THE JOURNAL OF CHILD PSYCHOLOGY AND PSYCHIATRY
ACAMH
Journal of Child Psychology and Psychiatry *:* (2012), pp **–** doi:10.1111/jcpp.12000

Research Review: Maternal prenatal distress and poor nutrition – mutually influencing risk factors affecting infant neurocognitive development

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Background: Accumulating data from animal and human studies indicate that the prenatal environment plays a significant role in shaping children's neurocognitive development. Clinical, epidemiologic, and basic science research suggests that two experiences relatively common in pregnancy – an unhealthy maternal diet and psychosocial distress – significantly affect children's future neurodevelopment. These prenatal experiences exert their influence in the context of one another and yet, almost uniformly, are studied independently. **Scope and Method of Review:** In this review, we suggest that studying neurocognitive development in children in relation to both prenatal exposures is ecologically most relevant, and methodologically most sound. To support this approach, we selectively review two research topics that demonstrate the need for dual exposure studies, including exemplar findings on (a) the associations between pregnant women's inadequate maternal intake of key nutrients – protein, fat, iron, zinc, and choline – as well as distress in relation to overlapping effects on children's neurocognitive development; and (b) cross-talk between the biology of stress and nutrition that can amplify each experience for the mother and fetus,. We also consider obstacles to this kind of study design, such as questions of statistical methods for 'disentangling' the exposure effects, and aim to provide some answers. **Conclusion:** Studies that specifically include both exposures in their design can begin to determine the relative and/or synergistic impact of these prenatal experiences on developmental trajectories – and thereby contribute most fully to the understanding of the early origins of health and disease. **Keywords:** Prenatal, stress, micronutrient, neurocognitive development, fetal origins.

Introduction

Children's neurocognitive development can cast long shadows on their futures, dramatically influencing their psychosocial adaptation and academic/occupational trajectories (Knudsen, Heckman, Cameron, & Shonkoff, 2006; Shonkoff & Garner, 2012). Data indicate that the prenatal environment plays a significant role in shaping neurocognitive development. Clinical, epidemiologic, and basic science research suggests that experiences common in pregnancy, such as diet, distress, environmental pollutants, and exercise, significantly affect children's future neurodevelopment (Bale et al., 2010). These prenatal experiences exert their influence in the context of one another and however, almost uniformly, are studied independently. In what follows, we review evidence to support the inclusion of two of these variables – maternal psychosocial distress and an unhealthy diet – in the same studies.

We begin with brief discussions of the fetal origins of disease hypothesis, evidence for the co-occurrence of fetal exposure to maternal distress and poor nutrition, as well as *in utero* brain development – the latter is aimed at highlighting the processes that will later be identified as vulnerable to the impact of maternal distress and inadequate nutrient intake. Next, we provide background information from two distinct research domains that demonstrate the need for dual exposure studies. Specifically, we discuss: (a) the prenatal maternal distress and nutrient intake literatures, focusing on the overlapping infant neurocognitive outcomes and the need to identify, which variable may have an independent effect, or if there are synergistic ones; and (b) data at the cellular level and relevant biological processes in the mother that are at the nexus of nutrient regulation and stress physiology such that both nutrition and mental health factors are, in fact, affecting the fetus via related biological pathways. We close by responding to some of the methodological challenges in the proposed 'dual variable' approach, and summarize our argument for this integrative work.

As this is a 'concept' study intended to function as a heuristic model and not a comprehensive review, we chose research articles as exemplars to illustrate our points. Moreover, we narrowed our inclusion of salient articles to those looking at neurocognitive outcomes (i.e., attention, learning, and memory, and related neurobiological processes), as opposed to

Conflicts of interest statement: No conflicts declared.

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behavioral (i.e., temperament, emotion regulation). In several places, we refer readers to review articles that aim to critically summarize the fetal origins research related to maternal mental health and nutrition exposures. Finally, with respect to prenatal exposure to maternal psychosocial stress, studies vary regarding the measurement of it, for example, self-reported stress, depressive symptoms, anxiety, and pregnancy specific stress; consequently, in our discussion of these data, we use the term 'distress' to refer to maternal psychosocial functioning when summarizing articles using different assessment tools.

The early origins hypothesis

Under the rubric of 'biological Freudianism' (Dubos, Savage, & Schaedler, 1966), today's hypothesis of long-lasting health effects stemming from early environmental influences, even prenatal ones, was an active area of epidemiologic and animal research more than a quarter century ago (Ravelli, Stein, & Susser, 1976). Now known as the developmental origins of health and disease hypothesis (DOHAD), this approach is actively applied to the study of neurobehavioral and neurocognitive development (Bale et al., 2010) as well as other outcomes (e.g., Godfrey & Barker, 2001; Massin, Withofs, Maeyns, & Ravet, 2001; Tamashiro & Moran, 2010). This hypothesis, or conceptual model, is consistent with the approach to psychopathology specified in the strategic plan of the NIMH (National Institute of Mental Health, 2008), which aims to understand disorders 'as unfolding developmental processes', to 'predict who is at risk' and to 'preempt' the disease process. The DOHAD model of mental illness offers a 'third', potentially preventable, pathway for some of the familial transmission of risk for at-risk developmental trajectories: in addition to shared genetics and the postnatal environment, pregnant women's psychosocial functioning, in particular, their mental health status and the quality of their diet, may impact fetal development, with long-term implications for the child's future health. A systematic review of these two literatures, maternal prenatal mental health factors, and maternal prenatal nutrient factors, affecting child development, is beyond the scope of this study. The reader is referred to the following article in these two areas: (Bale et al., 2010; Charil, Laplante, Vaillancourt, & King, 2010; Georgieff, 2007; Georgieff & Rao, 2001; Glover, 2011; Sandman, Davis, Buss, & Glynn, 2011; Swanson & Wadhwa, 2008; Talge, Neal, & Glover, 2007). The recent and dramatic increase in knowledge concerning perinatal brain development (see below) has added considerably to the DOHAD perspective: the period of brain construction is certainly a time of vulnerability to variation in species–expectable environmental input (Markham & Greenough, 2004).

The correlation between maternal high distress and poor prenatal nutrition

The social gradient in mortality – the strong correlation between lower socioeconomic position and compromised health – identifies behaviors, such as diet, and psychosocial factors, such as life stress, as co–occurring and significant contributors to health status (Stringhini et al., 2010). In addition to constraints on food availability, stress contributes to unhealthy eating (Teegarden & Bale, 2008); this appears to be true during pregnancy as well (Hurley, Caulfield, Sacco, Costigan, & Dipietro, 2005). Specifically, in one of the few studies on this topic, pregnant women who reported higher levels of stress and anxiety ate more food overall and consumed less folate, possibly due to decreased fruit intake (Hurley et al., 2005). On the one hand, these associations between distress and diet were modest (highest $r = .24$); however, they were based on a sample made up of predominantly white, well-educated pregnant women who may experience low levels of psychosocial and material hardship (Hurley et al., 2005).

