Maternal obesity as a risk factor for brain development and mental health in the offspring

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Abstract

Maternal obesity plays a key role in the health trajectory of the offspring. Although research on this topic has largely focused on the potential of this condition to increase the risk for obesity in the offspring, it is becoming more and more evident that it can also significantly impact cognitive function and mental health. The mechanisms underlying these effects are starting to be elucidated and point to the placenta as a critical organ that may mediate changes in the response to stress, immune function and oxidative stress. Long-term effects of maternal obesity may rely upon epigenetic changes in selected genes that are involved in metabolic and trophic regulations of the brain. More recent evidence also indicates the gut microbiota as a potential mediator of these effects. Overall, understanding cause-effect relationships can allow the development of preventive measures that could rely upon dietary changes in the mother and the offspring. Addressing diets appears more feasible than developing new pharmacological targets and has the potential to affect the multiple interconnected physiological pathways engaged by these complex regulations, allowing prevention of both metabolic and mental disorders.

Keywords maternal obesity; pregnancy; fetal programming; mood disorders; placenta; oxidative stress.

Abbreviations

11β-HSD: 11ß-hydroxysteroid dehydrogenase
AD: Alzheimer's disease
ADHD: attention deficit hyperactivity disorder
AHRR: aryl-hydrocarbon receptor repressor
ASD: autism spectrum disorder
BDNF: brain-derived neurotrophic factor
BMI: body mass index
CpG: 5'-cytosine-phosphate-guanine-3'
CVD: cardiovascular disease
DOHaD: developmental origin of health and disease
GDM: gestational diabetes mellitus
GC: glucocorticoid
GR: glucocorticoid receptors
GSH: glutathione
HPA: hypothalamic-pituitary-adrenal
HFD: high fat diet
KO: knock out
NAC: N-Acetyl-Cysteine
NAc: nucleus accumbens
OS: oxidative stress
PD: Parkinson's disease
PFC: prefrontal cortex
PBMC: peripheral blood mononuclear cells
PUFA: polyunsaturated fatty acid
RCT: randomized controlled trial
ROS: reactive oxygen species
T2D: type 2 diabetes
VTA: ventral tegmental area

Highlights

- Maternal obesity affects mental health in the offspring.
- Changes in redox signaling underlie both metabolic and cognitive effects of maternal obesity on the offspring.
- Dysbiosis and epigenetic changes could underlie the transgenerational transmission of the effects of maternal obesity.
- Quality of prenatal diet is a potentially modifiable target for reducing the risk of mental disorders in the offspring.

Introduction

Overweight and obesity are dramatically rising in low- and middle-income areas, particularly in urban settings (https://www.who.int/end-childhood-obesity/publications/echo-report/en/). The prevalence of obesity is increasing across all populations and age groups: although genetic factors may play a role in modulating vulnerability to weight gain and fat accumulation, they cannot explain the exponential increase in obesity we are currently witnessing (Congdon, 2019). Indeed, globalization and urbanization have gradually led to the so-called *nutrition transition* i.e. a reduction of physical activity associated to the increase in consumption of low-cost and easily accessible ultra-processed, energy-dense, nutrient-poor foods (https://www.who.int/end-childhood-obesity/publications/echo-report/en/). Such a spread of unhealthy lifestyles results in an energy unbalance that favors fat storage, eventually strengthening the ground for the settlement of an obesogenic environment (Townshend and Lake, 2017).

Maternal obesity affects 30% of pregnant women and excess weight gain occurs in 40% of gestations. The "Commission on Ending Childhood Obesity" (established by WHO) in its 2016 final report, has tackled the early life environment (including preconception and pregnancy) as a critical time for long-lasting and trans-generational effects of the metabolic derangement underlying obesity - and the associated comorbidities - as well as a window of opportunity to prevent them (https://www.who.int/end-childhood-obesity/publications/echo-report/en/). Although a great deal of research has focused on the mechanisms that can lead to offspring obesity, there is evidence for an effect of maternal obesity on cognition and mental health of the offspring (Buss et al., 2012;Casas et al., 2013;Hinkle et al., 2012;Hinkle et al., 2013;Rivera et al., 2015;Rodriguez, 2010). Indeed, exposure to maternal obesity or to an unhealthy maternal diet and metabolic diseases (diabetes and hypertension), can all increase the risk of for later-life cognitive disabilities and psychiatric disorders such as attention deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASDs), anxiety, depression, schizophrenia and eating disorders in the offspring (Buss, et al., 2012;Dinan and Cryan, 2017;Hinkle, et al., 2012;Hinkle, et al., 2013;Rivera, et al., 2015;Yatsunenko et al., 2012).

Obesity in pregnancy results in neuroendocrine, metabolic and immune/inflammatory changes which can affect fetal exposure to hormones and nutrients, disrupting the development of those neural pathways critical for the regulation of behavior and cognition. Inflammation during pregnancy may alter functional connectivity and may be associated with altered behavioral

regulation and reduced working memory performance in early childhood. Changes in microbiota composition as a result of maternal obesity may play a role in these effects. Indeed, the gut microbiota develops and stabilizes in early life phases (Yatsunenko, et al., 2012), which are crucial for the programming of tissues and organs, including the brain by e.g. modulation of the immune system (Dinan and Cryan, 2017;El Aidy et al., 2016) hormones, neurotransmitters and metabolites acting on brain physiology.

Postnatal nutrition (also targeting microbiota) may thus represent an important strategy for combating metabolic-associated cognitive impairment. In fact, the beneficial effects of diets, nutrients and foods (e.g. Mediterranean diets, omega-3) on mental health and cognitive performance are starting to be recognized (Bellisario et al., 2014;Bruce et al., 2002;Davari et al., 2013;Dimmitt et al., 2010;Dinan and Cryan, 2016;Kelly et al., 2016;Milior et al., 2016;Mrizak et al., 2014;Patterson et al., 2016;Sherwin et al., 2016).

This review will focus on the contribution played by maternal obesity in shaping the metabolic and behavioral phenotype of the offspring by affecting the developmental programming of the fetus. Main emphasis will be given to changes in oxidative stress (OS) pathways and epigenetic modifications as possible mechanisms mediating the effect of maternal obesity and early exposure to high caloric diets (eg. westernized diet rich in fats and sugars, high fat diet - HFD). The most recent evidence coming from epidemiological and preclinical studies will be reviewed taking also into account the role played by maternal obesity in early programming of the offspring gut microbiota. Finally, the potentiality of strategies aimed at preventing/counteracting the negative effects of prenatal obesity will be considered, including antioxidants and probiotics/prebiotic administration during pregnancy and to the offspring.

Developmental Origin of Health and Disease (DOHaD). Evolutionary and epidemiological perspectives

Mammalian development unfolds as a gradual process, which is continuously adjusted to the needs and challenges posed by the environment (in this review we will specifically focus on the intrauterine development) within the constraints of the genetic asset of the individual. From an evolutionary perspective, the elevated plasticity characterizing the developmental program is perfectly suited at generating a plethora of best adapted phenotypes that allow the perpetuation of the species with regard to the eco-ethological niches they will colonize (Bateson, 2001;Bateson et al., 2004). While such plasticity helps the individual to adjust to changes in the environment, it can also provide a substrate for increased vulnerability later in life, thus resulting in a double edge sward. The overall outcome of the developmental program will depend heavily upon the interplay among the genetic background of the organism, the intrauterine milieu and the stability of the extra-uterine (external) environmental conditions with respect to those that primed fetal developmental trajectories (Bateson, et al., 2004).

Early life experiences thus become embedded biological traces in an animal's physiology, resulting either in increased vulnerability or to greater resilience for the onset of disease states. The seminal studies of Barker and colleagues have contributed to provide evidence for a strong association between environmental challenges during pregnancy, altered fetal growth and health outcomes later in life (Barker et al., 1993;Seckl, 1998) giving rise to the concept of the DOHaD. In fact, the observation that those regions in England showing the highest infant mortality, with regard to low birth weight, were also characterized by the highest rates of mortality from cardiovascular disease (CVD) led to the hypothesis that those babies who survived were at greater risk of CVD later in life (Barker, et al., 1993;Barker and Osmond, 1986;Barker et al., 1989). Most intriguingly, the relationship between reduced birth weight and the onset of diseases at adult age (e.g. hypertension or type 2 diabetes - T2D) was unrelated to lifestyle risk factors (Cirulli F. et al., 1994;Harris and Seckl, 2011;Leon et al., 1996;Osmond et al., 1993). In addition, studies on twins provide scarce evidence for a main role of genes in these associations (Baird et al., 2001;Bateson, et al., 2004) thus indicating that vulnerability to adult diseases might rely upon fetal life experiences as a result of the redirection of the developmental trajectory.

Although for historical reasons Barker's theory was focused on the effects of prenatal undernutrition (see for instance the studies on the "Dutch famine" eg. (Roseboom, 2019) and

references therein), nowadays it is rather maternal obesity and its sequelae for metabolic and mental health that poses serious public health concerns (Congdon, 2019;Jehn and Brewis, 2009). Indeed, recent studies clearly suggest that maternal obesity, both before becoming pregnant and throughout gestation, is associated with negative short- and long-term health outcomes. Among all, a general developmental delay in children and poorer physical and mental abilities during aging are most often observed (see for instance the studies carried out on the Helsinki Birth Cohort (Berry et al., 2018;Eriksson et al., 2014;LifeCycle Project-Maternal et al., 2019;Mina et al., 2017;Westberg et al., 2016)) with OS playing a key role as a mediator of both short and long-term effects (Berry, et al., 2018;Edlow, 2017). Higher maternal body mass index (BMI) has also being associated with shorter telomeres length as assessed in leukocytes in elderly women (Guzzardi et al., 2016) moreover, umbilical cord gene expression profiling has identified patterns consistent with neurodegeneration/premature brain aging in fetuses of obese compared with lean women (Edlow et al., 2016b) suggesting long-term sequelae of early metabolic stress. To this regard, Alzheimer's disease (AD), a neurodegenerative disease affecting old age, has been recently defined as 'Type-3-Diabetes' because of some common molecular and cellular mechanisms with type 1 diabetes and T2D and insulin resistance associated with memory impairment and cognitive decline in old subjects (Kandimalla et al., 2017) suggesting that an early obesogenic environment might set the stage for a shared vulnerability to both metabolic and mental health issues.

The obesogenic womb and its sequelae

While for the mother the negative effects of obesity are readily observed as they affect fertility (ability to become pregnant) and may lead to obstetric complications, the effects on the offspring may not be immediately evident at birth although they have the potential to have both short- and long-term consequences (Alfaradhi and Ozanne, 2011;Contu and Hawkes, 2017;Iozzo et al., 2014;Moussa et al., 2016;Tenenbaum-Gavish and Hod, 2013).

