycrop KA, Burdge GC, McLean C, et al., 2011 Epigenetic gene promoter methylation at birth is associated with child's later adiposity. Diabetes, 60. doi:10.2337/db10-0979

Godfrey KM, Sheppard A, Gluckman PD, Lillycrop KA, Burdge GC, McLean C, et al., 2011 Epigenetic Gene Promoter Methylation at Birth Is Associated With Child's Later Adiposity. Diabetes, 60(5), 1528–1534. doi:10.2337/db10-0979 [PubMed: 21471513]

Gohir W, Ratcliffe EM, & Sloboda DM, 2015b Of the bugs that shape us: maternal obesity, the gut microbiome, and long-term disease risk. Pediatr Res, 77(1–2), 196–204. doi:10.1038/pr.2014.169 [PubMed: 25314580]

Gohir W, Whelan FJ, Surette MG, Moore C, Schertzer JD, & Sloboda DM, 2015a Pregnancy-related changes in the maternal gut microbiota are dependent upon the mother's periconceptional diet. Gut Microbes, 6(5), 310–320. doi:10.1080/19490976.2015.1086056 [PubMed: 26322500]

Gur TL, & Bailey MT, 2016 Effects of Stress on Commensal Microbes and Immune System Activity. Adv Exp Med Biol, 874, 289–300. doi:10.1007/978-3-319-20215-0_14 [PubMed: 26589225]

Haire-Joshu D, & Tabak R, 2016 Preventing Obesity Across Generations: Evidence for Early Life Intervention. Annual Review of Public Health, 37(1), 253–271. doi:doi:10.1146/annurev-publhealth-032315-021859

Hanson M, Godfrey KM, Lillycrop KA, Burdge GC, & Gluckman PD, 2011 Developmental plasticity and developmental origins of non-communicable disease: theoretical considerations and epigenetic mechanisms. Progress in biophysics and molecular biology, 106(1), 272–280. [PubMed: 21219925]

Heerwagen MJ, Stewart MS, de la Houssaye BA, Janssen RC, & Friedman JE, 2013 Transgenic increase in N-3/n-6 Fatty Acid ratio reduces maternal obesity-associated inflammation and limits adverse developmental programming in mice. PLoS One, 8(6), e67791. doi:10.1371/journal.pone.0067791 [PubMed: 23825686]

Heerwagen MJR, Miller MR, Barbour LA, & Friedman JE, 2010 Maternal obesity and fetal metabolic programming: a fertile epigenetic soil. American Journal of Physiology - Regulatory, Integrative and Comparative Physiology, 299(3), R711–R722. doi:10.1152/ajpregu.00310.2010

Heim C, & Binder EB, 2012 Current research trends in early life stress and depression: review of human studies on sensitive periods, gene-environment interactions, and epigenetics. Exp Neurol, 233(1), 102–111. doi:10.1016/j.expneurol.2011.10.032 [PubMed: 22101006]

Heim C, Shugart M, Craighead WE, & Nemeroff CB, 2010 Neurobiological and psychiatric consequences of child abuse and neglect. Dev Psychobiol, 52(7), 671–690. doi:10.1002/dev.20494 [PubMed: 20882586]

Hellmuth C, Lindsay KL, Uhl O, Buss C, Wadhwa PD, Koletzko B, et al., 2016 Association of maternal prepregnancy BMI with metabolomic profile across gestation. Int J Obes. doi:10.1038/ijo.2016.153

Hollingsworth K, Callaway L, Duhig M, Matheson S, & Scott J, 2012 The association between maltreatment in childhood and pre-pregnancy obesity in women attending an antenatal clinic in Australia. PLoS One, 7(12), e51868. doi:10.1371/journal.pone.0051868 [PubMed: 23300572]

Hou RL, Jin WY, Chen XY, Jin Y, Wang XM, Shao J, et al., 2014 Cord blood C-peptide, insulin, HbA1c, and lipids levels in small- and large-for-gestational-age newborns. Med Sci Monit, 20, 2097–2105. doi:10.12659/msm.890929 [PubMed: 25357084]

Hulme PA, 2000 Symptomatology and health care utilization of women primary care patients who experienced childhood sexual abuse1. Child Abuse Negl, 24(11), 1471–1484. doi:10.1016/S0145-2134(00)00200-3 [PubMed: 11128178]

Hunsberger M, Lanfer A, Reeske A, Veidebaum T, Russo P, Hadjigeorgiou C, et al., 2013 Infant feeding practices and prevalence of obesity in eight European countries - the IDEFICS study. Public Health Nutr, 16(2), 219–227. doi:10.1017/s1368980012003850 [PubMed: 22916704]

Hussey JM, Chang JJ, & Kotch JB, 2006 Child maltreatment in the United States: prevalence, risk factors, and adolescent health consequences. Pediatrics, 118(3), 933–942. doi:10.1542/peds.2005-2452 [PubMed: 16950983]

Institute of Medicine. 2011 Early Childhood Obesity Prevention Policies. Washington, DC: The National Academies Press 10.17226/13124.