In contrast, a recent epidemiological study of population based survey data of pregnancy or the year prior to giving birth (one sample, $n = 18{,}000$, the other, $n = 143{,}000$) found that in both samples, over 30% of the women were poor or low income, (defined as income ≤100% of the federal poverty level (FPL)) and 20% nearly poor (101–200% of the FPL) (Braveman et al., 2010). Sixty percent of these low-income women experienced at least one major stressor while pregnant (i.e., financial difficulties, job loss, incarceration) and nearly 30% reported food insecurity, defined as experiencing two of the following due to financial constraints: having to cut or skip a meal, eat less than considered adequate, or go hungry (Braveman et al., 2010). The possibility of experiencing multiple stressors, such as job loss, divorce, difficulty paying bills as well as compromised food intake, increased significantly with decreasing income: 14% of poor and 7% of near poor women faced four or more hardships compared with 2%, 1%, and 0.2% of women with incomes that were 201–300% FPL, 301–400% FPL, and over 400% FPL, respectively. The likelihood of prenatal exposure to both maternal distress and overall under–nutrition exists, and even more so among women of low socioeconomic status – and this does not include the more typical situation of maternal distress, adequate calories yet inadequate micronutrient intake. A primary implication of these dual exposures for DOHAD research is worth considering. Given the overlap in brain and behavioral outcomes of maternal prenatal distress and insufficient nutrient intake, when associations are identified in studies of only one of these prenatal variables, is it possible that one exposure is serving as a proxy for the other? Characterizing the contributions of maternal prenatal distress and nutrition to child neurocognitive development – in the context of one another – is an

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ecologically valid and necessary research strategy, albeit not a simple one to carry out methodologically (see below).

Brain development before birth

Although brain development or adaptation is a lifelong process, the phase occurring *in utero* is one of the most dramatic and vulnerable. During gestation, fetal neurons proliferate, differentiate, migrate, and aggregate, a process that is genetically determined, epigenetically directed, and environmentally influenced (Tau & Peterson, 2010). Nutrition and growth factors regulate brain development, whereas the biological attributes of maternal prenatal disease, psychological distress, and inadequate nutrient intake affect it. Neuronal migration peaks between gestational weeks 12–20, and is largely completed by weeks 26–29 (Tau & Peterson, 2010). Upon completion of their migration, neurons extend axons and dendrites to appropriate synaptic partners. Dendritic arborization and synaptogenesis accelerate in the 3rd trimester to produce thickening of the developing cortex. The peak period of synaptogenesis begins at the 34th week, at which point approximately 40,000 new synapses are formed every second (Tau & Peterson, 2010). The auditory and visual cortices begin to develop rapidly, starting around 24 weeks, as do areas underlying receptive language and higher neurocognitive functions (Monk, Webb, & Nelson, 2001). In what follows, the specification of fetal brain areas affected by prenatal exposure to nonoptimal maternal distress and nutrition, will, in part, identify developmental processes, such as synaptic plasticity, neurogenesis, and dendritic arborization, as vulnerable to the influences of these two maternal factors.

Two research domains that support dual exposure studies

Prenatal maternal exposures and infant neurocognitive outcomes

Studies on the potential effects of maternal prenatal distress and maternal prenatal inadequate nutrition in relation to children's neurocognitive development are numerous and distinct from each other, however, they have profoundly overlapping outcomes. Data indicate that both exposures impact memory and attention, and brain systems, such as the hippocampus central to these neurocognitive functions. These studies rely on some of the same outcome measures, particularly with respect to infant cognitive assessments, although tests of variation in features of brain functioning are more common in the nutrition domain.

Prenatal distress and effects on brain and neurocognitive development As indicated, there is persuasive evidence supporting the hypothesis that prenatal maternal affect dysregulation is a risk factor for children's neurocognitive development, and much of it is described in review articles (Bale et al., 2010; Charil et al., 2010; Glover, 2011; Sandman et al., 2011; Swanson & Wadhwa, 2008; Talge et al., 2007). Our summary of these data include a significant weakness nearly uniformly evident in this research area: With the rare exception of a few studies that use an objective quantification of stressful life events (or animal models), results from the majority of articles are based on maternal self report, as opposed to standardized, observer-based, clinically-relevant assessments, and thus are difficult to interpret regarding what level of maternal prenatal distress is significant for child neurocognitive development. The issue is confounded by the use of different instruments to measure distress and results coming from samples that vary with respect to demographic and social-economic factors.

In a prospective study from 2001, high self-reported anxiety during late pregnancy (defined as 1 SD above the mean on Spielberger's State Trait Anxiety Scale (STAI) (Spielberger, 1983)) was associated with decrements at 24-months old on the Mental Development Index (MDI) of the Bayley Scales of Infant Development, which assesses sensory-perceptual skills, memory, learning, problem-solving ability, object constancy, vocalization, and language development (Brouwers, van Baar, & Pop, 2001). Twenty-two percent of children from prenatally anxious mothers had a developmental delay of 3 months, whereas only 6% of children from nonanxious women scored in this range. Late pregnancy anxiety also predicted decrements in attention at 12 months, as judged by the Behavioral Rating Scale (BRS) associated with the Bayley (although no differences emerged at this age on the MDI tests) (Brouwers et al., 2001). The authors interpret the more significant Bayley findings at 24 versus 12 months as a result of greater variability in infant behavior in older children, allowing for an adequate range for assessment, although they acknowledge the possibility of a longer period of child exposure to maternal postnatal anxiety predicted from the prenatal period and influencing child development. In another recent report, pregnancy-specific anxiety (e.g., worries about the health of the baby), but not STAI–rated anxiety, depression, or perceived stress), was associated with infant mental development at 12 months on the Bayley Scales such that higher pregnancy–specific anxiety early in pregnancy (prior to 16 weeks) judged on a 10–40 point Likert scale was associated with lower MDI scores at 12 months. Specifically, at gestational week 13, a 5-point increase in pregnancy specific anxiety was associated with a 2-point decrease on the MDI. Herein too, although, there were no associations between the maternal prenatal factors and infant development assessed at earlier periods (e.g., 3 and 6 months old) (Davis & Sandman, 2010) (See Table 1).