Most importantly, in addition to the effects on metabolic programming, long-term longitudinal and associative studies provide evidence for a direct association between prenatal metabolic stress and an increased risk to develop neuropsychiatric, mood disorders and cognitive disabilities (see (Howell and Powell, 2017) and references therein). It should be mentioned that being obese during childhood may, by itself, trigger the onset of behavioral and emotional issues leading in turn to stigmatization and poor socialization, all conditions that may reduce

educational attainment and trigger the onset or precipitation of psychiatric disorders (Miller et al., 2015;Pizzi and Vroman, 2013). However, there is now evidence that, independently from offspring obesity, maternal obesity is associated with neurobehavioral problems in the offspring, although proving cause-effect mechanisms is rather hard in humans, given the many confounds deriving from the many intervening (genetic and environmental) variables involved in these effects. Nonetheless, there are now quite a number of epidemiological studies indicating that compared to children born from mothers having normal weight, children of obese mothers have a greater chance to show behavioral problems or being diagnosed with a neurodevelopmental disorder, such as ADHD (Godfrey et al., 2017). Regarding cognitive deficits, studies on the UK Millennium cohort have provided evidence for a negative relationship between maternal BMI and children's general cognitive ability at 7 years (Basatemur et al., 2013). A large synthesis and meta-analyses of the literature has more recently evaluated the association between pre-pregnancy overweight or obesity (in relation to normal weight) and subsequent childhood neurodevelopmental outcomes (Sanchez et al., 2018). This meta-analysis supports previous preclinical and observational studies indicating that children born from mothers obese prior to and during pregnancy are at increased risk for neurodevelopmental disorders.

Notwithstanding the above-mentioned evidence, it is rather difficult to establish whether maternal obesity affects neurobehavioral development in the offspring directly. In addition, maternal intelligence quotient, socio-economic status, breastfeeding vs. formula, maternal mental health, maternal diet and other postnatal lifestyle influences may concur to effects of maternal obesity (Contu and Hawkes, 2017;Godfrey, et al., 2017;Soubry et al., 2013). These questions can be more easily asked using animal models which allow to distinguish the confounding variables present in human studies, which are mostly observational in nature. In animal models, maternal obesity is mainly modelled by feeding dams before and/or during gestation with high fat-diets (HFD). Overall results from these studies enlarge and strengthen clinical and epidemiological evidence, indicating that offspring of obese mothers are characterized by social impairments, anxiety and depressive-like symptoms, in addition to cognitive disability and hyperactivity (Sullivan et al., 2015). One main important question that has being asked through preclinical models is whether pre-pregnancy obesity and maternal obesity exert the same effects on the offspring. This is an important point that can redirect prevention policies: it is much easier to address weight gain problems during pregnancy than act upon an obesity condition that might be acquired much before gestation. A recent

preclinical study appears to support epidemiological evidence indicating that prenatal and pregnancy windows have independent programming effects on the offspring. Preconception exposure affects body composition and adiposity while gestation exposure affects metabolism and tissue immune cell phenotypes (Chang et al., 2019). Overall, the current evidence suggests that pre-pregnancy obesity, rather than weight gain during gestation, may be most harmful to the fetus.

The field is very complex as also shown by inconclusive evidence provided by a very recent meta-analysis addressing results coming from animal models (Menting et al., 2019). Indeed, while clear effects of maternal obesity were observed on locomotor activity and anxiety, both increased by the metabolic maternal challenge, no significant effect was revealed by the meta-analysis on learning and memory performance in the offspring (Menting, et al., 2019). Although animal models may have some limitations, they have also been fundamental for understanding that the effects of an obesogenic environment experienced during fetal life depend upon multiple and not-exclusive pathways, which may lead to long-term pathological outcomes.

Mechanisms underlying fetal programming by maternal obesity

In complex organisms there is a finely-tuned crosstalk between physiological and behavioral responses, ultimately leading to the avoidance or to the adaptation to challenges. While acute responses to short-term stressors are pivotal to restore homeostasis, the management of a chronic stress condition imposes a non-negligible burden to the organisms ("allostatic load") that might affect growth, metabolism, reproduction, inflammatory/immune and neuroendocrine function (de Kloet et al., 2005;Maccari and Morley-Fletcher, 2007;McEwen, 1998;Seckl, 2004).

Pregnancy is a highly demanding task involving physiological adaptations leading to a shift in the homeostatic balance (Mannaerts et al., 2018). Such changes, which would result in a pathological state in non-pregnant women, are (usually) well tolerated in healthy (pregnant) subjects. Although obesity *per se* cannot be considered a pathological condition, it represents a major risk factor for the onset and/or precipitation of many metabolic and cardiovascular non-communicable disease in addition to mood disorders (Armani et al., 2017;Chaput et al., 2012;Wurtman and Wurtman, 2018). Thus, being pregnant and obese at the same time may turn out to be an extremely stressful condition leading to a maternal allostatic load that will be

affecting the fetus. This will engage multiple, not mutually exclusive, mechanisms (during sensitive developmental phases), affecting tissue organization and organs' physiology in the offspring (Harris and Seckl, 2011;Iozzo, et al., 2014). Among these mechanisms, hyperactivity of the HPA axis and the associated excessive glucocorticoids (GCs) secretion, OS and inflammation, as well as gut microbiota dysbiosis, (just to mention a few) may all contribute to mediate the effects of maternal obesity, ultimately leading to vulnerability to neurodevelopmental and psychiatric morbidity in the offspring which could be embedded, through epigenetic changes, in selected genes.

Maternal metabolic stress shaping brain development

There is abundant preclinical and clinical evidence to indicate that adverse socio-economic conditions, in addition to physical, emotional or sexual abuse, are well-established risk factors for mood disorders (Ehlert, 2013;McEwen, 2000;McLaughlin et al., 2015;Raikkonen and Pesonen, 2009;Roseboom, 2019;Roth and Sullivan, 2005). As the studies of Barker and colleagues (Barker, et al., 1993;Seckl, 1998) previously detailed in this review, have listed body weight at birth within the set of risk factors that can increase susceptibility for adult diseases, maternal obesity needs to be listed as another yet adverse condition capable to affect offspring's development. Although, counterintuitively, obesity may involve a form of malnourishment, as it entails "poor nutrition". Indeed, one has to consider that, even when food is relatively prevalent, it may lack vitamins, minerals or other fundamental nutrients.

In order to understand the mechanisms underlying the detrimental effects of maternal obesity on brain developmental trajectories, we need to consider that this condition is likely to rely upon the same mechanisms regulating responses to stress (Cirulli F., 2017;McEwen, 2000). Acute activation of this pathway represents a "positive stress response", allowing the organism to face an acute threat. Under circumstances of chronic or overwhelming adversity - and in the absence of social support – responses to stress may become maladaptive for the individual and lead to pathological states because of an inability to face the current threats (or "allostatic load") (McEwen et al., 2015). The signaling pathways involved in the elaboration of stressful and metabolic signals, which are deranged during early development, might then be significantly modified in their functioning when a "second hit" occurs during critical periods, such as adolescence, or at adulthood (Bock et al., 2014;Boersma et al., 2014;Cirulli F., Berry A, Alleva E., 2003a;Daskalakis et al., 2013;Ehlert, 2013;Entringer et al., 2015;Provencal and Binder, 2015). Thus, the effects of metabolic or psychological stressors experienced at later stages will

be more disruptive in those individuals who have been exposed to stressors early during development.

Comorbidity between metabolic and behavioral disorders suggests shared developmental pathways and common mediators. Our group, together with many others, have clearly identified neurotrophins, such as BDNF, and GCs as main effectors of brain plasticity and metabolic regulations in response to stressful events (Cirulli F., Berry A, Alleva E., 2003a;Cirulli F. and Alleva, 2009;Cirulli F. et al., 2003;Levine, 1957;McEwen, 2000;Meaney et al., 1989).

There is a plethora of data from clinical and preclinical studies suggesting that the type and quantity of micronutrients, high levels of leptin and insulin as well as elevations in inflammatory mediators, such as interleukins and tumor necrosis factor can play a fundamental role in affecting developmental trajectories of the fetus by crossing the placental barrier (Godfrey, et al., 2017). Central to the maternal-fetal regulation is indeed the placenta (Fig. 1). This temporary organ, the main mother-fetus interface, is able to convey stress signals to the fetus by modulating the entry of hormones, glucose, amino acids, vitamins and ions necessary for fetal growth and development (Bale et al., 2010;Cirulli F., 2017;Fowden et al., 2009). Since elevated levels of GCs can be detrimental for the fetus, a specific enzyme, the 11ß-hydroxysteroid dehydrogenase type 2 (11β-HSD-2), acts as a shield, guaranteeing their rapid inactivation and allowing an optimal amount of these hormones to be transferred to the fetus for organs maturation. It is rather interesting that psychological stressors and metabolic/nutritional challenges can both affect the expression or the activity of the 11β-HSD-2 enzyme, with high levels of GCs reaching the fetus, resulting in increased susceptibility for psychiatric disorders and metabolic complications linked to an increased risk of insulin resistance and T2D, in addition to CVD and metabolic disorders associated with obesity (Eriksson, et al., 2014;Mansur et al., 2015;Mina et al., 2015;Rivera, et al., 2015;Stout et al., 2015).

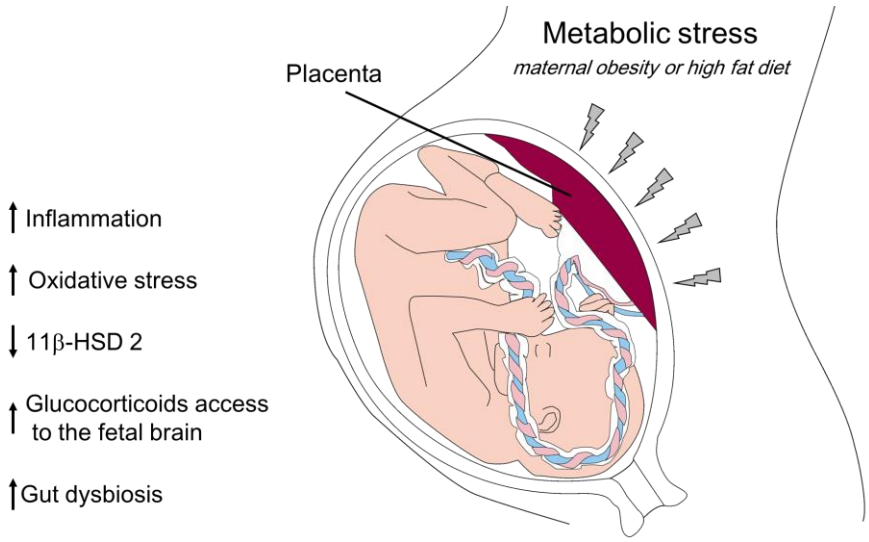

Fig. 1. Potential mechanisms underlying the effects of maternal obesity on fetal development. The placenta is the critical mother-fetus interface transducing metabolic stress into changes in the developing organism underlying the short- and long-term effects of maternal obesity (see text for a detailed description).