Jakubowski KP, Cundiff JM, & Matthews KA, 2018 Cumulative childhood adversity and adult cardiometabolic disease: A meta-analysis. Health Psychol, 37(8), 701–715. doi:10.1037/hea0000637 [PubMed: 30024227]

Jenmalm MC, 2017 The mother–offspring dyad: microbial transmission, immune interactions and allergy development. Journal of Internal Medicine. doi:10.1111/joim.12652

Josefson JL, Zeiss DM, Rademaker AW, & Metzger BE, 2014 Maternal leptin predicts adiposity of the neonate. Horm Res Paediatr, 81(1), 13–19. doi:10.1159/000355387 [PubMed: 24334975]

Jovanovic T, Smith A, Kamkwalala A, Poole J, Samples T, Norrholm SD, et al., 2011 Physiological markers of anxiety are increased in children of abused mothers. J Child Psychol Psychiatry, 52(8), 844–852. doi:10.1111/j.1469-7610.2011.02410.x [PubMed: 21501167]

Keenan K, Hipwell AE, Class QA, & Mbayiwa K, 2018 Extending the developmental origins of disease model: Impact of preconception stress exposure on offspring neurodevelopment. Developmental psychobiology, 60(7), 753–764. doi:10.1002/dev.21773 [PubMed: 30144041]

Kelly AS, Barlow SE, Rao G, Inge TH, Hayman LL, Steinberger J, et al., 2013 Severe Obesity in Children and Adolescents: Identification, Associated Health Risks, and Treatment Approaches A Scientific Statement From the American Heart Association. Circulation, 128(15), 1689–1712. [PubMed: 24016455]

Kermack WO, McKendrick AG, & McKinlay PL, 1934 Death-rates in Great Britain and Sweden: Expression of Specific Mortality Rates as Products of Two Factors, and some Consequences thereof. J Hyg (Lond), 34(4), 433–457. [PubMed: 20475246]

Kirchner S, Kieu T, Chow C, Casey S, & Blumberg B, 2010 Prenatal exposure to the environmental obesogen tributyltin predisposes multipotent stem cells to become adipocytes. Mol Endocrinol, 24(3), 526–539. doi:10.1210/me.2009-0261 [PubMed: 20160124]

Klaassens ER, van Noorden MS, Giltay EJ, van Pelt J, van Veen T, & Zitman FG, 2009 Effects of childhood trauma on HPA-axis reactivity in women free of lifetime psychopathology. Prog Neuropsychopharmacol Biol Psychiatry, 33(5), 889–894. doi:10.1016/j.pnpbp.2009.04.011 [PubMed: 19389455]

Krisher RL, 2004 The effect of oocyte quality on development. J Anim Sci, 82 E-Suppl, E14–23. [PubMed: 15471793]

Laker RC, Wlodek ME, Connelly JJ, & Yan Z, 2013 Epigenetic origins of metabolic disease: The impact of the maternal condition to the offspring epigenome and later health consequences. Food Science and Human Wellness, 2(1), 1–11. doi:10.1016/j.fshw.2013.03.002

Lakshman R, Elks CE, & Ong KK, 2012 Childhood obesity. Circulation, 126(14), 1770–1779. doi:10.1161/circulationaha.111.047738 [PubMed: 23027812]

Lane M, Zander-Fox DL, Robker RL, & McPherson NO, 2015 Peri-conception parental obesity, reproductive health, and transgenerational impacts. Trends in Endocrinology & Metabolism, 26(2), 84–90. doi:10.1016/j.tem.2014.11.005 [PubMed: 25523615]

Langley-Evans SC (2006). Fetal Programming and Adult Disease Programming of Chronic Disease through Fetal Exposure to Undernutrition. Wallingford: CABI Publishing.

Latham KE, 2015 Endoplasmic reticulum stress signaling in mammalian oocytes and embryos: life in balance. Int Rev Cell Mol Biol, 316, 227–265. doi:10.1016/bs.ircmb.2015.01.005 [PubMed: 25805126]

Lefebvre R, Fallon B, Van Wert M, & Filippelli J, 2017 Examining the Relationship between Economic Hardship and Child Maltreatment Using Data from the Ontario Incidence Study of Reported Child Abuse and Neglect-2013 (OIS-2013). Behavioral sciences (Basel, Switzerland), 7(1), 6. doi:10.3390/bs7010006

Leon-Mimila P, Villamil-Ramirez H, Villalobos-Comparan M, Villarreal-Molina T, Romero-Hidalgo S, Lopez-Contreras B, et al., 2013 Contribution of common genetic variants to obesity and obesity-related traits in mexican children and adults. PLoS One, 8(8), e70640. doi:10.1371/journal.pone.0070640 [PubMed: 23950976]

Leonard SA, Petito LC, Rehkopf DH, Ritchie LD, & Abrams B, 2017 Maternal History of Child Abuse and Obesity Risk in Offspring: Mediation by Weight in Pregnancy. Child Obes, 13(4), 259–266. doi:10.1089/chi.2017.0019 [PubMed: 28440693]

Lewis A, Austin E, Knapp R, Vaiano T, & Galbally M, 2015 Perinatal Maternal Mental Health, Fetal Programming and Child Development. Healthcare, 3(4), 1212. [PubMed: 27417821]