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Table 1 Prenatal maternal distress: offspring outcomes

	Effects on brain-based measures	Effects on cognitive measures
Distress (maternal report)		
Anxiety	At birth, variation in Auditory Evoked Responses slow wave activity in response to mother versus stranger voice (Harvison et al., 2009); brainstem evoked responses to auditory stimuli indicative of faster processing (DiPietro et al., 2010)	Lower scores on the Mental Development Index of the Bayley Scales at 24 months (Brouwers et al., 2001)(though one study showed higher scores at 24 months) (DiPietro et al., 2006); poor attention at 12 months on a behavior rating scale (Brouwers et al., 2001)(; ADHD symptoms at 6.5 (O'Connor et al., 2003) and 8–9 years old (van den Bergh & Marcoen, 2004)
Pregnancy–specific anxiety	Reduced gray matter in specific areas of the cortex at 6–9 years old (Buss et al., 2010)	Lower scores on the Bayley at 12 months (Davis & Sandman, 2010)
Stress		Lower scores on the Bayley at 8 (Huizink et al., 2003) and 14–19 months (Bergman et al., 2007)
Distress (objective measure)		
Stressful events		Lower scores on the Bayley at 24 mos (Laplante et al., 2004) and on the Weschler IQ test at 5.5 years old (Laplante et al., 2008)
Stress (animal studies)		
Rodents	Altered synaptic plasticity, particularly in the hippocampus (Yang et al., 2006); decreased hippocampal neurogenesis (Lemaire et al., 2000); reduction in dendritic arborization and synaptic loss in the hippocampus (Barros et al., 2006)	Impaired learning and memory retention (Cherian et al., 2009; Hayashi et al., 1998; Yang et al., 2006)
Nonhuman primates	Deteriorization of pyramidal neurons in the fetal hippocampus and smaller hippocampal volumes at 2 years old (Coe et al., 2003)	Poorer orientation, shorter orienting episodes, increased distraction, respond slowly to novel stimuli (Schneider, 1992; Schneider & Coe, 1993; Schneider et al., 1999)

Other studies also report neurocognitive impairments associated with exposure to antenatal maternal distress: lower scores on the Bayley MDI and Psychomotor Development Index (PDI) at 3, 8, 14–19, and 24 months of age (Buitelaar, Huizink, Mulder, de Medina, & Visser, 2003; Huizink, Robles de Medina, Mulder, Visser, & Buitelaar, 2003) (Bergman, Sarkar, O'Connor, Modi, & Glover, 2007). In children 6.5 (O'Connor, Heron, Golding, & Glover, 2003) and 8–9 years old (van den Bergh & Marcoen, 2004), maternal prenatal anxiety is associated with maternal reports of attention deficit disorder (ADHD) symptoms, a possible sequelae to underlying weaknesses in neurocognitive functioning (van den Bergh & Marcoen, 2004; van den Bergh et al., 2006; O'Connor et al., 2003). Specifically, pregnant women at 32 weeks gestation scoring in the top 15% on an anxiety scale similar to the STAI went on to have children with greater rates of inattention/hyperactivity symptoms at 6.5 years old (Odds Ratio for boys, 1.85, for girls, 2.10). This prenatal influence remained significant for boys, although not for girls, after accounting for multiple assessments of maternal postpartum distress (O'Connor et al., 2003). In the study with 8–9 year old children, higher maternal anxiety on the Dutch version of the STAI at 12–22 gestational weeks was associated with children having ADHD symptoms based on maternal, teacher, and observer reports (van den Bergh & Marcoen, 2004). Finally, some researchers have approached the assessment of prenatal stress without the reliance on self-report methods, instead using objective measures based on a characterization of exposure negative life events following traumatic events (e.g., lack of electricity or displacement following an ice storm in Canada). With this approach, greater stress during pregnancy predicted poorer neurocognitive capacities at 2 years of age using the Bayley Scales (Laplante et al., 2004); levels of objectively measured stress (although not self-reported stress) accounted for 27.5% and 41.4% of the variance on the MDI for those infants whose mothers experienced the Canadian ice storm in the first or second trimester, respectively (Laplante et al., 2004). The inverse association between objectively measured stress in relation to the ice storm and cognitive development also was evident when the children were tested at 5.5 years of age using the Wechsler Scale for preschoolers, although it is important to note that all children scored within the normal range (Laplante, Brunet, Schmitz, Ciampi, & King, 2008).

Of the few brain-based studies of prenatal distress effects in humans (relative to the number of such projects in the prenatal nutrition domain), one reported different electroencephalographic patterns in response to auditory stimuli (mother's vs. a stranger's voice) between neonates exposed to low and high maternal prenatal anxiety (Harvison, Molfese, Woodruff-Borden, & Weigel, 2009). Specifically, neonates of women with low prenatal anxiety (also based on a self report scale similar to the STAI and defined as below the manual's set point for the

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highest level of mild anxiety) demonstrated more negative frontal, event-related potential (ERP) low wave activity on hearing their mother's versus a stranger's voice, a finding the authors interpreted as indicating greater attentional allocation given to the mother. Infants of high anxious women showed the opposite pattern, that is, greater negative activity to their mother's voice, which was interpreted as consistent with later difficulties in the sphere of attention as it mediates self regulation capacities seen in older children with prenatal distress exposure (van den Bergh, Van Calster, Smits, Van Huffel, & Lagae, 2008). However, citing work from one of our labs (MG) (Deregnier, Nelson, Thomas, Wewerka, & Georgieff, 2000; Siddappa et al., 2004), Harvison et al. note the uncertainty regarding which neurocognitive processes are implicated in neonatal auditory ERP components [we view it as reflecting emerging components of recognition memory (see below)], and the directionality and interpretation of the expected differences in responses related to the different stimuli (mother versus stranger).

In contrast, DiPietro et al. showed that higher prenatal distress (composite scores of self-reported anxiety and depressive symptoms) were associated with higher Bayley MDI and PDI scores at age 2 (accounting for small effects, 5.7–6.8% unique variance) (DiPietro, Novak, Costigan, Atella, & Reusing, 2006), and brainstem evoked responses to auditory stimuli indicative of faster processing, interpreted as accelerated neurologic development (DiPietro et al., 2010). On the other hand, pregnancy specific anxiety was associated with lower PDI scores (DiPietro et al., 2006), although the authors interpret these data as anomalous and possibly meaningful only as predictive of future mother–child interactions which, in turn, affected psychomotor development. Importantly, participants in this study were from a middle class population whose 'high stress' may not be comparable to that experienced by those in lower SES groups in other studies. Interestingly, in the ice storm studies from Canada, results showed a trend toward mid–level maternal prenatal stress, versus more significant stress levels, to be facilitative of development (Laplante et al., 2008), and in some animal studies, short–lasting, 'mild' prenatal stress exposure is associated with enhanced neurogenesis of hippocampal neurons, whereas long–lasting, 'severe' stress is related to detrimental effects in this brain region (Calabrese, 2008).

Most recently, a report based on MRI findings with children whose mothers were followed throughout pregnancy demonstrated that pregnancy–specific anxiety (as assessed on the 10–40 point Likert scale previously described), experienced at 19 weeks gestation, predicted reduced gray matter density in specific areas in the cortex, as well as in the left middle temporal lobe, extending to the entorhinal cortex, and to the parahippocampal gyrus at 6–9 years of age (Buss, Davis, Muftuler, Head, & Sandman, 2010). These results were region–specific, as there was no association between prenatal stress and overall measures of gray matter. No cognitive data were presented, although these brain areas, in particular, the prefrontal cortex and medial temporal lobe, play central roles in memory and attention. The possibility must be considered that the prenatal maternal factor primarily 'foreshadows' qualities of the long-term postnatal environment, which really are the agents of influence. (There is a burgeoning literature on research with animals and humans aiming to tease apart the prenatal and postnatal environmental influences on children's development (e.g., Bosch et al., 2012; Laurent et al., 2012).