In recent studies we have clearly shown that HFD feeding during pregnancy (in mouse models), independently from maternal obesity, is a stressful challenge that is able to influence negatively the fetus, which is already exposed to excess GC as a result of maternal pregnancy status (Bellisario, et al., 2014;Bellisario et al., 2015;Eriksson, et al., 2014). HFD-feeding in female mice before conception and during pregnancy, in fact, increases levels of maternal stress hormones and is associated with both reduced 11β-HSD-2 enzymatic activity and expression of the 11β-HSD-1 gene in the placenta (Bellisario, et al., 2015). Exposure to a diet with high fat content has also been shown to disrupt maternal behavior at parturition with deleterious consequences on the offspring (Bellisario, et al., 2015). These dysregulations, observed in HFD-fed dams, might be caused by changes in neural activity in brain regions responsible for olfactory processing and social recognition, ultimately leading to inappropriate maternal behavior (Bellisario, et al., 2015). These effects are less apparent in animal models of reduced OS, especially in female subjects, suggesting that diet-induced metabolic dysfunction, neuroendocrine response and sex/gender all play a role in these regulations (see later in this review) (Bellisario, et al., 2014).

Worth noticing, these data also confirm clinical evidence showing that the presence of high levels of GC during gestation can affect the expression of GC-sensitive genes in the central nervous system, as well as in the periphery, with important effects on HPA axis function and

regulation (Mina, et al., 2017;Mina, et al., 2015). These effects are reminiscent of a solid literature in animal models indicating that prenatal maternal stress affects HPA axis activity and stress regulation through changes in GC receptors in limbic regions of the brain (Brunton and Russell, 2010;McGowan et al., 2008;Welberg and Seckl, 2001). We can thus hypothesize that, by affecting the amount of GC reaching the fetus, HFD during pregnancy could lead to similar short- and long-term effects already described for prenatal stress.

A further intriguing aspect is related to the modulating effect of the HPA axis on immune function and inflammation. The group of Sasaki (Sasaki et al., 2014) investigated the expression of several inflammatory genes linked to GC signaling (Sorrells et al., 2009) as a result of perinatal exposure to HFD (Bilbo and Tsang, 2010). Results suggest a dysregulation of pro- and anti-inflammatory genes linked to HFD exposure in utero with NF-kB and IL-6 transcripts being increased in the hippocampus in HFD-exposed offspring. Moreover, increased expression of the cytokine IL-6 in the hypothalamus (De Souza et al., 2005) and cortex (White et al., 2009) is an established consequence of prolonged HFD exposure in utero.

Chronic systemic inflammation characterizes both maternal obesity and pregnancy. Obese pregnant women have higher levels of circulating pro-inflammatory cytokines while maternal BMI is directly correlated with (maternal) pro-inflammatory cytokine concentrations and the activation of pro-inflammatory placental pathways. Changes in fetal cytokine expression, fetal neuronal damage and changes in gene expression in the neonatal brain have been previously related to placental and intrauterine inflammation (Edlow, 2017). Inflammation during pregnancy might alter the connectivity of brain networks and be associated with altered neurobehavioral regulations and reduced memory performance in early childhood. Indeed, it has been recently reported that maternal IL-6 during pregnancy correlates with newborn brain connectivity and can predict future working memory in offspring (Rudolph et al., 2018). Thus, changes in inflammatory mediators could be important biomarkers to be used to estimate long-term effects of maternal obesity on brain function.

Role of the microbiota

Long-lasting effects on fetus and newborn resulting from exposure to maternal obesity during pregnancy could also be explained by an alteration in the composition of the gut microbiota during critical developmental windows (Cryan, 2016). Each individual owns a unique gut microbiota profile composed by different strains of bacteria. Changes in this balance may lead

to a condition of dysbiosis (Rinninella et al., 2019). Recent studies associate dysbiosis with different gastrointestinal and metabolic diseases such as diabetes and obesity but also with neurodegenerative and mental disorders, including AD and Parkinson's disease (PD), ASDs, schizophrenia and depression (Heiss and Olofsson, 2019). This suggests that the balance of the gut microbial composition may play a key role in the regulation of different developmental processes (De Palma et al., 2015;Dinan and Cryan, 2016;El Aidy, et al., 2016;Foster et al., 2016;Kelly, et al., 2016;Luczynski et al., 2016).

The early life phases are crucial for the development of the microbiota and to define its ultimate role in the programming of tissues and organs (Dimmitt, et al., 2010). A number of studies show that the gut microbiota influences brain function (Dinan and Cryan, 2016;El Aidy, et al., 2016;Foster, et al., 2016). Notwithstanding the fact that the infant gut microbiota has been worldwide considered to be determined after birth, recent evidences have shown how the whole intrauterine environment (placenta, amniotic fluid, meconium and umbilical cord blood) is actually colonized by specific bacterial species (Collado et al., 2016). These data robustly suggest the transmission of microorganisms from the mother to the fetus ahead of birth and this plays a pivotal role in the determination of the offspring microbiota (Aagaard et al., 2014;Collado, et al., 2016;Koleva et al., 2015;Satokari et al., 2009). Transfer of microbes and microbiome metabolites between mother and infant can also occur during delivery and lactation and can be affected by maternal health and metabolism, in addition to mode of delivery and use of antibiotics (Soderborg et al., 2016). Hence, dysbiosis and obesity during pregnancy can dramatically affect microbiota composition of the mother as well as microbial transmission and, in turn, microbial transmission to the fetus (Basu et al., 2011), maternal diet having one of the largest known impacts on these regulations.

The maternal gut microbiota differs in maternal obesity, particularly in the latter half of pregnancy, with overweight women being characterized by an increase in the Firmicutes phylum (Staphylococcus) as well as increases in some Proteobacteria (Soderborg, et al., 2016). Elevated levels of microbe-derived plasma endotoxin appear to be one potential mechanism by which maternal microbes in obesity could affect the developing fetus; this might increase translocation of bacteria-derived products across the intestinal mucosa, contributing to systemic and placental inflammation and insulin resistance (Basu, et al., 2011).

Adverse effects of maternal obesity or excess gestational weight gain have in fact been linked to inflammation in the placenta. Although the specific mechanisms through which the bacterial transmission is carried out are not currently well known, a new concept which is developing is

that the placenta microbiota may be the intermediary of the microbial passage from the mother to the baby and may affect fetal development (Pelzer et al., 2017). An important subject for future studies is the role of placenta microbiota and its interaction with other maternally-derived variables, including life style, diet, BMI and pregnancy complications, which could all alter placental microbiota (Pelzer, et al., 2017).

Role of Oxidative Stress

OS characterizes biological systems in aerobic conditions; it results from an unbalance between pro-oxidant and anti-oxidant molecules, with oxidants overriding the defense system of the organism. During normal healthy pregnancy, OS and its mediators - reactive oxygen species (ROS) - are increased within certain boundaries as the result of a physiological mild inflammatory state, to stimulate cell proliferation and proper fetal development (Dennery, 2007;Mannaerts, et al., 2018). However, if OS overrides safety levels, complications might arise both for the mother and the offspring (Edlow, 2017;Hracsko et al., 2008;Mannaerts, et al., 2018). OS is increased in many different pathological conditions including obesity, T2D, and metabolic syndrome and can be triggered by chronic consumption of HFD. There is clear evidence for disrupted oxidative signaling in psychiatric disorders. Alterations in multiple biomarkers of OS have been observed in ADHD, bipolar disorder, ASD, depression, and schizophrenia (Hovatta et al., 2010). Markers of oxidative damage to neurons have also been observed in post-mortem samples in several psychiatric diseases. It is of interest that mitochondrial disorders with a clear genetic origin are also associated with an elevated incidence of psychiatric disorders, especially mood disorders and psychosis. Increased ROS generation might lead to random damage to proteins, lipids and DNA and excessive OS during pregnancy might result in pathological conditions of the placenta, the embryo, and the fetus, also leading to epigenetic changes and altered gene expression in the fetus due to DNA damage (Del Rio et al., 2005;Mannaerts, et al., 2018). The placenta is a main source of OS and this organ, in obese women, is characterized by greater levels of OS markers when compared to that of lean women (Saben et al., 2014). Edlow and colleagues found an upregulation of genes related to OS response as a result a global gene expression profiling carried out in the amniotic fluid from obese women (Edlow et al., 2014). Intriguingly, among these, Apolipoprotein D, a protein that is highly expressed in the brain and is upregulated in psychiatric conditions and neurological disorders (Muffat and Walker, 2010;Sutcliffe and Thomas, 2002), was found to

be increased by nine-fold in fetuses of obese compared with lean women (Edlow, 2017;Edlow, et al., 2014).

A growing body of evidence suggest that OS may play a role in the etiology of mood disorders (Hovatta, et al., 2010). A number of studies indicate that exposure to chronic stress may perturb the overall body energy balance acting not only on the neuroendocrine system but also on mitochondrial remodeling, affecting OS balance in the body and in the brain (Picard and McEwen, 2014;Picard and McEwen, 2018;Picard et al., 2018). Recent work suggests that isoprostanes (biomarkers of lipid peroxidation) are selectively upregulated in adolescents who have experienced early childhood adversities, suggesting that dysregulation of stress-sensitive systems during early life stages can have persisting, and potentially deleterious, impact on brain structure-function development acting through OS-linked mechanisms (Horn et al., 2019). The mammalian brain is very sensitive to OS insults being characterized by high metabolic rate, poor antioxidant defenses and reduced capacity for cellular regeneration (Floyd and Carney, 1992). Thus, a prenatal insult such as an obesogenic womb, characterized by elevated levels of inflammation and OS, has the potential to affect dramatically the neurodevelopmental programming of the fetus, setting the stage for later life vulnerability to psychiatric disorders.