Lin X, Lim IY, Wu Y, Teh AL, Chen L, Aris IM, et al., 2017 Developmental pathways to adiposity begin before birth and are influenced by genotype, prenatal environment and epigenome. BMC Med, 15(1), 50. doi:10.1186/s12916-017-0800-1 [PubMed: 28264723]

Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, et al., 2015 Genetic studies of body mass index yield new insights for obesity biology. Nature, 518(7538), 197–206. doi:10.1038/nature14177 [PubMed: 25673413]

Luo ZC, Nuyt AM, Delvin E, Fraser WD, Julien P, Audibert F, et al., 2013 Maternal and fetal leptin, adiponectin levels and associations with fetal insulin sensitivity. Obesity (Silver Spring), 21(1), 210–216. doi:10.1002/oby.20250 [PubMed: 23505188]

Luoto R, Collado MC, Salminen S, & Isolauri E, 2013 Reshaping the gut microbiota at an early age: functional impact on obesity risk? Ann Nutr Metab, 63 Suppl 2, 17–26. doi:10.1159/000354896

Luzzo KM, Wang Q, Purcell SH, Chi M, Jimenez PT, Grindler N, et al., 2012 High fat diet induced developmental defects in the mouse: oocyte meiotic aneuploidy and fetal growth retardation/brain defects. PLoS One, 7(11), e49217. doi:10.1371/journal.pone.0049217 [PubMed: 23152876]

Matthews KA, Chang YF, Thurston RC, & Bromberger JT, 2014 Child abuse is related to inflammation in mid-life women: role of obesity. Brain Behav Immun, 36, 29–34. doi:10.1016/j.bbi.2013.09.013 [PubMed: 24076375]

Matthews SG, 2000 Antenatal glucocorticoids and programming of the developing CNS. Pediatric research, 47(3), 291–300. [PubMed: 10709726]

McLaughlin KA, Sheridan MA, & Lambert HK, 2014 Childhood adversity and neural development: deprivation and threat as distinct dimensions of early experience. Neurosci Biobehav Rev, 47, 578–591. doi:10.1016/j.neubiorev.2014.10.012 [PubMed: 25454359]

McPherson K, 2014 Reducing the global prevalence of overweight and obesity. Lancet, 384(9945), 728–730. doi:10.1016/S0140-6736(14)60767-4 [PubMed: 24880831]

Mestan K, Ouyang F, Matoba N, Pearson C, Ortiz K, & Wang X, 2010 Maternal obesity, diabetes mellitus and cord blood biomarkers in large-for-gestational age infants. J Pediatr Biochem, 1(3), 217–224. [PubMed: 21814537]

Midei AJ, Matthews KA, & Bromberger JT, 2010 Childhood abuse is associated with adiposity in midlife women: possible pathways through trait anger and reproductive hormones. Psychosom Med, 72(2), 215–223. doi:10.1097/PSY.0b013e3181cb5c24 [PubMed: 20064904]

Midei AJ, Matthews KA, Chang YF, & Bromberger JT, 2013 Childhood physical abuse is associated with incident metabolic syndrome in mid-life women. Health Psychol, 32(2), 121–127. doi:10.1037/a0027891 [PubMed: 22775234]

Miller GE, Engen PA, Gillevet PM, Shaikh M, Sikaroodi M, Forsyth CB, et al., 2016 Lower Neighborhood Socioeconomic Status Associated with Reduced Diversity of the Colonic Microbiota in Healthy Adults. PLoS One, 11(2), e0148952. doi:10.1371/journal.pone.0148952 [PubMed: 26859894]

Min MO, Minnes S, Kim H, & Singer LT, 2013 Pathways linking childhood maltreatment and adult physical health. Child Abuse Negl, 37(6), 361–373. doi:10.1016/j.chiabu.2012.09.008 [PubMed: 23195701]

Mogi K, Nagasawa M, & Kikusui T, 2011 Developmental consequences and biological significance of mother-infant bonding. Prog Neuropsychopharmacol Biol Psychiatry, 35(5), 1232–1241. doi:10.1016/j.pnpbp.2010.08.024 [PubMed: 20817069]

Moog N, Buss C, Entringer S, Sandman CA, & Wadhwa PD, 2012 Exposure to childhood trauma among pregnant women is associated with increased placental CRH production over gestation. European Journal of Psychotraumatology, 3(Supp 1), 19554 -

Moog NK, Buss C, Entringer S, Shahbaba B, Gillen DL, Hobel CJ, et al., 2016 Maternal exposure to childhood trauma is associated during pregnancy with placental-fetal stress physiology. Biological psychiatry, 79(10), 831–839. doi:10.1016/j.biopsych.2015.08.032 [PubMed: 26444076]

Moog NK, Entringer S, Heim C, Wadhwa PD, Kathmann N, & Buss C, 2017b Influence of maternal thyroid hormones during gestation on fetal brain development. Neuroscience, 342, 68–100. doi:10.1016/j.neuroscience.2015.09.070 [PubMed: 26434624]

Moog NK, Heim CM, Entringer S, Kathmann N, Wadhwa PD, & Buss C, 2017a Childhood maltreatment is associated with increased risk of subclinical hypothyroidism in pregnancy. Psychoneuroendocrinology, 84, 190–196. doi:10.1016/j.psyneuen.2017.07.482 [PubMed: 28755549]