Animal studies on the effects of prenatal maternal stress on offspring development corroborative the human findings, and, through their experimental design, provide causal evidence. These studies reveal similar – although more specific – results: variations in memory, attention, as well as global indices of psychomotor and mental functioning. Rodent studies using restraint or crowding to induce acute or chronic stress in pregnant rats show that prenatal stress results in impaired memory retention and acquisition (Cherian, Bairy, & Rao, 2009; Hayashi et al., 1998; Yang, Han, Cao, Li, & Xu, 2006). Nonhuman primate infants, whose mothers were exposed to repeated or acute stress, exhibit poorer orientation, have shorter duration of orienting episodes, are more distractible, and respond more slowly to novel stimuli than infants of prenatally undisturbed mothers (Schneider, 1992; Schneider & Coe, 1993; Schneider, Roughton, Koehler, & Lubach, 1999).

In animal models, the neurobiology underlying the cognitive impairments is relatively well described, and, as already indicated, key processes of brain development are affected. Prenatal stress exposure appears to alter synaptic plasticity and enhance the effects of acute stress on synaptic plasticity in the hippocampus, which is thought to be, in part, the mechanism for the impaired spatial learning and memory seen in prenatally stressed offspring (Yang et al., 2006). Prenatal stress exposure also has been shown to decrease hippocampal neurogenesis in adult rats (Lemaire, Koehl, Le Moal, & Abrous, 2000) and juvenile monkeys (Coe et al., 2003), resulting in reduced hippocampal volume. Prenatal stress exposure also is associated with a reduction in dendritic arborization and synaptic loss in the hippocampus (Barros, Duhalde-Vega, Caltana, Brusco, & Antonelli, 2006). In the Rhesus monkey, prenatal stress leads to deterioration of pyramidal neurons in the fetal hippocampus. Even at 2 years of age, dexamethasone exposed monkeys – those exposed to an injection of the synthetic steroid hormone dexamethasone to model the stress-based release of the stress hormone corticosterone – still demonstrate smaller hippocampal volumes on MRI and secrete higher levels of cortisol when stressed (Coe et al.,

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2003). These effects are long-lasting,as they are observed over the entire lifespan of the offspring (Lemaire et al., 2000). Prenatal stress exposure can induce long-term changes in various neurobiological systems of the offspring, including the hypothalamic–pituitary–adrenal (HPA) axis, cerebellum, and hippocampus (Day, Koehl, Deroche, Le Moal, & Maccari, 1998). Increased basal and stress-induced plasma concentrations of adrenocorticotropin (McCormick & Mathews, 2007), prolongation of stress-induced corticosterone secretion (Maccari et al., 1995; McCormick & Mathews, 2007; Weinstock, Matlina, Maor, Rosen, & McEwen, 1992), and decreased binding capacity of hippocampal corticosteroid receptors (Maccari et al., 1995), also have been reported.

The pathways by which maternal prenatal distress may affect infant neurocognitive development are under intense investigation. One of the primary hypotheses is distress-linked activation of the maternal HPA axis (O'Donnell, O'Connor, & Glover, 2009), which also can impact maternal nutrient absorption, see below. Animal studies using intramuscular injection of dexamethasone show dose–dependent, inversely associated changes in the number of hippocampal neurons (Uno et al., 1990) and a reduction in hippocampal volume (Uno et al., 1994). On the other hand, the injection of stress-equivalent levels of corticosterone into adrenalectomized, pregnant rats can reproduce behavioral effects in offspring, such as increased fear reactivity, but not learning effects, as tested by object recognition (Salomon, Bejar, Schorer-Apelbaum, & Weinstock, 2011).

Several studies with humans have found associations between elevated maternal cortisol and decrements in infant neurocognitive development, that is, lower scores on the Bayley MDI (Bergman, Sarkar, Glover, & O'Connor, 2010; Davis & Sandman, 2010; Huizink et al., 2003). However, in two articles reporting maternal distress, cortisol, and distress exerted independent effects, and in the Davis and Sandman study (Davis & Sandman, 2010), as in others (Davis & Sandman, 2010; Davis et al., 2007; Kivlighan, DiPietro, Costigan, & Laudenslager, 2008; Petraglia et al., 2001; Werner et al., 2012), maternal distress and cortisol levels were, for the most part, not associated. These findings indicate that other factors, such as increased maternal catecholamines, or changes in placental functioning (Glover, Bergman, Sarkar, & O'Connor, 2008; Glover, O'Connor, & O'Donnell, 2009), may be necessary to produce neurocognitive effects in the offspring related to maternal prenatal distress. Specifically, one recent study showed that pregnant women's anxiety strongly moderates the association between maternal plasma and amniotic fluid cortisol such that there was little relationship in low anxious women, and a very strong association in high anxious women (Glover et al., 2008). This novel finding indicates that maternal distress may affect placental functioning, possibly via regulation of a placental enzyme, 11β HSD-2, the main barrier to the placental passage of cortisol (Glover et al., 2008).

Taken together, there is substantial human and animal data showing that maternal prenatal distress has a significant influence on infant neurocognitive development. Animal studies have allowed for the characterization of the underlying neurobiology of these effects, whereas brain-based studies with humans are beginning. That these neurocognitive outcomes overlap with those associated with inadequate maternal nutrient intake is rarely considered.

Prenatal nutrition and effects on brain and neurocognitive development All nutrients are important for neuronal and glial cell growth and development, but some have more well-described effects during the prenatal period, specifically, on brain circuitry involved in basic neurocognitive processes relevant to behavioral adaptation (Table 2) (Georgieff & Rao, 2001). Across brain regions, deficits in maternal nutrient intake early in pregnancy have a greater impact on cell proliferation, and thus, cell number, whereas deficits later in pregnancy affect cell differentiation, including size and complexity, which, in the case of neurons, includes synaptogenesis and dendritic arborization (Georgieff & Rao, 2001).

Similar to research in prenatal distress exposure, the significance of maternal nutrient intake for offspring development is evident in recent studies with humans, and has been established through animal studies that allow for investigation of the mechanisms that underlie these effects. Moreover, in nutrition studies with humans, in addition to assessment of general abilities, specific cognitive tasks coupled frequently with electrophysiological measurement have been used to characterize variation in specific cognitive skills, such as recognition memory or cross-modal learning.