Preclinical data enlarge and corroborate this body of evidence and the p66Shc-/- mouse model - that our group has thoroughly characterized - provides a striking example of how prenatal HFD feeding might impinge upon OS pathways to affect fetal programming and healthspan (Berry et al., 2012;Berry et al., 2007;Berry et al., 2010;Berry and Cirulli, 2013;Berry et al., 2008). p66Shc is a mammalian gene that regulates apoptosis by increasing intracellular OS and affects lipid metabolism by promoting fat storage (Berniakovich et al., 2008;Trinei et al., 2009). p66Shc is a protein acting specifically in the mitochondrion as a redox enzyme that generates H_2O_2 and whose function is in a cause-effect relationship with that of insulin/IGF1(Berniakovich, et al., 2008). Genetically modified mice lacking the p66Shc gene (p66Shc-/-, knock out mice - KO) are resistant to OS insults and to HFD-induced obesity, resulting overall in a healthier and long-lived phenotype, showing greater brain and behavioral plasticity associated to increased central levels of the neurotrophin BDNF (Berry, et al., 2012;Berry, et al., 2007;Berry, et al., 2010;Berry and Cirulli, 2013;Berry, et al., 2008). Prenatal exposure to HFD in these KO mice leads to a gender-specific resilience to both stressful and metabolic challenges (Bellisario, et al., 2014). Administration of a HFD during peri-conceptional time and throughout pregnancy resulted, in fact, in reduced body weight at birth

and into a greater catch-up, particularly in males, while female offspring showed increased BMI as well as higher leptin levels. By contrast, p66Shc-/- subjects were overall protected (Bellisario, et al., 2014), p66Shc-/- females being characterized by an improved ability to cope with both metabolic and neuroendocrine stressors and showing enhanced glucose tolerance and insulin resistance. Moreover, while prenatal HFD led to a hyperactive HPA axis in wild type offspring, this was not observed in p66Shc-/- mice (particularly in females) overall suggesting that sex-hormones might play an important part in the directing the effects of a metabolically stressful maternal challenge during fetal development (Bellisario, et al., 2014). Data on gender differences have been further extended by Edlow and colleagues (Edlow et al., 2016) who found that maternal obesity results specifically associated with sex-specific differences in fetal size and fetal brain gene expression signatures, males being the most vulnerable sex. In these studies, ROS metabolism was found to be affected by HFD (Edlow, et al., 2016) further strengthening the important role played by OS mediators in maternal obesity.

Translating these preclinical findings to humans, investigating a group of women enrolled from the Helsinki Birth Cohort, we found a long-term increase in p66Shc mRNA in peripheral blood mononuclear cells (PBMC) of old frail subjects born from obese mothers (Berry, et al., 2018). Moreover, when these women were stratified according to their BMI, PBMC p66Shc expression levels were reduced in subjects with a BMI $\geq$ 30.4 kg/m2 following physical exercise. This piece of data is particularly interesting for a number of reasons. First of all, it confirms a role for oxidative stress in human subjects in the signaling pathway linking maternal obesity to the health outcome in the offspring. Secondly it suggests that maternal obesity may play a role in the long-term programming of the mitochondrial function and metabolism (also through changes in the p66Shc expression) affecting the aging process. Moreover, it indicates that metabolic-challenging stimuli, such as physical exercise, may affect the expression of p66Shc, particularly in obese subjects, pointing to this molecule as a potential new target for therapeutic intervention studies (Berry, et al., 2018;Berry and Cirulli, 2013).

Long-lasting effects of maternal obesity - epigenetic signatures

Epigenetic modifications have been proposed as a key causal mechanism linking maternal adiposity and offspring outcome. Long-term effects of early nutritional experiences are potentially mediated by post-translational modifications of DNA, post-translational modification of histones and non-coding RNAs. One of the most interesting consequences of

these mechanisms is that they can account for transgenerational transmission of traits (Bock, et al., 2014;Daskalakis, et al., 2013;Provencal and Binder, 2015;Szyf, 2012;Szyf et al., 2005;Turecki et al., 2014).

To date, very little work has been performed to determine epigenetic changes in the brains of human offspring born to obese mothers. DNA methylation changes have been reported in cord blood and microRNA levels in amniotic fluid in human studies of maternal obesity, indicating a potential role for these epigenetic mechanisms in the long-term effects of maternal obesity on the offspring (Godfrey, et al., 2017). Cohort studies analyzing BMI extremes in these data sets found associations between maternal BMI and offspring DNA methylation at birth and at 3 years. However, more work is needed to study these regulations.

In candidate gene approach studies, one of the most important findings concerns the observation that aryl-hydrocarbon receptor repressor (AHRR) DNA methylation is 2.1% higher in offspring of obese vs. normal weight mothers; as robust links have been found between maternal smoking and offspring AHRR methylation (Reynolds et al., 2015), these observations suggest that methylation of these gene may be involved in the link between multiple adverse conditions, including maternal obesity, on offspring outcomes.

Among the classical epigenetic mechanisms, DNA methylation is an attractive target for investigation because levels of folic acid, a co-factor in the production of the methyl donor methionine, are decreased in the amniotic fluid of obese pregnant women (Contu and Hawkes, 2017;Mohd-Shukri et al., 2015). In clinical studies, maternal depressive symptoms during pregnancy have been found to correlate with increased DNA methylation of the GR (NR3C1) in male infants and to result in decreased BDNF IV DNA methylation in both sexes at 2 months of age (Braithwaite et al., 2015). BDNF plays also a critical role in the integration and optimization of behavioral and metabolic responses: by acting in the brain and periphery, it increases insulin sensitivity and parasympathetic tone (Cirulli F. and Alleva, 2009). Low levels of circulating BDNF characterize individuals with obesity and T2D, which implies a main role for this neurotrophin in obesity and metabolism (Mou et al., 2015). While methylation of the NRC31 has been related to prenatal early adversity in numerous studies (van der Knaap et al., 2015), these results indicate that genes involved both in stress responsivity and in feeding behavior are epigenetically regulated, supporting the notion of joint programming of these stress-activated pathways and allowing for more detailed studies of the mechanisms underlying comorbidity of mental and metabolic disorders (Rivera, et al., 2015).

Preclinical studies performed in animal models (Vucetic et al., 2010) have indicated decreased DNA methylation in the promoter regions of the mu-opioid receptor genes as well as globally in brain regions associated with reward such as the ventral tegmental area (VTA), PFC, and nucleus accumbens (NAc) of offspring born to obese mothers (Carlin et al., 2013). Supplementation of maternal HFD with methyl donors during gestation and lactation was able to restore some of these effects (Carlin, et al., 2013). Prenatal methyl supplementation has also been shown to reverse deficits in motivated behavior in offspring exposed to a HFD indicating that early life is a sensitive time during which dietary methyl donor supplementation can alter PFC-dependent cognitive behaviors (McKee et al., 2017). Differential expression of 37 microRNAs, rather than changes in DNA methylation (Edlow, 2017) have been reported in the brains of embryonic mice born to mothers fed a HFD vs. control diet.

Preventive strategies

As mentioned above, maternal obesity affects multiple interconnected physiological pathways engaged by complex regulations. Thus, addressing diets and dietary (particularly antioxidants) supplementation might provide a "broad-spectrum" promising a feasible strategy to prevent/counteract the disruptive effects of the obesogenic womb, especially considering the difficulty in the development of new target-specific pharmacological interventions. In this paragraph we will specifically focus on some of the most promising dietary intervention that include also oral supplementation with the antioxidant N-Acetyl-Cysteine (NAC).

NAC is the rate-limiting substrate in the biosynthesis of glutathione (GSH). It is a ROS scavenger and its clinical efficacy as well as safety have been recently documented in many pathological conditions (see Mokhtari et al., 2017 and references therein for a complete review). NAC is currently one of the most promising targets for neuropsychiatric disorders. Its most interesting feature is that its efficacy appears cross-diagnostic (acting on neurotransmitter systems such as glutamate, antioxidants as well as inflammatory pathways (Berk et al., 2013)), while being relatively safe. Determining precisely how antioxidants - in particular NAC -work is crucial both to understand the basic biology of mental disorders and in order to devise adjunctive therapies that can work on these pathways. Indeed, the apparent universality of NAC action is intriguing and implies that it may target downstream pathways underlying co-morbidity between stress and metabolic responses. Although there is only preliminary data of the efficacy of NAC in many of psychiatric disorders, the field is expanding with many

additional trials that could be of interest also in the field of maternal obesity pathways (Berk, et al., 2013).

So far, some preclinical studies have focused on the effects of this molecule in the context of maternal obesity. NAC administration during pregnancy in mice might counteract apoptosis and ROS-related genotoxicity by increasing glutathione levels and decreasing mitochondrial membrane depolarization (Amin et al., 2008). Indeed, mice lacking the rate-limiting enzyme for GSH synthesis show a range of behavioral disorders and treatment with NAC reverses some of these deficits, restoring GSH levels (Berk, et al., 2013). NAC may also contribute to maintain oxidative balance through the action of the cysteine/cystine cycle (Elshorbagy et al., 2012). We have recently observed that the administration of NAC in animal models throughout pregnancy is able to buffer the effects of HFD on both the mother and the offspring. In our studies, offspring of mice supplemented with NAC during fetal life showed improved glucose tolerance, in addition to a reduced activation of the HPA axis, when exposed to stress (Berry et al., 2018). Worth noticing, results obtained through in vivo NAC supplementation parallel the protective effects observed in the p66Shc-/- mice (a mouse model of reduced oxidative stress; see above) strengthening the link among metabolic stress experienced during fetal life, fetal programming and OS/mitochondrial pathways (Berry, et al., 2018;Berry, et al., 2007;Berry and Cirulli, 2013;Giorgio et al., 2012;Hovatta, et al., 2010).

In addition to NAC, plant-based-antioxidant-rich diets could protect against free radical production and oxidative damage, potentially preventing obesity and comorbidities. As an example, luteolin supplementation of obese, HFD-fed adult mice has been found to be associated with better cardiometabolic features and reduced inflammatory and oxidative stress markers (Gentile et al., 2018). Research on these diets could extend to the prenatal period in the future.

Poor prenatal diets have been often associated with poorer maternal and offspring mental health outcomes. Thus, the quality of maternal diet represents a potentially important and modifiable target for reducing the risk of mental disorders both in mothers and in the offspring (Lindsay et al., 2017). To this regard, longitudinal studies in clinical populations are warranted in order to provide further insights for the development and design of future and more effective intervention trials for improved maternal and child health outcomes (Lindsay, et al., 2017). So far, observational data in humans has pointed to polyunsaturated fatty acids (PUFAs), including omega-3 and omega-6 fatty acids, as possible candidate therapeutics in maternal obesity. In

particular, in human pregnancy studies data suggest that omega-3 PUFA may play a critical role not only on fetal neurodevelopment, but also for supporting positive maternal mood, decreasing stress, anxiety and depression in the pre- and postnatal periods (Lindsay, et al., 2017). Maternal omega-3 fatty acid deficiency has been associated with increased risk of offspring ASD and ADHD. Human pilot studies relying on the supplementation of obese pregnant women with omega-3 fatty acids demonstrated a reduction in maternal and placental inflammation (see (Lindsay, et al., 2017) for a review).