Moon RJ, Harvey NC, Robinson SM, Ntani G, Davies JH, Inskip HM, et al., 2013 Maternal plasma polyunsaturated fatty acid status in late pregnancy is associated with offspring body composition in childhood. J Clin Endocrinol Metab, 98(1), 299–307. doi:10.1210/jc.2012-2482 [PubMed: 23162098]

Moussa HN, Alrais MA, Leon MG, Abbas EL, & Sibai BM, 2016 Obesity epidemic: impact from preconception to postpartum. Future Science OA, 2(3), FSO137. doi:10.4155/fsoa-2016-0035 [PubMed: 28031980]

Much D, Brunner S, Vollhardt C, Schmid D, Sedlmeier EM, Bruderl M, et al., 2013 Effect of dietary intervention to reduce the n-6/n-3 fatty acid ratio on maternal and fetal fatty acid profile and its relation to offspring growth and body composition at 1 year of age. Eur J Clin Nutr, 67(3), 282–288. doi:10.1038/ejcn.2013.2 [PubMed: 23340492]

Muhlhausler BS, Duffield JA, & McMillen IC, 2007 Increased maternal nutrition stimulates peroxisome proliferator activated receptor-gamma, adiponectin, and leptin messenger ribonucleic acid expression in adipose tissue before birth. Endocrinology, 148(2), 878–885. doi:10.1210/en.2006-1115 [PubMed: 17068138]

Mumford SL, Michels KA, Salaria N, Valanzasca P, & Belizán JM, 2014 Preconception care: it's never too early. Reproductive Health, 11(1), 1–3. doi:10.1186/1742-4755-11-73 [PubMed: 24383405]

Nader PR, Huang TT, Gahagan S, Kumanyika S, Hammond RA, & Christoffel KK, 2012 Next steps in obesity prevention: altering early life systems to support healthy parents, infants, and toddlers. Child Obes, 8(3), 195–204. doi:10.1089/chi.2012.0004 [PubMed: 22799545]

Nagl M, Steinig J, Klinitzke G, Stepan H, & Kersting A, 2015 Childhood maltreatment and pre-pregnancy obesity: a comparison of obese, overweight, and normal weight pregnant women. Arch Womens Ment Health. doi:10.1007/s00737-015-0573-5

Nayak CD, Agarwal V, & Nayak DM, 2013 Correlation of cord blood lipid heterogeneity in neonates with their anthropometry at birth. Indian J Clin Biochem, 28(2), 152–157. doi:10.1007/s12291-012-0252-5 [PubMed: 24426201]

Newton S, Braithwaite D, & Akinyemiju TF, 2017 Socio-economic status over the life course and obesity: Systematic review and meta-analysis. PLoS One, 12(5), e0177151. doi:10.1371/journal.pone.0177151 [PubMed: 28510579]

Niegel S, Ystrom E, Hagtvet KA, & Vollrath ME, 2008 Difficult Temperament, Breastfeeding, and Their Mutual Prospective Effects: The Norwegian Mother and Child Cohort Study. Journal of Developmental & Behavioral Pediatrics, 29(6), 458–462. doi:10.1097/DBP.0b013e3181877a88 [PubMed: 19093326]

Oddy WH, Mori TA, Huang RC, Marsh JA, Pennell CE, Chivers PT, et al., 2014 Early infant feeding and adiposity risk: from infancy to adulthood. Ann Nutr Metab, 64(3–4), 262–270. doi:10.1159/000365031 [PubMed: 25300269]

Oken E, & Gillman MW, 2003 Fetal origins of obesity. Obes Res, 11(4), 496–506. [PubMed: 12690076]

Olshansky SJ, Passaro DJ, Hershow RC, Layden J, Carnes BA, Brody J, et al., 2005 A potential decline in life expectancy in the United States in the 21st century. N Engl J Med, 352(11), 1138–1145. [PubMed: 15784668]

Ormond KE, Mortlock DP, Scholes DT, Bombard Y, Brody LC, Faucett WA, et al., 2017 Human Germline Genome Editing. Am J Hum Genet, 101(2), 167–176. doi:10.1016/j.ajhg.2017.06.012 [PubMed: 28777929]

Padmanabhan V, Cardoso RC, & Puttabyatappa M, 2016 Developmental Programming, a Pathway to Disease. Endocrinology, 157(4), 1328–1340. doi:10.1210/en.2016-1003 [PubMed: 26859334]

Palma-Gudiel H, Córdova-Palomera A, Eixarch E, Deuschle M, & Fananas L, 2015 Maternal psychosocial stress during pregnancy alters the epigenetic signature of the glucocorticoid receptor gene promoter in their offspring: a meta-analysis. Epigenetics, 10(10), 893–902. [PubMed: 26327302]

Planalp EM, & Braungart-Rieker JM, 2013 Temperamental precursors of infant attachment with mothers and fathers. Infant Behav Dev, 36(4), 796–808. doi:10.1016/j.infbeh.2013.09.004 [PubMed: 24103401]

Plant DT, Barker ED, Waters CS, Pawlby S, & Pariante CM, 2013 Intergenerational transmission of maltreatment and psychopathology: the role of antenatal depression. Psychol Med, 43(3), 519–528. doi:10.1017/S0033291712001298 [PubMed: 22694795]

Portha B, Chavey A, & Movassat J, 2011 Early-life origins of type 2 diabetes: fetal programming of the beta-cell mass. Experimental diabetes research, 2011(doi:10.1155/2011/105076), 16 pages.