The list of nutrients with known prenatal effects on child neurocognitive development is extensive (i.e., copper, protein, iodine, B vitamins, folate etc.; see (Georgieff, 2007), for a review). In this discussion, we highlight a few selected nutrients including: fats, including long chain polyunsaturated fatty acids (LC-PUFA), protein and zinc, iron, and choline. These nutrients were chosen for the following reasons: (a) they have demonstrated effects on brain development; (b) they are commonly deficient as studies of typical nutrient consumption patterns of pregnant women in the U.S. and U.K. suggest that, for substantial proportions of this population (50–70%), dietary recommendations for most of these micronutrients are not met (Derbyshire, Davies, Costarelli, & Dettmar, 2009; Siega-Riz, Bodnar, & Savitz, 2002); (c) they have a role in stress responses; and (d) their metabolism may be altered by stress. The following sections describe the strictly nutritional effects of these selected nutrients on brain

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Table 2 Nutrients with particularly large effects on early brain development/behavior and the interaction with the stress response

	Effects on brain development (Fuglestad et al., 2008)	Effects on behavior	Stress alters nutrient metabolism	Deficiency alters stress response
Macronutrients				
Specific fats (LC-PUFA)	Myelin, synaptosomes	Augmentation aids attention at 1, 2 years old; too much may accelerate cognitive decline (Colombo et al., 2004; Helland et al., 2003; Niculescu & Lupu, 2009)	No	Yes
Protein	Structure, neurotrophic factors	IUGR associated poor visual recognition memory, lower scores on Weschler at 7 years old (Fuglestad et al., 2008)	Yes	Yes
Glucose	Primary fuel/energy source		Yes	Yes
Micronutrients				
Zinc	Growth factors, synaptic boutons	Delays in attention and motor development; poor short term memory in animals (Golub et al., 1985; Kirksey et al., 1994)	Yes	Yes
Iron	Myelin, monoamine synthesis, energy metabolism	Lower global intelligence scores; poor scores on attention and motor development at age 5; decrements in recognition memory; lack of discrimination to mother's voice based on ERP protocol; poor delayed imitation recall memory at 1 year old (Nelson et al., 2000; Rizzo et al., 1997; Siddappa et al., 2004; Tamura et al., 2002)	Yes	Yes
Copper	Iron transport		No	No
Iodine	Thyroid synthesis		No	No
Vitamins				
Choline	Methylation, myelin, neurotransmitters	(in rodents) decrements in visual–spatial and auditory memory (Zeisel, 2009)	Yes	Yes
Vitamin A	Structural development, anti-oxidant		No	No
Folate	One-carbon metabolism		Yes	No

development in the nonstressed human and animal model. In subsequent sections, we will discuss the two-way interaction between stress and metabolism of these nutrients.

Fats Long-chain polyunsaturated fatty acids (LCPUFAs) are a type of macronutrient that has been specifically linked to neurodevelopment. LCPUFAs include docosahexenoic acid (DHA) and arachidonic acid. The mother delivers these compounds transplacentally especially during the last trimester of pregnancy. They are essential in cell membranes, intracellular communication, signal transduction, and monoamine metabolism, thus affecting neurodevelopment (Carlson, 1997; Innis, 2003). They are critically important for visual development in primates and likely humans (Neuringer, Connor, Lin, Barstad, & Luck, 1986).

There is evidence that prenatal LCPUFA supplementation affects neurocognitive development in humans. In a randomized, double-blinded study of DHA supplementation, children born to women who received DHA supplementation during pregnancy and 3 months of lactation performed better on neurocognitive tasks (mental processing composite of the Kaufman Assessment Battery for Children) at 4 years of age (Helland, Smith, Saarern, Saugstad, & Drevon, 2003). Additional maternal supplementation studies have correlated maternal DHA levels at the time of birth with the child's performance on attentional tasks at 1 and 2 years of age (Colombo et al., 2004).

While certain types of fats, such as LCPUFAs, may be beneficial to the developing brain, there is mounting evidence that an overall high fat diet including increased saturated fat may induce deleterious effects on the developing brain. A few epidemiologic studies suggest that a fat-rich diet may accelerate age-related neurocognitive decline and the onset of dementia in humans (Kalmijn, 2000). Fewer data are available in humans regarding the role of obesity and high fat diets in brain development. Recent animal data demonstrate altered neurodevelopment in rodents exposed prenatally to a high fat diet. In study by Niculescu et al., rodents were fed 8 weeks of a high-fat (60% of calories) diet prior and during gestation. This maternal exposure induced small for gestational age status and significant changes in fetal hippocampal development as indicated by regional-specific changes in proliferation

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of neural precursors, decreased apoptosis, and decreased neuronal differentiation within the dentate gyrus (Niculescu & Lupu, 2009). Additional studies examining the role of inflammation in high fat diets, leading to potential developmental consequences, are being undertaken currently.

Protein Protein is typically used by the human body for somatic (tissue) protein and serum protein synthesis. The effect of protein-energy status on neurodevelopment and brain growth has been studied extensively. The most significant neurocognitive effects of protein-energy malnutrition appear when imposed on a rapidly growing brain as during fetal and early postnatal life. Restriction of macronutrients, especially protein, during fetal life result in deceleration of growth termed 'intrauterine growth restriction' (IUGR). Maternal hypertension accounts for as many as 75% of the cases of IUGR (Fuglestad et al., 2008).

The neurocognitive effects of restricted fetal nutrition delivery and impaired brain growth have been linked in multiple studies. Research has demonstrated a fivefold higher prevalence of mild neurocognitive abnormalities at 2 years of age after fetal IUGR (Spinillo et al., 1993), weak preference for novelty on visual recognition memory tasks (Gottleib, Blasini, & Bray, 1988), and reduced verbal ability (Pollitt & Gorman, 1994) in IUGR infants. Strauss and Dietz (Strauss & Dietz, 1998) matched IUGR infants to sibling controls who were appropriate weight for age, thus attempting to control for postnatal environment, and demonstrated significant decrease in broad measures, such as the Wechsler Intelligence Scale, for Children IQ and Bender-Gestalt scores at 7 years if head growth had been compromised in the fetal period, but no effect if intrauterine head growth had been spared.

The neuroanatomic bases of developmental impairment with early protein-energy malnutrition have been supported by animal models of IUGR and human autopsy studies. The human studies show significant reductions in brain DNA, RNA, and protein content (Winick & Nobel, 1966). Certain areas (cerebellum, hippocampus, cerebral cortex) demonstrate more profound effects, suggesting the developing brain prioritizes protein and energy during times of deficiency. Animal models support findings of reduced neuronal DNA and RNA, as well as reduced mRNA for neuronal and glial structural proteins, reductions in synaptic structures, number, and neurotransmitter peptide production (Bass, Netsky, & Young, 1970; Jones & Dyson, 1981; Wiggins, Fuller, & Enna, 1984). Malnutrition also downregulated growth factors of the CNS that is critical for normal brain development (Nishijima, 1986).