In preclinical studies it has been shown that prenatal exposure to dietary omega-3 fatty acids is able to stage key relationships between metabolic signals and BDNF methylation, creating an epigenetic memory and a reservoir of neuroplasticity that can protect the brain against later insults (Tyagi et al., 2015). In animal models, early life methyl donor supplementation has been used as a strategy to alter one carbon metabolism and DNA methylation in a sex-dependent manner (McKee, et al., 2017). In particular, supplementation of methyl donors in HFD fed dams has been able to attenuate weight gain and decrease fat preference (males) as well as to change gene expression and global hypomethylation in the brain of the offspring (McKee, et al., 2017). A methyl-balanced diet can also prevent the effects of prenatal stress on binge eating behavior (Schroeder et al., 2017). In addition, early micronutrient supplementation can protect from early life stress-induced cognitive impairments, thus reinforcing the notion of common pathways that are engaged by early nutrition and early life stress (Naninck et al., 2017).

We have previously argued that the negative effects of maternal obesity on mental disorders in the offspring may be mediated, at least in part, by gut dysbiosis. Changes in the microbiome and its metabolites offer the opportunity for non-invasive risk-screening and risk-reduction by tailored dietary formulations and diets, since earliest stages of life. Changing the composition of the gut microbiota through the use of probiotics and prebiotics could become a new strategy for reducing the risk of metabolic disorders in both the mother and offspring. In order to do this, it is necessary to identify clinically relevant markers and build early predictive models, which might help tailoring appropriate dietary interventions. Dietary interventions aimed at modifying gut microbiota development and composition in the first phases of life may promote cognitive and emotional development. The use of pre- and probiotics has been shown to rapidly modify the microbial community and reduce (at least temporarily) adiposity and chronic inflammation in animal models of obesity and in limited human studies. As far as clinical studies are concerned, there have only been a handful of randomized clinical trials (RCTs) that

examined the effects of probiotics administered during pregnancy with the aim of improving insulin sensitivity and reducing GDM diagnosis, with limited success. In one RCT either Bifidobacterium lactis alone or B. lactis plus Lactobacillus rhamnoses GG probiotic was administered to pregnant women 14 days before a scheduled Caesarean delivery (Baldassarre et al. 2018). Modulation of the gut microbiota by prebiotics, probiotics or by fecal microbiota transplantation has been used in the management of certain neurological disorders, including autism and depression, as well as their associated gastrointestinal symptoms, and increasing numbers of clinical trials suggest the beneficial effects of such treatments. Fermentable fiber influences gut microbiota composition and the production of short chain fatty acids; these, in turn, have been demonstrated to affect mood in animal models, as well as influence neurotransmitters such as serotonin although additional studies are needed to determine the role of different microbes in the physiology of the host and pathogenesis, as well as how the gut microbiota can be modulated for beneficial effects. Most of the interventions used mainly concern the prenatal phases, but they could be extended postnatally. It is rather difficult to discern the effects of prenatal maternal obesity to maternal obesity during lactation. Based upon an animal model, as an example, we were able to show that lactating mice fed a high fat diet during pregnancy (and not lactation) still showed inappropriate maternal behavior after parturition (Bellisario, et al., 2015). There is evidence from epidemiological studies that overweight and obese women are less likely to breastfeed than normal weight women (Amir and Donath, 2007).

We believe that it is especially important to stress here is that all the data above mentioned have to be taken with due caution given the relative paucity and high levels of heterogeneity of the studies present in the literature. In particular, it is imperative that further controlled trials be performed in order to determine the type of antioxidants vs pre- and probiotics and the most appropriate dose.

Based upon the above-mentioned considerations, and data gathered through RCTs, we can draw some hypothetical scenarios on the proper timing of an ideal intervention and their possible consequences. We expect that the negative effects of being exposed to maternal obesity might manifest themselves at different time points throughout life, also in relation to a second hit (being this a stressful event or another obesogenic stimulus), starting from the early developmental phases to adolescence, up until aging. We hypothesize different potential windows of intervention: the earlier we intervene the greater and long-lasting the benefit.

Ideally, the timing of the intervention should be set during brain development (before critical periods are closed) and, hopefully before the end of adolescence/puberty. Adolescence is a critical time for brain and behavioral development ultimately leading to the transition from childhood to adulthood. This peculiar time is characterized by a massive neuronal remodeling powerfully shaped by hormones, thus representing a very vulnerable time in life as well as a window of opportunity. With late interventions (middle-age or old age) we might still be able to act on residual neuronal plasticity, ameliorating the outcome of neurodegenerative disorders such as AD or PD (see Fig. 2).

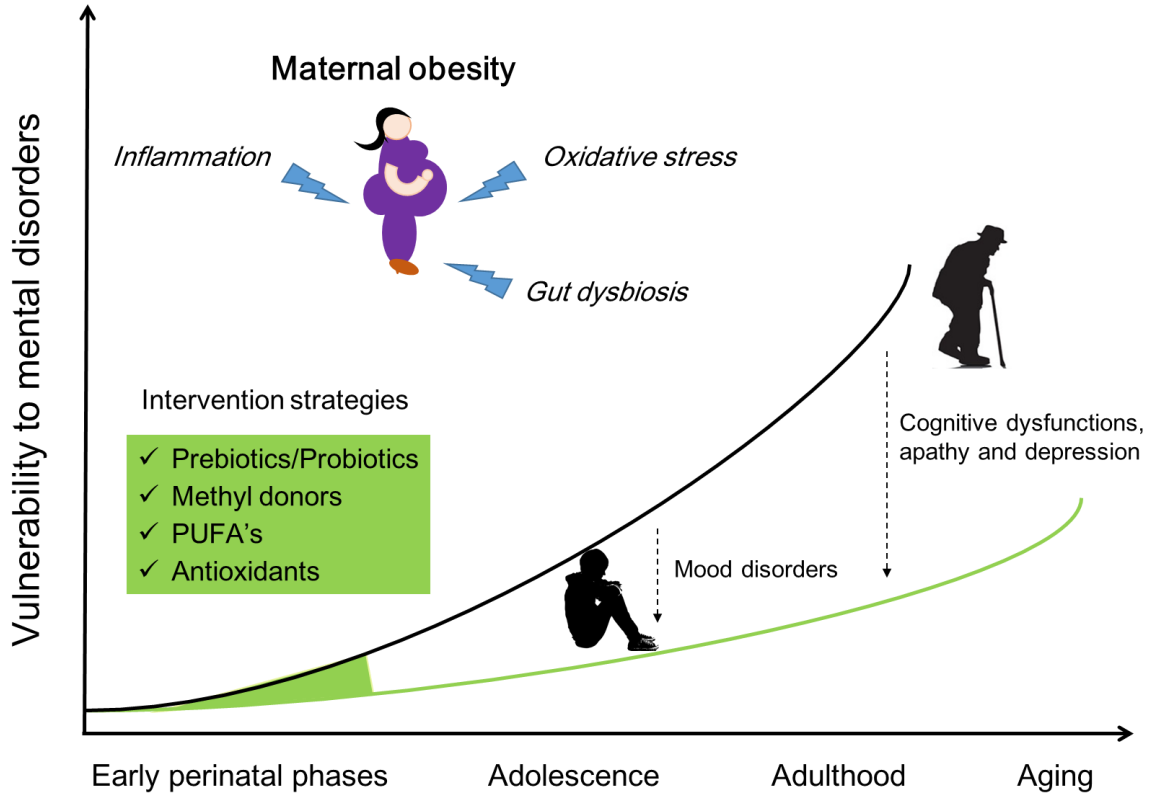

Fig. 2. Hypothetical scenarios on the proper timing of the interventions and their possible consequences. The ability of the organism to cope with the sequelae of the obesogenic womb (oxidative stress, gut dysbiosis and inflammation) decreases throughout life as a result of the physiological decrease in neuronal and behavioral plasticity. Different windows of intervention may be foreseen with earlier timing (perinatal phases until adolescence) leading to greater and longer-lasting benefits, later interventions (adulthood until aging) being able to act only on residual neuronal plasticity, ameliorating the outcome of age-related neurodegenerative disorders. The earlier the intervention (green area within the curves) the greater the potential to reduce disease risk later in life (dashed arrows). *Figure modified from Godfrey KM, Gluckman PD, Hanson MA. Developmental origins of metabolic disease: life course and intergenerational perspectives. Trends in endocrinology and metabolism: TEM. 2010;21(4):199-205.*

Conclusions

Although initial research linking prenatal development with major non-communicable disorders in later life focused on the effects of fetal undernutrition, nowadays it is rather maternal obesity and its sequelae for metabolic and mental health that poses serious public health concerns throughout the world (Congdon, 2019;Jehn and Brewis, 2009). Indeed, an ever-increasing body of epidemiological data - that are corroborated by preclinical evidence - suggest that exposure to an obesogenic womb might strongly impact offspring healthspan throughout life, setting the stage for an increased vulnerability to a number of pathological conditions including obesity, CVD, stroke, T2D and asthma (just to mention few), in addition to neuropsychiatric disorders. As recently pointed out by Godfrey and colleagues (Godfrey, et al., 2017), there is a need of thorough large-scale studies tackling, for example, the differential impact played by maternal diet and maternal obesity as well as maternal obesity during pregnancy vs obesity during the lactation period. There may be a mix of psychological, behavioral and cultural factors underlying such effects.

These studies should be performed including populations differing in terms of culture as well as ethnicity and collecting detailed data on the cognitive and behavioral phenotype of both parents and offspring; in addition, a comprehensive assessment of diet and of measures of adiposity should be performed (Godfrey, et al., 2017).

From an evolutionary perspective, foraging behavior in harsh environments, a condition opposed to maternal obesity and characterized by limited and intermittent food availability, has most likely contributed to shape our brain to deal more effectively with spatial navigation, decision-making, social relationships and even creativity (Berry and Cirulli, 2013;Mattson, 2019). Globalization and urbanization, by favoring sedentary lifestyle and the consumption of high-caloric foods, are gradually leading to a change in the energetic niche experienced both prenatally and early postnatally by humans with consequences that are hard to predict: the ultimate outcome of such a metabolic shift is now starting to show an impact on pre- as well as post-natal developmental trajectories with potential disruptive effects on cognitive processes and susceptibility to mental disorders. Epigenetic changes and dysbiosis linked to such processes have the potential to propagate these modifications to future generations.