Poston L, Bell R, Croker H, Flynn AC, Godfrey KM, Goff 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(10), 767–777. doi:10.1016/S2213-8587(15)00227-2 [PubMed: 26165396]

Radaelli T, Uvena-Celebrezze J, Minium J, Huston-Presley L, Catalano P, & Hauguel-de Mouzon S, 2006 Maternal interleukin-6: marker of fetal growth and adiposity. J Soc Gynecol Investig, 13(1), 53–57. doi:10.1016/j.jsgi.2005.10.003

Rakers F, Bischoff S, Schiffner R, Haase M, Rupprecht S, Kiehntopf M, et al., 2015 Role of catecholamines in maternal-fetal stress transfer in sheep. Am J Obstet Gynecol, 213(5), 684.e681–689. doi:10.1016/j.ajog.2015.07.020 [PubMed: 26212181]

Rasmussen LJH, Moffitt TE, Arseneault L, Danese A, Eugen-Olsen J, Fisher HL, et al., 2019 Association of Adverse Experiences and Exposure to Violence in Childhood and Adolescence With Inflammatory Burden in Young People. JAMA pediatrics, 174(1), 1–11. doi:10.1001/jamapediatrics.2019.3875

Regnault N, Botton J, Heude B, Forhan A, Hankard R, Foliguet B, et al., 2011 Higher cord C-peptide concentrations are associated with slower growth rate in the 1st year of life in girls but not in boys. Diabetes, 60(8), 2152–2159. doi:10.2337/db10-1189 [PubMed: 21700880]

Rich-Edwards JW, Spiegelman D, Lividoti Hibert EN, Jun HJ, Todd TJ, Kawachi I, et al., 2010 Abuse in childhood and adolescence as a predictor of type 2 diabetes in adult women. Am J Prev Med, 39(6), 529–536. doi:10.1016/j.amepre.2010.09.007 [PubMed: 21084073]

Rikknen K, Matthews KA, & Kuller LH, 2002 The relationship between psychological risk attributes and the metabolic syndrome in healthy women: Antecedent or consequence? Metabolism, 51(12), 1573–1577. doi:10.1053/meta.2002.36301 [PubMed: 12489070]

Roberts AL, Galea S, Austin SB, Corliss HL, Williams MA, & Koenen KC, 2014 Women's experience of abuse in childhood and their children's smoking and overweight. Am J Prev Med, 46(3), 249–258. doi:10.1016/j.amepre.2013.11.012 [PubMed: 24512863]

Roberts AL, Lyall K, Rich-Edwards JW, Ascherio A, & Weisskopf MG, 2013 Association of maternal exposure to childhood abuse with elevated risk for autism in offspring. JAMA Psychiatry, 70(5), 508–515. doi:10.1001/jamapsychiatry.2013.447. [PubMed: 23553149]

Robinson MR, English G, Moser G, Lloyd-Jones LR, Triplett MA, Zhu Z, et al., 2017 Genotype-covariate interaction effects and the heritability of adult body mass index. Nat Genet, 49(8), 1174–1181. doi:10.1038/ng.3912 [PubMed: 28692066]

Santacruz A, Collado MC, García-Valdés L, Segura MT, Martín-Lagos JA, Anjos T, et al., 2010 Gut microbiota composition is associated with body weight, weight gain and biochemical parameters in pregnant women. British Journal of Nutrition, 104(1), 83–92. doi:10.1017/S0007114510000176 [PubMed: 20205964]

Schaefer-Graf UM, Graf K, Kulbacka I, Kjos SL, Dudenhausen J, Vetter K, et al., 2008 Maternal lipids as strong determinants of fetal environment and growth in pregnancies with gestational diabetes mellitus. Diabetes Care, 31(9), 1858–1863. doi:10.2337/dc08-0039 [PubMed: 18606978]

Schaefer-Graf UM, Meitzner K, Ortega-Senovilla H, Graf K, Vetter K, Abou-Dakn M, et al., 2011 Differences in the implications of maternal lipids on fetal metabolism and growth between gestational diabetes mellitus and control pregnancies. Diabetic Medicine, 28(9), 1053–1059. doi:10.1111/j.1464-5491.2011.03346.x [PubMed: 21658120]

Scher CD, Forde DR, McQuaid JR, & Stein MB, 2004 Prevalence and demographic correlates of childhood maltreatment in an adult community sample. Child Abuse Negl, 28(2), 167–180. doi:10.1016/j.chiabu.2003.09.012 [PubMed: 15003400]

Scholtens DM, Muehlbauer MJ, Daya NR, Stevens RD, Dyer AR, Lowe LP, et al., 2014 Metabolomics Reveals Broad-Scale Metabolic Perturbations in Hyperglycemic Mothers During Pregnancy. Diabetes Care, 37(1), 158–166. doi:10.2337/dc13-0989 [PubMed: 23990511]