It is important to recognize that the neurologic effects discussed above may be due primarily to isolated protein-energy malnutrition; however, it is more than likely a contribution from concurrent micronutrient deficiencies or chronic intrauterine hypoxia. One of the micronutrients that most commonly accompany protein malnutrition is zinc deficiency.

Zinc Although indices of overall intelligence do not appear to vary in relation to prenatal zinc deficiency, some data indicate that infants born to zinc–deficient mothers show delays in attention and motor development (Kirksey et al., 1994). Animal research demonstrates that gestational zinc deprivation is associated with decrements in learning (Lokken, Halas, & Sandstead, 1973; Sandstead, Fosmire, McKenzie, & Halas, 1975), including poor short-term memory (Golub, Gershwin, Hurley, Hendrickx, & Saito, 1985).

Studies assessing zinc biology in animal and primate models have shown this nutrient to be a cofactor in enzymes that mediate protein and nucleic acid biochemistry (Georgieff, 2007). Deficiencies in zinc nutrition during prenatal development lead to decreased brain DNA, RNA, and protein content (Duncan & Hurley, 1978). Zinc regulates insulin–like growth factor I, and growth hormone receptor gene expression (McNall, Etherton, & Fosmire, 1995). Neuronally, presynaptic boutons are dependent on adequate zinc for delivery of neurotransmitters to the synaptic cleft (Frederickson & Danscher, 1990). Inadequate maternal prenatal zinc leads to reduced regional brain mass and truncated dendritic arbors in the cerebellum, limbic system, and cerebral cortex in the offspring (Frederickson & Danscher, 1990) Overall, zinc is particularly important for the development of the medial temporal lobe, frontal lobe, and cerebellum (for review of these findings, see (Georgieff, 2007)).

Iron Inadequate prenatal iron and/or maternal prenatal diabetes (associated with perinatal iron deficiency) is associated with decrements in measures of global intelligence (Rizzo, Metzger, Dooley, & Cho, 1997). Infants with cord ferritin concentrations in the lowest quartile had inferior neurodevelopment at age 5 in domains of language, fine and gross motor movement, and attention (Tamura et al., 2002). In a series of reports, our group (MG) has sought to identify the specific neurological processing delays associated with inadequate prenatal iron that may underlie these decrements in functioning. We have shown differences in hippocampally-based recognition memory development in infants of diabetic mothers. Infants of diabetic mothers born with iron deficiency had impaired auditory recognition memory for their mother's voice at birth as assessed using an ERP paradigm (Siddappa et al., 2004). Control infants showed a significant negative slow wave response to hearing a stranger's voice compared with their mother's, whereas the iron deficient group did not show this discrimination (Siddappa et al., 2004). At 12 months, newborn ERP differences predicted

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the Bayley PDI (Deregnier et al., 2000). Similarly, 6-month-old infants viewed photos of the maternal versus a stranger's face (Nelson et al., 2000). Infants of healthy women had different ERP responses to the two stimuli, whereas the offspring of women with diabetes did not, again implying a failure of discriminative memory.

Other reports show associations between maternal prenatal iron deficiency and reduced, cross-modal, imitative, and explicit (delayed imitation recall) memory performance in the first postnatal year (DeBoer, Wewerka, Bauer, Georgieff, & Nelson, 2005; Nelson, Wewerka, Borscheid, Deregnier, & Georgieff, 2003; Nelson et al., 2000) as well as poorer performances on tests of general motor and neurocognitive development, such as on the Bayley Scales (Deregnier et al., 2000; Siddappa et al., 2004). Most recently, we found behavioral and electrophysiological effects at 40 months of age: infants born to diabetic women showed impaired explicit memory for event sequences when the task demands were high, and exhibited longer latencies and less positive slow wave activity, consistent with delays in encoding and recollective processes (Riggins, Miller, Bauer, Georgieff, & Nelson, 2009).

Rodent models of gestational dietary iron deficiency (which isolates the iron effect from the glucose intolerance and hypoxia also involved in diabetes) show decrements in spatial navigation, trace fear conditioning (learning), and procedural memory (Felt & Lozoff, 1996) (Beard et al., 2006; McEchron, Cheng, Liu, Connor, & Gilmartin, 2005). These behavioral effects suggest functional abnormalities in the hippocampus and striatum, as well as neurochemical abnormalities (Felt et al., 2006; Georgieff, 2007; McEchron, Goletiani, & Alexander, 2010; Rao, Tkac, Townsend, Gruetter, & Georgieff, 2003). Myelination, dendritogenesis, synaptogenesis, and neurotransmission – all involved in the development of the fetal brain – depend on sufficient availability of iron (Lozoff & Georgieff, 2006). Iron deficiency in rodents has been shown to produce less linear growth of dendrites, as well as more tangled dendritic branches in the hippocampus, smaller overall brain weight, and smaller hippocampal weight (Jorgenson, Wobken, & Georgieff, 2003). In addition to these structural abnormalities, biochemical effects include reduced oxidative metabolism in the hippocampus and frontal cortex (Georgieff, 2007) and altered fatty acid and myelin profiles throughout the brain have been observed (Georgieff, 2007; Wu et al., 2008).

Choline Choline is considered part of a category of nutrients termed one-carbon metabolites. Choline influences cell proliferation in the developing brain, (Zeisel, 2004). The application of the basic research in rodents on maternal prenatal choline deficiency has yet to be applied to humans in the areas of neurocognitive development. The offspring of the choline-deficient dams show decrements in visual-spatial and auditory memory throughout the rest of their lives (Zeisel, 2009).

In contrast, significant increases in maternal choline intake during pregnancy – 4× the typical level – are associated with enhanced visual spatial and auditory memory that also persists throughout the rodents' lives (Zeisel, 2009). Rodent offspring whose mothers were fed choline–inadequate diets exhibit less mitosis in the hippocampus, septum, striatum, anterior neocortex, and mid-posterior neocortex and more apoptosis in the hippocampus and septum than their nondeficient counterparts (Albright, Friedrich, Brown, Mar, & Zeisel, 1999; Albright, Tsai, Friedrich, Mar, & Zeisel, 1999; Craciunescu, Albright, Mar, Song, & Zeisel, 2003). Decreased mitosis in the anterior neocortex and increased apoptosis in the septum persist even after choline fortification (Craciunescu et al., 2003). Choline deficiency may result in reduced weight and/or size of the hippocampus and other related brain areas (Albright, Tsai, et al., 1999) (Albright, Friedrich, et al., 1999; Craciunescu et al., 2003).