While public health countermeasures that can rapidly break the vicious cycle of maternal and offspring obesity are mandatory, we are definitively in need of basic knowledge and appropriate longitudinal, controlled studies that can address the basic mechanisms underlying

such regulation, allowing for appropriate intervention but, more importantly, indicating appropriate biomarkers and effective preventive measures.

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Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

References

Aagaard K, Ma J, Antony KM, Ganu R, Petrosino J, Versalovic J (2014) The placenta harbors a unique microbiome. Sci Transl Med 6:237ra265.

Alfaradhi MZ, Ozanne SE (2011) Developmental programming in response to maternal overnutrition. Front Genet 2:27.

Amir LH, Donath S (2007) A systematic review of maternal obesity and breastfeeding intention, initiation and duration. BMC Pregnancy Childbirth 7:9.

Armani A, Berry A, Cirulli F, Caprio M (2017) Molecular mechanisms underlying metabolic syndrome: the expanding role of the adipocyte. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 31:4240-4255.

Baird J, Osmond C, MacGregor A, Snieder H, Hales CN, Phillips DI (2001) Testing the fetal origins hypothesis in twins: the Birmingham twin study. Diabetologia 44:33-39.

Bale TL, Baram TZ, Brown AS, Goldstein JM, Insel TR, McCarthy MM, Nemeroff CB, Reyes TM, et al. (2010) Early life programming and neurodevelopmental disorders. Biol Psychiatry 68:314-319.

Barker DJ, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS (1993) Fetal nutrition and cardiovascular disease in adult life. Lancet 341:938-941.

Barker DJ, Osmond C (1986) Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. Lancet 1:1077-1081.

Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ (1989) Weight in infancy and death from ischaemic heart disease. Lancet 2:577-580.

Basatemur E, Gardiner J, Williams C, Melhuish E, Barnes J, Sutcliffe A (2013) Maternal prepregnancy BMI and child cognition: a longitudinal cohort study. Pediatrics 131:56-63.

Basu S, Haghiac M, Surace P, Challier JC, Guerre-Millo M, Singh K, Waters T, Minium J, et al. (2011) Pregravid obesity associates with increased maternal endotoxemia and metabolic inflammation. Obesity (Silver Spring) 19:476-482.

Bateson P (2001) Fetal experience and good adult design. International journal of epidemiology 30:928-934.

Bateson P, Barker D, Clutton-Brock T, Deb D, D'Udine B, Foley RA, Gluckman P, Godfrey K, et al. (2004) Developmental plasticity and human health. Nature 430:419-421.

Bellisario V, Berry A, Capoccia S, Raggi C, Panetta P, Branchi I, Piccaro G, Giorgio M, et al. (2014) Gender-dependent resiliency to stressful and metabolic challenges following prenatal exposure to high-fat diet in the p66(Shc-/-) mouse. Front Behav Neurosci 8:285.

Bellisario V, Panetta P, Balsevich G, Baumann V, Noble J, Raggi C, Berry A, Seckl J, et al. (2015) High-fat diet during pregnancy acts as a stressor increasing maternal glucocorticoids' signaling to the fetus and disrupting maternal behavior in a mouse model. Psychoneuroendocrinology 61:10-10.

Berk M, Malhi GS, Gray LJ, Dean OM (2013) The promise of N-acetylcysteine in neuropsychiatry. Trends Pharmacol Sci 34:167-177.

Berniakovich I, Trinei M, Stendardo M, Migliaccio E, Minucci S, Bernardi P, Pelicci PG, Giorgio M (2008) p66Shc-generated oxidative signal promotes fat accumulation. J Biol Chem 283:34283-34293.

Berry A, Amrein I, Notzli S, Lazic SE, Bellisario V, Giorgio M, Pelicci PG, Alleva E, et al. (2012) Sustained hippocampal neurogenesis in females is amplified in P66(Shc-/-) mice: An animal model of healthy aging. Hippocampus 22:2249-2259.

Berry A, Bellisario V, Panetta P, Raggi C, Magnifico MC, Arese M, Cirulli F (2018) Administration of the Antioxidant N-Acetyl-Cysteine in Pregnant Mice Has Long-Term

Positive Effects on Metabolic and Behavioral Endpoints of Male and Female Offspring Prenatally Exposed to a High-Fat Diet. Front Behav Neurosci 12.

Berry A, Bucci M, Raggi C, Eriksson JG, Guzzardi MA, Nuutila P, Huovinen V, Iozzo P, et al. (2018) Dynamic changes in p66Shc mRNA expression in peripheral blood mononuclear cells following resistance training intervention in old frail women born to obese mothers: a pilot study. Aging Clin Exp Res 30:871-876.

Berry A, Capone F, Giorgio M, Pelicci PG, de Kloet ER, Alleva E, Minghetti L, Cirulli F (2007) Deletion of the life span determinant p66Shc prevents age-dependent increases in emotionality and pain sensitivity in mice. Exp Gerontol 42:37-45.

Berry A, Carnevale D, Giorgio M, Pelicci PG, de Kloet ER, Alleva E, Minghetti L, Cirulli F (2010) Greater resistance to inflammation at adulthood could contribute to extended life span of p66(Shc-/-) mice. Exp Gerontol 45:343-350.

Berry A, Cirulli F (2013) The p66(Shc) gene paves the way for healthspan: evolutionary and mechanistic perspectives. Neurosci Biobehav Rev 37:790-802.

Berry A, Greco A, Giorgio M, Pelicci PG, de Kloet R, Alleva E, Minghetti L, Cirulli F (2008) Deletion of the lifespan determinant p66(Shc) improves performance in a spatial memory task, decreases levels of oxidative stress markers in the hippocampus and increases levels of the neurotrophin BDNF in adult mice. Exp Gerontol 43:200-208.

Bilbo SD, Tsang V (2010) Enduring consequences of maternal obesity for brain inflammation and behavior of offspring. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 24:2104-2115.

Bock J, Rether K, Groger N, Xie L, Braun K (2014) Perinatal programming of emotional brain circuits: an integrative view from systems to molecules. Frontiers in neuroscience 8:11.

Boersma GJ, Lee RS, Cordner ZA, Ewald ER, Purcell RH, Moghadam AA, Tamashiro KL (2014) Prenatal stress decreases Bdnf expression and increases methylation of Bdnf exon IV in rats. Epigenetics 9:437-447.

Braithwaite EC, Kundakovic M, Ramchandani PG, Murphy SE, Champagne FA (2015) Maternal prenatal depressive symptoms predict infant NR3C1 1F and BDNF IV DNA methylation. Epigenetics 10:408-417.

Bruce J, Davis EP, Gunnar MR (2002) Individual differences in children's cortisol response to the beginning of a new school year. Psychoneuroendocrinology 27:635-650.

Brunton PJ, Russell JA (2010) Prenatal social stress in the rat programmes neuroendocrine and behavioural responses to stress in the adult offspring: sex-specific effects. J Neuroendocrinol 22:258-271.

Buss C, Entringer S, Davis EP, Hobel CJ, Swanson JM, Wadhwa PD, Sandman CA (2012) Impaired executive function mediates the association between maternal pre-pregnancy body mass index and child ADHD symptoms. PloS one 7:e37758.

Carlin J, George R, Reyes TM (2013) Methyl donor supplementation blocks the adverse effects of maternal high fat diet on offspring physiology. PloS one 8:e63549.

Casas M, Chatzi L, Carsin AE, Amiano P, Guxens M, Kogevinas M, Koutra K, Lertxundi N, et al. (2013) Maternal pre-pregnancy overweight and obesity, and child neuropsychological development: two Southern European birth cohort studies. International journal of epidemiology 42:506-517.

Chang E, Hafner H, Varghese M, Griffin C, Clemente J, Islam M, Carlson Z, Zhu A, et al. (2019) Programming effects of maternal and gestational obesity on offspring metabolism and metabolic inflammation. Scientific reports 9:16027.

Chaput JP, Doucet E, Tremblay A (2012) Obesity: a disease or a biological adaptation? An update. Obes Rev 13:681-691.

Cirulli F (2017) Interactions between early life stress and metabolic stress in programming of mental and metabolic health. Curr Opin Behav Sci 14:65-71.
Cirulli F, Alleva E (2009) The NGF saga: from animal models of psychosocial stress to stress-related psychopathology. Front Neuroendocrinol 30:379-395.
Cirulli F, Berry A, Alleva E (2003) Early disruption of the mother-infant relationship: effects on brain plasticity and implications for psychopathology. Neurosci Biobehav R 27:73-82.
Cirulli F, Berry A, Alleva E. (2003a) Early disruption of the mother-infant relationship: effects on brain plasticity and implications for psychopathology. Neurosci Biobehav Rev 27:73-82.
Cirulli F, Santucci D, Laviola G, Alleva E, Levine S (1994) Behavioral and hormonal responses to stress in the newborn mouse: effects of maternal deprivation and chlordiazepoxide. Developmental psychobiology 27:301-316.
Collado MC, Rautava S, Aakko J, Isolauri E, Salminen S (2016) Human gut colonisation may be initiated in utero by distinct microbial communities in the placenta and amniotic fluid. Scientific reports 6:23129.
Congdon P (2019) Obesity and Urban Environments. Int J Environ Res Public Health 16.
Contu L, Hawkes CA (2017) A Review of the Impact of Maternal Obesity on the Cognitive Function and Mental Health of the Offspring. Int J Mol Sci 18.
Cryan JF (2016) Stress and the Microbiota-Gut-Brain Axis: An Evolving Concept in Psychiatry. Can J Psychiatry 61:201-203.
Daskalakis NP, Bagot RC, Parker KJ, Vinkers CH, de Kloet ER (2013) The three-hit concept of vulnerability and resilience: toward understanding adaptation to early-life adversity outcome. Psychoneuroendocrinology 38:1858-1873.
Davari S, Talaei SA, Alaei H, Salami M (2013) Probiotics treatment improves diabetes-induced impairment of synaptic activity and cognitive function: behavioral and electrophysiological proofs for microbiome-gut-brain axis. Neuroscience 240:287-296.
de Kloet ER, Joels M, Holsboer F (2005) Stress and the brain: from adaptation to disease. Nat Rev Neurosci 6:463-475.
De Palma G, Blennerhassett P, Lu J, Deng Y, Park AJ, Green W, Denou E, Silva MA, et al. (2015) Microbiota and host determinants of behavioural phenotype in maternally separated mice. Nature communications 6:7735.
De Souza CT, Araujo EP, Bordin S, Ashimine R, Zollner RL, Boschero AC, Saad MJ, Velloso LA (2005) Consumption of a fat-rich diet activates a proinflammatory response and induces insulin resistance in the hypothalamus. Endocrinology 146:4192-4199.
Del Rio D, Stewart AJ, Pellegrini N (2005) A review of recent studies on malondialdehyde as toxic molecule and biological marker of oxidative stress. Nutr Metab Cardiovasc Dis 15:316-328.
Dennery PA (2007) Effects of oxidative stress on embryonic development. Birth Defects Res C Embryo Today 81:155-162.
Dimmitt RA, Staley EM, Chuang G, Tanner SM, Soltau TD, Lorenz RG (2010) Role of postnatal acquisition of the intestinal microbiome in the early development of immune function. Journal of pediatric gastroenterology and nutrition 51:262-273.
Dinan TG, Cryan JF (2016) Mood by microbe: towards clinical translation. Genome Med 8:36.
Dinan TG, Cryan JF (2017) Microbes, Immunity, and Behavior: Psychoneuroimmunology Meets the Microbiome. Neuropsychopharmacology 42:178-192.
Edlow AG (2017) Maternal obesity and neurodevelopmental and psychiatric disorders in offspring. Prenatal diagnosis 37:95-110.
Edlow AG, Guedj F, Pennings JL, Sverdlov D, Neri C, Bianchi DW (2016) Males are from Mars, and females are from Venus: sex-specific fetal brain gene expression signatures in a mouse model of maternal diet-induced obesity. Am J Obstet Gynecol 214:623 e621-623 e610.