Schwartz MW, S. RJ, Zeltser LM, Drewnowski A, Ravussin E, Redman LM, Leibel RL, 2017 Obesity Pathogenesis: An Endocrine Society Scientific Statement. Endocrine Reviews, er.2017–00111. doi:doi:10.1210/er.2017-00111

Serdula MK, Ivery D, Coates RJ, Freedman DS, Williamson DF, & Byers T, 1993 Do obese children become obese adults? A review of the literature. Prev Med, 22(2), 167–177. [PubMed: 8483856]

Silverman JG, Decker MR, Reed E, & Raj A, 2006 Intimate partner violence around the time of pregnancy: association with breastfeeding behavior. J Womens Health (Larchmt), 15(8), 934–940. doi:10.1089/jwh.2006.15.934 [PubMed: 17087617]

Slopen N, Loucks EB, Appleton AA, Kawachi I, Kubzansky LD, Non AL, et al., 2015 Early origins of inflammation: An examination of prenatal and childhood social adversity in a prospective cohort study. Psychoneuroendocrinology, 51, 403–413. doi:10.1016/j.psyneuen.2014.10.016 [PubMed: 25462912]

Sluyter JD, Scragg RK, Plank LD, Waqa GD, Fotu KF, & Swinburn BA, 2013 Sizing the association between lifestyle behaviours and fatness in a large, heterogeneous sample of youth of multiple ethnicities from 4 countries. Int J Behav Nutr Phys Act, 10, 115. doi:10.1186/1479-5868-10-115 [PubMed: 24119635]

Soderborg TK, Borengasser SJ, Barbour LA, & Friedman JE, 2016 Microbial transmission from mothers with obesity or diabetes to infants: an innovative opportunity to interrupt a vicious cycle. Diabetologia, 59(5), 895–906. doi:10.1007/s00125-016-3880-0 [PubMed: 26843076]

Somm E, Schwitzgebel VM, Vauthay DM, Camm EJ, Chen CY, Giacobino JP, et al., 2008 Prenatal nicotine exposure alters early pancreatic islet and adipose tissue development with consequences on the control of body weight and glucose metabolism later in life. Endocrinology, 149(12), 6289–6299. doi:10.1210/en.2008-0361 [PubMed: 18687784]

Sorbo MF, Lukasse M, Brantsaeter AL, & Grimstad H, 2015 Past and recent abuse is associated with early cessation of breast feeding: results from a large prospective cohort in Norway. BMJ Open, 5(12), e009240. doi:10.1136/bmjopen-2015-009240

Soubry A, Hoyo C, Jirtle RL, & Murphy SK, 2014 A paternal environmental legacy: Evidence for epigenetic inheritance through the male germ line. Bioessays, 36(4), 359–371. doi:10.1002/bies.201300113 [PubMed: 24431278]

Sovio U, Mook-Kanamori DO, Warrington NM, Lawrence R, Briollais L, Palmer CN, et al., 2011 Association between common variation at the FTO locus and changes in body mass index from infancy to late childhood: the complex nature of genetic association through growth and development. PLoS Genet, 7(2), e1001307. doi:10.1371/journal.pgen.1001307 [PubMed: 21379325]

Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, et al., 2010 Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. Nat Genet, 42(11), 937–948. doi:10.1038/ng.686 [PubMed: 20935630]

Stephenson J, Heslehurst N, Hall J, Schoenaker DAJM, Hutchinson J, Cade JE, et al., 2018 Before the beginning: nutrition and lifestyle in the preconception period and its importance for future health. Lancet (London, England), 391(10132), 1830–1841. doi:10.1016/S0140-6736(18)30311-8

Sternthal MJ, Enlow MB, Cohen S, Canner MJ, Staudenmayer J, Tsang K, et al., 2009 Maternal interpersonal trauma and cord blood IgE levels in an inner-city cohort: a life-course perspective. J Allergy Clin Immunol, 124(5), 954–960. doi:10.1016/j.jaci.2009.07.030 [PubMed: 19748657]

Stirrat LI, O'Reilly JR, Barr SM, Andrew R, Riley SC, Howie AF, et al., 2016 Decreased maternal hypothalamic-pituitary-adrenal axis activity in very severely obese pregnancy: Associations with birthweight and gestation at delivery. Psychoneuroendocrinology, 63, 135–143. doi:10.1016/j.psyneuen.2015.09.019 [PubMed: 26444587]

Stirrat LI, O'Reilly JR, Riley SC, Howie AF, Beckett GJ, Smith R, et al., 2014 Altered maternal hypothalamic-pituitary-adrenal axis activity in obese pregnancy is associated with macrosomia and prolonged pregnancy. Pregnancy Hypertens, 4(3), 238. doi:10.1016/j.preghy.2014.03.028

Tamayo T, Christian H, & Rathmann W, 2010 Impact of early psychosocial factors (childhood socioeconomic factors and adversities) on future risk of type 2 diabetes, metabolic disturbances and obesity: a systematic review. BMC Public Health, 10, 525. doi:10.1186/1471-2458-10-525 [PubMed: 20809937]