Overall, variation in maternal dietary choline intake is thought to influence fetal brain development by four mechanisms: (a) perturbation of acetylcholine biosynthesis, (b) changes in membrane synthesis, (c) accumulation of toxic levels of homocysteine, and (d), perturbation of methylation reactions [See for a review (Zeisel, 2009)]. The latter mechanism, by which choline maybe acting as a methyl donor, is under intensive study, as such epigenetic transformations can be long–lasting and heritable (Bale et al., 2010; Zeisel, 2009). Choline has been much more extensively studied in this context compared with other one-carbon metabolites (e.g., folate). The effect of psychological stress on one-carbon metabolism during development has not been studied. However, a relation between activation of the HPA axis (cortisol) and declining choline levels has been reported in adults (Ozarda Ilcol, Ozyurt, Kilicturgay, Uncu, & Ulus, 2002). The decline in serum choline concentration in humans during and after surgery is associated with the elevation of cortisol, adrenocorticotropic hormone, prolactin, and beta-endorphin concentrations. Thus, there may be reason to explore the interaction of cortisol and choline during critical periods of neurodevelopment.

Prenatal maternal nutrition and distress: two exposures with similar outcomes

As evidenced by human and animal studies, prenatal exposure to maternal distress and poor nutrient status both are associated with decrements in neurocognitive development, particularly in relation to memory and learning, and specifically with regard to variation in the structural, functional, and neurochemical aspects of the hippocampus. Compared with human research of prenatal maternal distress, that examining prenatal maternal nutrition effects

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has utilized far more targeted cognitive tasks and electrophysiological methods that can characterize specific brain -behavior differences, in addition to general assessments of overall neurocognitive development. No studies to date have simultaneously studied these prenatal exposures in relation to offspring neurocognitive development; however, the overlapping outcomes is one factor strongly indicating the need to determine if there are effects of maternal distress or poor nutrition when studied in the presence of the other.

A biological perspective: the nexus of nutrient regulation and stress physiology

We have described numerous studies that show evidence of independent effects of prenatal maternal distress and nutrition on children's brain-behavior development. However, at the level of biology, the hormonal, cellular, and molecular pathways that mediate these neurocognitive-behavioral outcomes are profoundly interactive – and this is rarely discussed in the extant literature. This biological 'cross talk' between maternal distress and nutrition processes further supports the importance of the dual assessment of these exposures (Table 1).

Biological considerations: a role for maternal distress in nutrient availability. Recent research suggests that noninfectious psychological stress responses utilize many of the same pathways as infectious stress to alter basic processes of nutrient metabolism, including absorption and prioritization. For example, evidence that maternal stress during pregnancy can influence the postpartum iron status of infants has been demonstrated in a nonhuman primate model (Coe, Lubach, & Shirtcliff, 2007). The mechanism is thought to be due, in part, to decreased maternal iron absorption and maternal iron sequestration potentially mediated by hepcidin. Hepcidin is a critical iron regulatory hormone that responds to both body iron status and inflammatory states to regulate intestinal absorption and within-body tissue distribution. Hepcidin, its receptor, and iron channel ferroportin, work in concert to control the dietary absorption, storage, and tissue distribution of iron. Hepcidin is feedback regulated by iron concentrations in the blood and liver, and by the red blood cell demand for iron. During infection and inflammation, and potentially psychosocial stress, hepcidin and ferroportin expression are modulated to decrease iron availability to invading pathogens. In addition, iron supply for red blood cell precursors is also restricted, thereby contributing to the anemia associated with infections and inflammatory conditions (Ganz & Nemeth, 2009). When experienced in a pregnant woman, this cascade of events is likely to impact infant outcomes as well via reductions in maternal iron stores, and thus less iron availability for the fetus. Conversely, adequate iron status is essential for normal white blood cell and cytokine function (Ceo et al., 2007). Thus, nutritional iron deficiency will blunt the ability of the organism to mount an adequate stress response, illustrating the two-way interaction of nutrition and stress.

There are other examples of the importance of maternal distress in altering maternal nutritional status. Distress, similar to chronic infectious stress, can induce insulin resistance and pro-inflammatory cytokine production with a resultant diversion of amino acids from protein production to maintain a steady carbon source for gluconeogenesis and energy production. This mechanism is supported by rodent models that demonstrate reduced hippocampal dendritic arborization following stress (Weinstock, 2001). In addition, increased cortisol levels promote glycogen and protein breakdown during times of distress, thereby inducing a state of protein catabolism and interrupting the anabolic process of neuronal growth and differentiation. This occurs in part by antagonizing the effect of anabolic hormones, such as insulin, and in part by diverting nutrients that are important for structural protein synthesis toward gluconeogenesis. Such a situation in a pregnant woman would have an impact on her nutrient status, and, consequently that of the fetus. In the fetus, the diversion of nutrients away from protein synthesis (as a result of nutrient shortage and/or exposure to increased maternal, stress-based cortisol levels) may have significant implications for both neuronal and somatic growth.

Finally, maternal prenatal distress can increase the risk for pregnancy induced hypertension (Landsbergis & Hatch, 1996), leading to atheromatous plugging of the placenta, which restricts nutrient delivery and can lead to growth restricted fetuses with micronutrient deficiencies. There is some data to indicate that psychosocial stress is associated with greater uterine artery resistance, which may affect nutrient delivery in the absence of growth restriction (Teixeira, Fisk, & Glover, 1999), although other articles have not confirmed these findings (Harville et al., 2008; Kent, Hughes, Ormerod, Jones, & Thilaganathan, 2002; Monk et al., 2012).

The association between pro-inflammatory cytokines and abnormal fetal neurodevelopment has been suggested by research linking maternal infections during pregnancy with increased risk for schizophrenia and autism (Brown & Susser, 2002; DiCicco-Bloom et al., 2006). In a study of the Rhesus monkey, influenza infection during pregnancy affected neural development in the monkey, reducing gray matter throughout most of the cortex and decreasing white matter in the parietal cortex (Short et al., 2010). In a mouse model with genetically enforced expression of the anti-inflammatory cytokine IL-10, it was shown that in addition to the disruptive effects of excess pro-inflammatory cytokines, a shift toward excess anti-inflammatory signaling in prenatal life also may lead to changes in neurocognitive and behavioral

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development, therefore identifying the balance between pro–and anti–inflammatory cytokines as a critical determinant of the impact on the developing brain (Meyer et al., 2008). Although the degree of maternal immune activation of cytokine pathways due to psychosocial, noninfectious stress remains unclear, it may be an important link to understanding how distress increases the pro-inflammatory state and affects offspring development.

Biological considerations: a role for maternal nutrition in distress exposure In rodent study by Bertram et al., a low protein maternal antenatal diet was associated with decreased expression of 11β HSD-2, a placental enzyme that inactivates cortisol, resulting in increased fetal exposure to maternal cortisol and possibly potentiating the effects of the future child's HPA activity (Bertram, Trowern, Copin, Jackson, & Whorwood, 2001), with ensuing effects on brain development as described above. Another study using a sheep model found that maternal under nutrition early in gestation showed sex-specific HPA axis effects in the offspring with increased adrenocortical responsiveness and output at 2.5 years in females only (Poore et al., 2010). These studies suggest that altered maternal prenatal nutrition can impact infant development via a consequence of nutrition-related changes in fetal exposure to maternal HPA axis functioning (Chadio et al., 2007).