Edlow AG, Hui L, Wick HC, Fried I, Bianchi DW (2016b) Assessing the fetal effects of maternal obesity via transcriptomic analysis of cord blood: a prospective case-control study. BJOG 123:180-189.

Edlow AG, Vora NL, Hui L, Wick HC, Cowan JM, Bianchi DW (2014) Maternal obesity affects fetal neurodevelopmental and metabolic gene expression: a pilot study. PloS one 9:e88661.

Ehlert U (2013) Enduring psychobiological effects of childhood adversity. Psychoneuroendocrinology 38:1850-1857.

El Aidy S, Stilling R, Dinan TG, Cryan JF (2016) Microbiome to Brain: Unravelling the Multidirectional Axes of Communication. Adv Exp Med Biol 874:301-336.

Elshorbagy AK, Smith AD, Kozich V, Refsum H (2012) Cysteine and obesity. Obesity (Silver Spring) 20:473-481.

Entringer S, Buss C, Wadhwa PD (2015) Prenatal stress, development, health and disease risk: A psychobiological perspective-2015 Curt Richter Award Paper. Psychoneuroendocrinology 62:366-375.

Eriksson JG, Sandboge S, Salonen MK, Kajantie E, Osmond C (2014) Long-term consequences of maternal overweight in pregnancy on offspring later health: findings from the Helsinki Birth Cohort Study. Ann Med 46:434-438.

Floyd RA, Carney JM (1992) Free radical damage to protein and DNA: mechanisms involved and relevant observations on brain undergoing oxidative stress. Ann Neurol 32 Suppl:S22-27.

Foster JA, Lyte M, Meyer E, Cryan JF (2016) Gut Microbiota and Brain Function: An Evolving Field in Neuroscience. Int J Neuropsychopharmacol 19.

Fowden AL, Sferruzzi-Perri AN, Coan PM, Constancia M, Burton GJ (2009) Placental efficiency and adaptation: endocrine regulation. The Journal of physiology 587:3459-3472.

Gentile D, Fornai M, Pellegrini C, Colucci R, Benvenuti L, Duranti E, Masi S, Carpi S, et al. (2018) Luteolin Prevents Cardiometabolic Alterations and Vascular Dysfunction in Mice With HFD-Induced Obesity. Front Pharmacol 9:1094.

Giorgio M, Berry A, Berniakovich I, Poletaeva I, Trinei M, Stendardo M, Hagopian K, Ramsey JJ, et al. (2012) The p66Shc knocked out mice are short lived under natural condition. Aging Cell 11:162-168.

Godfrey KM, Reynolds RM, Prescott SL, Nyirenda M, Jaddoe VW, Eriksson JG, Broekman BF (2017) Influence of maternal obesity on the long-term health of offspring. The lancet Diabetes & endocrinology 5:53-64.

Guzzardi MA, Iozzo P, Salonen MK, Kajantie E, Eriksson JG (2016) Maternal adiposity and infancy growth predict later telomere length: a longitudinal cohort study. International journal of obesity 40:1063-1069.

Harris A, Seckl J (2011) Glucocorticoids, prenatal stress and the programming of disease. Hormones and Behavior 59:279-289.

Heiss CN, Olofsson LE (2019) The role of the gut microbiota in development, function and disorders of the central nervous system and the enteric nervous system. J Neuroendocrinol 31:e12684.

Hinkle SN, Schieve LA, Stein AD, Swan DW, Ramakrishnan U, Sharma AJ (2012) Associations between maternal prepregnancy body mass index and child neurodevelopment at 2 years of age. International journal of obesity 36:1312-1319.

Hinkle SN, Sharma AJ, Kim SY, Schieve LA (2013) Maternal prepregnancy weight status and associations with children's development and disabilities at kindergarten. International journal of obesity 37:1344-1351.

Horn SR, Leve LD, Levitt P, Fisher PA (2019) Childhood adversity, mental health, and oxidative stress: A pilot study. PloS one 14:e0215085.

Hovatta I, Juhila J, Donner J (2010) Oxidative stress in anxiety and comorbid disorders. Neuroscience research 68:261-275.

Howell KR, Powell TL (2017) Effects of maternal obesity on placental function and fetal development. Reproduction 153:R97-R108.

Hracsko Z, Orvos H, Novak Z, Pal A, Varga IS (2008) Evaluation of oxidative stress markers in neonates with intra-uterine growth retardation. Redox Rep 13:11-16.

Iozzo P, Holmes M, Schmidt MV, Cirulli F, Guzzardi MA, Berry A, Balsevich G, Andreassi MG, et al. (2014) Developmental ORIgins of Healthy and Unhealthy AgeiNg: the role of maternal obesity--introduction to DORIAN. Obes Facts 7:130-151.

Jehn M, Brewis A (2009) Paradoxical malnutrition in mother-child pairs: untangling the phenomenon of over- and under-nutrition in underdeveloped economies. Econ Hum Biol 7:28-35.

Kandimalla R, Thirumala V, Reddy PH (2017) Is Alzheimer's disease a Type 3 Diabetes? A critical appraisal. Biochim Biophys Acta Mol Basis Dis 1863:1078-1089.

Kelly JR, Clarke G, Cryan JF, Dinan TG (2016) Brain-gut-microbiota axis: challenges for translation in psychiatry. Ann Epidemiol 26:366-372.

Koleva PT, Kim JS, Scott JA, Kozyrskyj AL (2015) Microbial programming of health and disease starts during fetal life. Birth Defects Res C Embryo Today 105:265-277.

Leon DA, Koupilova I, Lithell HO, Berglund L, Mohsen R, Vagero D, Lithell UB, McKeigue PM (1996) Failure to realise growth potential in utero and adult obesity in relation to blood pressure in 50 year old Swedish men. Bmj 312:401-406.

Levine S (1957) Infantile experience and resistance to physiological stress. Science 126:405.

LifeCycle Project-Maternal O, Childhood Outcomes Study G, Voerman E, Santos S, Inskip H, Amiano P, Barros H, Charles MA, et al. (2019) Association of Gestational Weight Gain With Adverse Maternal and Infant Outcomes. JAMA 321:1702-1715.

Lindsay KL, Buss C, Wadhwa PD, Entringer S (2017) The Interplay between Maternal Nutrition and Stress during Pregnancy: Issues and Considerations. Ann Nutr Metab 70:191-200.

Luczynski P, McVey Neufeld KA, Oriach CS, Clarke G, Dinan TG, Cryan JF (2016) Growing up in a Bubble: Using Germ-Free Animals to Assess the Influence of the Gut Microbiota on Brain and Behavior. Int J Neuropsychopharmacol.

Maccari S, Morley-Fletcher S (2007) Effects of prenatal restraint stress on the hypothalamus-pituitary-adrenal axis and related behavioural and neurobiological alterations. Psychoneuroendocrinology 32 Suppl 1:S10-15.

Mannaerts D, Faes E, Cos P, Briede JJ, Gyselaers W, Cornette J, Gorbanev Y, Bogaerts A, et al. (2018) Oxidative stress in healthy pregnancy and preeclampsia is linked to chronic inflammation, iron status and vascular function. PloS one 13:e0202919.

Mansur RB, Brietzke E, McIntyre RS (2015) Is there a "metabolic-mood syndrome"? A review of the relationship between obesity and mood disorders. Neurosci Biobehav Rev 52:89-104.

Mattson MP (2019) An Evolutionary Perspective on Why Food Overconsumption Impairs Cognition. Trends Cogn Sci 23:200-212.

McEwen BS (1998) Protective and damaging effects of stress mediators. N Engl J Med 338:171-179.

McEwen BS (2000) Effects of adverse experiences for brain structure and function. Biol Psychiatry 48:721-731.

McEwen BS, Gray JD, Nasca C (2015) 60 YEARS OF NEUROENDOCRINOLOGY: Redefining neuroendocrinology: stress, sex and cognitive and emotional regulation. The Journal of endocrinology 226:T67-83.

McGowan PO, Meaney MJ, Szyf M (2008) Diet and the epigenetic (re)programming of phenotypic differences in behavior. Brain research 1237:12-24.

McKee SE, Grissom NM, Herdt CT, Reyes TM (2017) Methyl donor supplementation alters cognitive performance and motivation in female offspring from high-fat diet-fed dams. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 31:2352-2363.

McLaughlin KA, Sheridan MA, Tibu F, Fox NA, Zeanah CH, Nelson CA, 3rd (2015) Causal effects of the early caregiving environment on development of stress response systems in children. Proceedings of the National Academy of Sciences of the United States of America 112:5637-5642.

Meaney MJ, Aitken DH, Viau V, Sharma S, Sarrieau A (1989) Neonatal handling alters adrenocortical negative feedback sensitivity and hippocampal type II glucocorticoid receptor binding in the rat. Neuroendocrinology 50:597-604.

Menting MD, van de Beek C, Mintjens S, Wever KE, Korosi A, Ozanne SE, Limpens J, Roseboom TJ, et al. (2019) The link between maternal obesity and offspring neurobehavior: A systematic review of animal experiments. Neurosci Biobehav Rev 98:107-121.