Teague AM, Fields DA, Aston CE, Short KR, Lyons TJ, & Chernausek SD, 2015 Cord blood adipokines, neonatal anthropometrics and postnatal growth in offspring of Hispanic and Native American women with diabetes mellitus. Reprod Biol Endocrinol, 13, 68. doi:10.1186/s12958-015-0061-9 [PubMed: 26111704]

Thomas C, Hypponen E, & Power C, 2008 Obesity and type 2 diabetes risk in midadult life: the role of childhood adversity. Pediatrics, 121(5), e1240–1249. doi:10.1542/peds.2007-2403 [PubMed: 18450866]

Thompson LP, & Al-Hasan Y, 2012 Impact of Oxidative Stress in Fetal Programming. Journal of Pregnancy, 2012, 8. doi:10.1155/2012/582748

Turner K, Reynolds-May MF, Zitek EM, Tisdale RL, Carlisle AB, & Westphal LM, 2013 Stress and Anxiety Scores in First and Repeat IVF Cycles: A Pilot Study. PLoS One, 8(5), e63743. doi:10.1371/journal.pone.0063743 [PubMed: 23717472]

Turner N, & Robker RL, 2015 Developmental programming of obesity and insulin resistance: does mitochondrial dysfunction in oocytes play a role? Mol Hum Reprod, 21(1), 23–30. doi:10.1093/molehr/gau042 [PubMed: 24923276]

Van Blerkom J, 2011 Mitochondrial function in the human oocyte and embryo and their role in developmental competence. Mitochondrion, 11(5), 797–813. doi:10.1016/j.mito.2010.09.012 [PubMed: 20933103]

van der Klaauw AA, & Farooqi IS, 2015 The hunger genes: pathways to obesity. Cell, 161(1), 119–132. doi:10.1016/j.cell.2015.03.008 [PubMed: 25815990]

Vega-Sanchez R, Barajas-Vega HA, Rozada G, Espejel-Nunez A, Beltran-Montoya J, & Vadillo-Ortega F, 2010 Association between adiposity and inflammatory markers in maternal and fetal blood in a group of Mexican pregnant women. Br J Nutr, 104(12), 1735–1739. doi:10.1017/s0007114510002825 [PubMed: 20650016]

Volpe GE, Ward H, Mwamburi M, Dinh D, Bhalchandra S, Wanke C, et al., 2014 Associations of Cocaine Use and HIV Infection With the Intestinal Microbiota, Microbial Translocation, and Inflammation. Journal of Studies on Alcohol and Drugs, 75(2), 347–357. [PubMed: 24650829]

Wadhwa PD, 2005 Psychoneuroendocrine processes in human pregnancy influence fetal development and health. Psychoneuroendocrinology, 30(8), 724–743. doi:10.1016/j.psyneuen.2005.02.004 [PubMed: 15919579]

Wadhwa PD, Entringer S, Buss C, & Lu MC, 2011 The contribution of maternal stress to preterm birth: issues and considerations. Clinics in perinatology, 38(3), 351–384. [PubMed: 21890014]

Wadhwa PD, Garite TJ, Porto M, Glynn L, Chicz-DeMet A, Dunkel-Schetter C, et al., 2004 Placental corticotropin-releasing hormone (CRH), spontaneous preterm birth, and fetal growth restriction: a prospective investigation. Am J Obstet Gynecol, 191(4), 1063–1069. [PubMed: 15507922]

Walsh D, McCartney G, Smith M, & Armour G, 2019 Relationship between childhood socioeconomic position and adverse childhood experiences (ACEs): a systematic review. Journal of Epidemiology and Community Health, 73(12), 1087. doi:10.1136/jech-2019-212738 [PubMed: 31563897]

Walsh JM, Byrne J, Mahony RM, Foley ME, & McAuliffe FM, 2014 Leptin, fetal growth and insulin resistance in non-diabetic pregnancies. Early Human Development, 90(6), 271–274. doi:10.1016/j.earlhumdev.2014.03.007 [PubMed: 24703297]

Walsh JM, McGowan CA, Mahony R, Foley ME, & McAuliffe FM, 2012 Low glycaemic index diet in pregnancy to prevent macrosomia (ROLO study): randomised control trial. Bmj, 345. doi:10.1136/bmj.e5605

Warwick ZS, & Schiffman SS, 1992 Role of dietary fat in calorie intake and weight gain. Neuroscience & Biobehavioral Reviews, 16(4), 585–596.