Taken together, these findings focused on biological process of prenatal distress and nutrition indicate that stress-induced maternal malnutrition, and nutrition mediated variation in the biological effectors of the maternal stress system, can have either a global or circuit specific effect on the offspring's developing brain. Nutrition and distress interact in a model analogous to a two-way street in which decreased maternal nutrient supply can lead to alterations in maternal stress–related physiology, whereas increased maternal distress also can lead to alterations in nutrient supply, both of which impact fetal brain development. This level of biological cross–talk further supports dual interrogation of maternal prenatal nutrition and distress in fetal origins studies.

Challenges in the 'Dual Variable' approach to DOHAD research

There are significant challenges to the proposed dual exposure research on maternal prenatal distress and nutrition. We briefly describe these challenges, and some potential responses to them.

Research design

Although it can be methodologically challenging to 'tease apart' the specific influence of one of these factors in the context of the other, statistical approaches exist for doing so, including creating extreme groups, i.e., high distress/poor nutrition and low distress/high nutrition pregnant women. Alternatively, two recent study addressed the issue of statistically 'disentangling' the effects of independent variables when they are highly correlated (Johnson & Meltzer, 2002; Smith, Koper, Francis, & Fahrig, 2009). Other methodological obstacles may exist that inhibit readily embarking on studies of these dual prenatal exposures: questions about the need for added power and the complexity of the study design; concerns about participant burden with the assessment of two significant maternal life domains (i.e., psychological experience and diet) as well as child outcomes. With respect to adequate statistical power and research demands on participants, databases from very large cohorts already exist, which include measures from pregnancy, such as prenatal nutrition and micronutrients as well as distress, i.e., the Norwegian Mother and Child Cohort Study (Magnus et al., 2006), and are currently enrolling participants, i.e., The National Children's Study.

Nutrient assessment

As nutrition assessment most typically occurs outside of the laboratory, the reliability and validity of methods for assessing it can seem daunting. The National Cancer Institute has launched a free, self-administered, web-based, dietary-recall assessment tool modeled on the gold standard – the National Health and Nutrition Examination Survey (Zimmerman et al., 2009). This is an automated program that includes over 1,100 food probes and 10,000 pictures of individual foods of varying portion sizes. With this system, repeat recalls are feasible and the program generates individual-level nutrient and food group estimates based on the United States Department of Agriculture MyPyramid Equivalents Database.

However, the potential fetal brain effects of maternal malnutrition may not be fully realized by consideration of maternal nutrient supply alone. Nutrient delivery to the fetal brain via maternal intestinal absorption, trafficking within the maternal body, transport across the placenta, trafficking within the fetal body and across the fetal blood brain barrier and, finally, assimilation into brain tissue growth, is a complex process involving multiple regulation points. General principles of nutrient uptake and assimilation are important to consider in this regulation. The quantity of nutrients available in the maternal diet mediates only part of the ultimate equation that regulates the intricate cellular growth and differentiation processes within the fetal brain. Many nutrients are not completely absorbed at the level of the gastrointestinal tract; rather their uptake is regulated by various factors, including, as already indicated, in the case of iron, the presence of nonnutritional factors, such as inflammatory cytokines, which can be activated during infection, obesity, and potentially,

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stress. The uptake of some nutrients (e.g., iron) is regulated by overall body stores, responding, by complex molecular signals, to perceived demand in an attempt to match supply requirements without resulting in overload. After nutrients are absorbed, they are trafficked to various organs for utilization. Therefore, in the case of the maternal-fetal unit, simple measurements of maternal nutrient intake may not accurately assess availability for fetal tissue growth and assays of maternal and cord blood levels of the nutrients and/or associated compounds are necessary.

Summary: ecologically valid studies of prenatal nutrition and distress exposure

Maternal prenatal psychosocial functioning and nutrient intake occur in the context of one another. It would be ideal if each of these prenatal exposures could have a unique signature effect on the developing infant brain, but this is unlikely given that they may co-occur, affect the same developing brain regions, e.g., the hippocampus, and within the mother, the biology of distress and nutrient absorption and delivery interact. To produce research with relevance for designing the most ecologically–valid prevention protocols, DOHAD studies should aim to consider simultaneously both exposures, and identify effects of one exposure in the presence of the other, and the impact when they co-occur. Ultimately, the identification of neurocognitive outcomes resulting from prenatal maternal nutrition and distress status will need to follow specific rules of developmental neuroscience. The maternal nutrient deficiency or distress experience must be present during a developmental time period when the brain either requires that nutrient for growth, or is vulnerable to a changed intrauterine environment linked to the biology of maternal distress. The neurocognitive weakness, assessed in behavior, should be subserved by a brain region or process that is known to be affected by the nutrient deficit or altered maternal stress physiology. To reach this cause–effect association, animal, epidemiological, clinical, and cellular studies will need to be engaged – each of them incorporating both exposures into their approaches.

Conclusion

It has been nearly 40 years since the seminal epidemiological research on birth cohorts from the Dutch Hunger Winter of 1944 explored associations between characteristics of pregnant women's lives and offspring's long–term neurocognitive and mental health development (Stein, Susser, Saenger, & Marolla, 1972; Susser & Lin, 1992). On the basis of adult children of women who were pregnant during World War II when food intake from a war–time blockade was reduced to 500–1500 kcal per day, these studies have shown that fetal development during the blockade is associated with a twofold increased risk for neurocognitive disorders (Susser, Hoek, & Brown, 1998). Two interpretations regarding the causal mechanisms of these effects have been suggested, one more dominant than the other: (a) deficiency in many micro– and macronutrients, such as iron and/or overall calorie nutrition (dominant), or (b), maternal distress, secondary to famine (less often cited), each having neurotoxic effects on the developing brain. In this review, we discuss exemplar papers showing significant and overlapping effects on neurocognitive development of exposure to prenatal maternal distress and poor nutrition, yet each paper covers just one of these exposures. With their potential for significant relevance to the prediction and prevention of psychopathology, current DOHAD studies that specifically include both exposures in their design can begin to determine the relative and/or synergistic impact of these prenatal experiences on developmental trajectories– but only if each is studied in the context of the other.

Acknowledgements

Support for this study was provided by NIMH (1R01MH077144-01A2) to C.M.

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Key points

- Maternal prenatal distress and poor nutrition each are associated with similar decrements in children's neurocognitive development, particularly hippocampally–based memory functioning.
- These prenatal experiences exert their influence in the context of one another – with bi-directional influences between biological processes that control nutrient regulation interacting with stress physiology in the mother and the fetus – however, almost uniformly are studied independently.
- For research on the fetal origins of risk for psychopathology to be most ecologically robust, and relevant to informing interventions, their design should simultaneously consider the relative and/or synergistic impact on developmental trajectories of exposure to both of these maternal prenatal experiences.

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Accepted for publication: 20 August 2012

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