Milior G, Lecours C, Samson L, Bisht K, Poggini S, Pagani F, Deflorio C, Lauro C, et al. (2016) Fractalkine receptor deficiency impairs microglial and neuronal responsiveness to chronic stress. Brain, behavior, and immunity 55:114-125.

Miller AL, Lee HJ, Lumeng JC (2015) Obesity-associated biomarkers and executive function in children. Pediatr Res 77:143-147.

Mina TH, Lahti M, Drake AJ, Denison FC, Raikkonen K, Norman JE, Reynolds RM (2017) Prenatal exposure to maternal very severe obesity is associated with impaired neurodevelopment and executive functioning in children. Pediatr Res 82:47-54.

Mina TH, Raikkonen K, Riley SC, Norman JE, Reynolds RM (2015) Maternal distress associates with placental genes regulating fetal glucocorticoid exposure and IGF2: Role of obesity and sex. Psychoneuroendocrinology 59:112-122.

Mohd-Shukri NA, Duncan A, Denison FC, Forbes S, Walker BR, Norman JE, Reynolds RM (2015) Health Behaviours during Pregnancy in Women with Very Severe Obesity. Nutrients 7:8431-8443.

Mou Z, Hyde TM, Lipska BK, Martinowich K, Wei P, Ong CJ, Hunter LA, Palaguachi GI, et al. (2015) Human Obesity Associated with an Intronic SNP in the Brain-Derived Neurotrophic Factor Locus. Cell reports 13:1073-1080.

Moussa HN, Alrais MA, Leon MG, Abbas EL, Sibai BM (2016) Obesity epidemic: impact from preconception to postpartum. Future Sci OA 2:FSO137.

Mrizak I, Grissa O, Henault B, Fekih M, Bouslema A, Boumaiza I, Zaouali M, Tabka Z, et al. (2014) Placental infiltration of inflammatory markers in gestational diabetic women. General physiology and biophysics 33:169-176.

Muffat J, Walker DW (2010) Apolipoprotein D: an overview of its role in aging and age-related diseases. Cell Cycle 9:269-273.

Naninck EF, Oosterink JE, Yam KY, de Vries LP, Schierbeek H, van Goudoever JB, Verkaik-Schakel RN, Plantinga JA, et al. (2017) Early micronutrient supplementation protects against early stress-induced cognitive impairments. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 31:505-518.

Osmond C, Barker DJ, Winter PD, Fall CH, Simmonds SJ (1993) Early growth and death from cardiovascular disease in women. Bmj 307:1519-1524.

Patterson E, Ryan PM, Cryan JF, Dinan TG, Ross RP, Fitzgerald GF, Stanton C (2016) Gut microbiota, obesity and diabetes. Postgrad Med J 92:286-300.

Pelzer E, Gomez-Arango LF, Barrett HL, Nitert MD (2017) Review: Maternal health and the placental microbiome. Placenta 54:30-37.

Picard M, McEwen BS (2014) Mitochondria impact brain function and cognition. Proceedings of the National Academy of Sciences of the United States of America 111:7-8.

Picard M, McEwen BS (2018) Psychological Stress and Mitochondria: A Conceptual Framework. Psychosom Med 80:126-140.

Picard M, McEwen BS, Epel ES, Sandi C (2018) An energetic view of stress: Focus on mitochondria. Front Neuroendocrinol 49:72-85.

Pizzi MA, Vroman K (2013) Childhood obesity: effects on children's participation, mental health, and psychosocial development. Occup Ther Health Care 27:99-112.

Provencal N, Binder EB (2015) The effects of early life stress on the epigenome: From the womb to adulthood and even before. Experimental neurology 268:10-20.

Raikkonen K, Pesonen AK (2009) Early life origins of psychological development and mental health. Scand J Psychol 50:583-591.

Reynolds LM, Wan M, Ding J, Taylor JR, Lohman K, Su D, Bennett BD, Porter DK, et al. (2015) DNA Methylation of the Aryl Hydrocarbon Receptor Repressor Associations With Cigarette Smoking and Subclinical Atherosclerosis. Circ Cardiovasc Genet 8:707-716.

Rinninella E, Raoul P, Cintoni M, Franceschi F, Miggiano GAD, Gasbarrini A, Mele MC (2019) What is the Healthy Gut Microbiota Composition? A Changing Ecosystem across Age, Environment, Diet, and Diseases. Microorganisms 7.

Rivera HM, Christiansen KJ, Sullivan EL (2015) The role of maternal obesity in the risk of neuropsychiatric disorders. Frontiers in neuroscience 9:194.

Rodriguez A (2010) Maternal pre-pregnancy obesity and risk for inattention and negative emotionality in children. Journal of child psychology and psychiatry, and allied disciplines 51:134-143.

Roseboom TJ (2019) Epidemiological evidence for the developmental origins of health and disease: effects of prenatal undernutrition in humans. The Journal of endocrinology 242:T135-T144.

Roth TL, Sullivan RM (2005) Memory of early maltreatment: neonatal behavioral and neural correlates of maternal maltreatment within the context of classical conditioning. Biol Psychiatry 57:823-831.

Rudolph MD, Graham AM, Feczko E, Miranda-Dominguez O, Rasmussen JM, Nardos R, Entringer S, Wadhwa PD, et al. (2018) Maternal IL-6 during pregnancy can be estimated from newborn brain connectivity and predicts future working memory in offspring. Nature neuroscience 21:765-772.

Saben J, Lindsey F, Zhong Y, Thakali K, Badger TM, Andres A, Gomez-Acevedo H, Shankar K (2014) Maternal obesity is associated with a lipotoxic placental environment. Placenta 35:171-177.

Sanchez CE, Barry C, Sabhlok A, Russell K, Majors A, Kollins SH, Fuemmeler BF (2018) Maternal pre-pregnancy obesity and child neurodevelopmental outcomes: a meta-analysis. Obes Rev 19:464-484.

Sasaki A, de Vega W, Sivanathan S, St-Cyr S, McGowan PO (2014) Maternal high-fat diet alters anxiety behavior and glucocorticoid signaling in adolescent offspring. Neuroscience 272:92-101.

Satokari R, Gronroos T, Laitinen K, Salminen S, Isolauri E (2009) Bifidobacterium and Lactobacillus DNA in the human placenta. Lett Appl Microbiol 48:8-12.

Schroeder M, Jakovcevski M, Polacheck T, Lebow M, Drori Y, Engel M, Ben-Dor S, Chen A (2017) A Methyl-Balanced Diet Prevents CRF-Induced Prenatal Stress-Triggered Predisposition to Binge Eating-like Phenotype. Cell Metab 25:1269-1281 e1266.

Seckl JR (1998) Physiologic programming of the fetus. Clin Perinatol 25:939-962, vii.

Seckl JR (2004) Prenatal glucocorticoids and long-term programming. Eur J Endocrinol 151 Suppl 3:U49-62.

Sherwin E, Rea K, Dinan TG, Cryan JF (2016) A gut (microbiome) feeling about the brain. Curr Opin Gastroenterol 32:96-102.

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 59:895-906.

Sorrells SF, Caso JR, Munhoz CD, Sapolsky RM (2009) The stressed CNS: when glucocorticoids aggravate inflammation. Neuron 64:33-39.

Soubry A, Schildkraut JM, Murtha A, Wang F, Huang Z, Bernal A, Kurtzberg J, Jirtle RL, et al. (2013) Paternal obesity is associated with IGF2 hypomethylation in newborns: results from a Newborn Epigenetics Study (NEST) cohort. BMC Med 11:29.

Stout SA, Espel EV, Sandman CA, Glynn LM, Davis EP (2015) Fetal programming of children's obesity risk. Psychoneuroendocrinology 53:29-39.

Sullivan EL, Riper KM, Lockard R, Valleau JC (2015) Maternal high-fat diet programming of the neuroendocrine system and behavior. Horm Behav 76:153-161.

Sutcliffe JG, Thomas EA (2002) The neurobiology of apolipoproteins in psychiatric disorders. Mol Neurobiol 26:369-388.

Szyf M (2012) The early-life social environment and DNA methylation. Clin Genet 81:341-349.

Szyf M, Weaver IC, Champagne FA, Diorio J, Meaney MJ (2005) Maternal programming of steroid receptor expression and phenotype through DNA methylation in the rat. Front Neuroendocrinol 26:139-162.

Tenenbaum-Gavish K, Hod M (2013) Impact of maternal obesity on fetal health. Fetal Diagn Ther 34:1-7.

Townshend T, Lake A (2017) Obesogenic environments: current evidence of the built and food environments. Perspect Public Health 137:38-44.

Trinei M, Berniakovich I, Beltrami E, Migliaccio E, Fassina A, Pelicci P, Giorgio M (2009) P66Shc signals to age. Aging (Albany NY) 1:503-510.

Turecki G, Ota VK, Belangero SI, Jackowski A, Kaufman J (2014) Early life adversity, genomic plasticity, and psychopathology. The lancet Psychiatry 1:461-466.

Tyagi E, Zhuang Y, Agrawal R, Ying Z, Gomez-Pinilla F (2015) Interactive actions of Bdnf methylation and cell metabolism for building neural resilience under the influence of diet. Neurobiology of disease 73:307-318.

van der Knaap LJ, Oldehinkel AJ, Verhulst FC, van Oort FV, Riese H (2015) Glucocorticoid receptor gene methylation and HPA-axis regulation in adolescents. The TRAILS study. Psychoneuroendocrinology 58:46-50.

Vucetic Z, Kimmel J, Totoki K, Hollenbeck E, Reyes TM (2010) Maternal high-fat diet alters methylation and gene expression of dopamine and opioid-related genes. Endocrinology 151:4756-4764.

Welberg LA, Seckl JR (2001) Prenatal stress, glucocorticoids and the programming of the brain. J Neuroendocrinol 13:113-128.

Westberg AP, Salonen MK, von Bonsdorff M, Kajantie E, Eriksson JG (2016) Maternal body mass index in pregnancy and offspring physical and psychosocial functioning in older age: findings from the Helsinki Birth Cohort Study (HBCS). Ann Med 48:268-274.

White CL, Purpera MN, Morrison CD (2009) Maternal obesity is necessary for programming effect of high-fat diet on offspring. American journal of physiology Regulatory, integrative and comparative physiology 296:R1464-1472.

Wurtman J, Wurtman R (2018) The Trajectory from Mood to Obesity. Curr Obes Rep 7:1-5.

Yatsunenko T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, Contreras M, Magris M, Hidalgo G, et al. (2012) Human gut microbiome viewed across age and geography. Nature 486:222-227.