Wasser H, Bentley M, Borja J, Davis Goldman B, Thompson A, Slining M, et al., 2011 Infants perceived as “fussy” are more likely to receive complementary foods before 4 months. Pediatrics, 127(2), 229–237. doi:10.1542/peds.2010-0166 [PubMed: 21220398]

Whitaker RC, Wright JA, Pepe MS, Seidel KD, & Dietz WH, 1997 Predicting obesity in young adulthood from childhood and parental obesity. N Engl J Med, 337(13), 869–873. [PubMed: 9302300]

Willyard C, 2014 Heritability: The family roots of obesity. Nature, 508(7496), S58–60. doi:10.1038/508S58a [PubMed: 24740129]

Winzer C, Wagner O, Festa A, Schneider B, Roden M, Bancher-Todesca D, et al., 2004 Plasma adiponectin, insulin sensitivity, and subclinical inflammation in women with prior gestational diabetes mellitus. Diabetes Care, 27(7), 1721–1727. [PubMed: 15220253]

Wojcicki JM, 2011 Maternal prepregnancy body mass index and initiation and duration of breastfeeding: a review of the literature. J Womens Health (Larchmt), 20(3), 341–347. doi:10.1089/jwh.2010.2248 [PubMed: 21434834]

Wojcicki JM, & Heyman MB, 2010 Let's Move--childhood obesity prevention from pregnancy and infancy onward. N Engl J Med, 362(16), 1457–1459. doi:10.1056/NEJMp1001857 [PubMed: 20393165]

Wu LL, Russell DL, Wong SL, Chen M, Tsai TS, St John JC, et al., 2015 Mitochondrial dysfunction in oocytes of obese mothers: transmission to offspring and reversal by pharmacological endoplasmic reticulum stress inhibitors. Development, 142(4), 681–691. doi:10.1242/dev.114850 [PubMed: 25670793]

Xia LP, Shen L, Kou H, Zhang BJ, Zhang L, Wu Y, et al., 2014 Prenatal ethanol exposure enhances the susceptibility to metabolic syndrome in offspring rats by HPA axis-associated neuroendocrine metabolic programming. Toxicol Lett, 226(1), 98–105. doi:10.1016/j.toxlet.2014.01.023 [PubMed: 24472613]

Yan X, Zhu MJ, Xu W, Tong JF, Ford SP, Nathanielsz PW, et al., 2010 Up-regulation of Toll-like receptor 4/nuclear factor-kappaB signaling is associated with enhanced adipogenesis and insulin resistance in fetal skeletal muscle of obese sheep at late gestation. Endocrinology, 151(1), 380–387. doi:10.1210/en.2009-0849 [PubMed: 19887565]

Yeshurun S, & Hannan AJ, 2019 Transgenerational epigenetic influences of paternal environmental exposures on brain function and predisposition to psychiatric disorders. Mol Psychiatry, 24(4), 536–548. doi:10.1038/s41380-018-0039-z [PubMed: 29520039]

Zhu MJ, Han B, Tong J, Ma C, Kimzey JM, Underwood KR, et al., 2008 AMP-activated protein kinase signalling pathways are down regulated and skeletal muscle development impaired in fetuses of obese, over-nourished sheep. J Physiol, 586(10), 2651–2664. doi:10.1113/jphysiol.2007.149633 [PubMed: 18372306]

Zielinski DS, 2009 Child maltreatment and adult socioeconomic well-being. Child Abuse Negl, 33(10), 666–678. doi:10.1016/j.chiabu.2009.09.001 [PubMed: 19811826]

Highlights

- Propensity for childhood obesity may be programmed in utero via gestational biology
- Maternal preconception states/conditions can influence fetal programming pathways
- Childhood maltreatment (CM) exposure is estimated to affect up to 40% of adult women
- CM exposure adversely affects maternal behavior, physiology, psychology and biology
- Intergenerational transmission of CM sequelae may influence child obesity risk

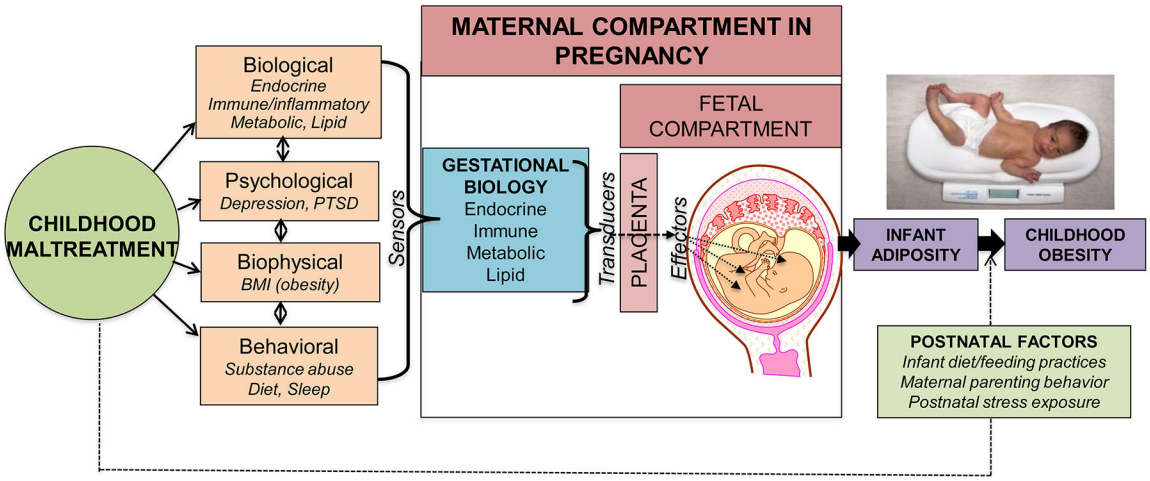

FIGURE 1:

Intergenerational transmission during gestation of the effects of maternal exposure to childhood maltreatment: a conceptual framework.