IV. THE COGNITIVE IMPLICATIONS OF OBESITY AND NUTRITION IN CHILDHOOD

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ABSTRACT The prevalence of childhood obesity in the United States has tripled since the 1980s and is strongly linked to the early onset of several metabolic diseases. Recent studies indicate that lower cognitive function may be another complication of childhood obesity. This review considers the research to date on the role of obesity and nutrition on childhood cognition and brain health. Although a handful of studies point to a maladaptive relationship between obesity and aspects of cognitive control, remarkably little is known regarding the impact of fat mass on brain development and cognitive function. Further, missing from the literature is the role of nutrition in the obesity-cognition interaction. Nutrition may directly or indirectly influence cognitive performance via several pathways including provision of key substrates for optimal brain health, modulation of gut microbiota, and alterations in systemic energy balance. However, in the absence of malnutrition, the functional benefits of specific nutrient intake on particular cognitive domains are not well characterized. Here, we examine the literature linking childhood obesity and cognition while considering the effects of nutritional intake. Possible mechanisms for these relationships are discussed and suggestions are made for future study topics. Although childhood obesity prevalence rates in some developed countries have recently stabilized, significant disparities remain among groups based on sex and socioeconomic status. Given that the elevated prevalence of pediatric overweight and obesity may persist for the foreseeable future, it is crucial to develop a comprehensive understanding of the influence of obesity and nutrition on cognition and brain health in the pediatric population.

The obesity epidemic continues to affect a remarkably high proportion of the world's population. It is projected that the percentage of adults who are overweight or obese around the world could increase from 33% in 2005 to 58% by 2030 (Kelly, Yang, Chen, Reynolds, & He, 2008). In the United States,

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over 30% of adults are obese and estimates of childhood overweight (≥85th percentile BMI-for-age) and obesity (≥95th percentile BMI-for-age) prevalence stand at approximately 32% and 17%, respectively (Ogden, Carroll, Kit, & Flegal, 2012). Consequently, the estimated deaths attributed to obesity and its comorbidities have increased by 77% since 1991 (Mokdad, Marks, Stroup, & Gerberding, 2004). Given that childhood obesity is projected to nearly double over the next 20 years, accumulation of excess fat mass has become the most pressing public health concern among children in the developed world (Wang, Beydoun, Liang, Caballero, & Kumanyika, 2008).

Although elevated BMI has been associated with adverse neurocognitive outcomes in adults, the impact of obesity on cognitive health in childhood remains unknown (Hildreth, Pelt, & Schwartz, 2012; Jeong, Nam, Son, Son, & Cho, 2005; Stanek et al., 2011). Current knowledge is equivocal and is based on studies that have widely divergent methodologies. Furthermore, the majority of studies in children examining the obesity-cognition interaction fail to assess nutritional intake, which might have independent or synergistic effects on both obesity and cognition. Although the human brain develops rapidly over the first 2 years of life, functional development of the hippocampus and frontal lobe—regions involved in relational memory and cognitive control (inhibition, working memory, and cognitive flexibility)— continues throughout childhood (Bryan et al., 2004; Johnson, 2001; Lenroot & Giedd, 2006; Thatcher, 1991). This protracted functional development may provide critical periods for impact by behavioral factors such as diet. However, the degree to which nutritional intake influences cognitive function throughout the lifespan may also be influenced by the preexisting nutritional and health status of the individual.

CHILDHOOD OBESITY: PREVALENCE AND CLINICAL IMPLICATIONS

Overweight and obesity are clinically defined as excessive fat accumulation that may impair health (Caterson & Gill, 2002). Given the high costs of fat mass assessment techniques, weight adjusted for height [expressed as body mass index (BMI), calculated as weight in kilograms divided by square of height in meters] is most commonly used for identifying overweight and obesity. Due to the variability in height and weight that occurs during growth, assessment of a child's BMI necessitates comparison to a reference population of the same gender and age (Ebbeling & Ludwig, 2008). Following the rapid rise in childhood obesity in the United States during the 1980s and 1990s (Ogden, Flegal, Carroll, & Johnson, 2002), during which obesity increased three-fold, significant increases between 1999–2000 and 2009–2010 were only seen at the highest BMI cut-off and among adolescent males (Ogden et al., 2012). Although a possible link between public health campaigns and

the recent stabilization of obesity prevalence has been suggested in countries including the United States, Switzerland, and Sweden, the reasons for this stabilization remain unclear (Ebbeling & Ludwig, 2008; Péneau et al., 2009). Nevertheless, in the United States, obesity remains a major public health threat since over 9% of all infants and toddlers have a high weight-for-recumbent length and 12% of 2–5 year-olds are considered obese. In addition, the BMI distribution has continually shifted to the right since the 1980s, suggesting that the severity of overweight has increased substantially (Stifel & Averett, 2009). These trends have resulted in a school-aged population that is significantly more obese than their historical counterparts and has a considerably higher risk for earlier onset of chronic disease.

The causes of childhood obesity have been the subject of considerable debate and are covered elsewhere (Harrison et al., 2011). Currently accepted theories implicate the interaction between genetic predisposition and social trends toward higher caloric intake and reduced energy expenditure (Moreno, Pigeot, & Ahrens, 2011). Parental obesity doubles the risk of adult obesity among both obese and nonobese children (Whitaker, Wright, Pepe, Seidel, & Dietz, 1997). Evidence from epigenetics (i.e., the study of stable inheritance of gene expression that occurs without modifications in underlying DNA sequence) indicates that genomes interact with environmental signals to affect subsequent health and disease risk (Jiménez-Chillarón et al., 2012; Wu & Suzuki, 2006). Epigenetic mechanisms include DNA methylation, histone modifications and, more recently, a variety of non-coding RNAs (Jiménez-Chillarón et al., 2012). The impact of such interactions may occur during and/or after intrauterine development. For example, fetal overnutrition as a consequence of maternal obesity may be implicated in the rise of childhood obesity (Danielzik, Langnase, Mast, Spethmann, & Muller, 2002). Also, infants born to women with gestational diabetes have significantly higher fat mass than infants of women without gestational diabetes (Catalano, Thomas, Huston Presley, & Amini, 2003). Maternal consumption of a high fat diet during gestation is related to subsequent excess fat accumulation in rat pups (Wu & Suzuki, 2006), independent of offspring diet. Collectively, there is converging evidence supporting the role of early environmental programming in the development of childhood obesity.

Although childhood obesity often persists into adulthood, the pathological processes of obesity-related morbidities begin in childhood (Biro & Wien, 2010). Obesity is strongly associated with a constellation of metabolic disorders marked by abdominal obesity, glucose intolerance, dyslipidemia, high blood pressure, and elevated proinflammatory markers (Després et al., 2008; Huang, Ball, & Franks, 2007). The early stages of atherosclerosis, the leading cause of cardiovascular and cerebrovascular events, can appear *in utero*, during infancy, or throughout childhood (Napoli et al., 1997, 1999).

Data from adult studies indicates that obesity may also cause structural changes in the brain. In a study in which diffusion tensor imaging (DTI) was used, scientists found among healthy adults that BMI was negatively related to white matter integrity in the corpus callosum and fornix fibers (Stanek et al., 2011). In a longitudinal study, increasing BMI during the onset of menopause was associated with a 15% decrease in cerebral gray matter volume in women after controlling for cardiovascular health markers (Soreca et al., 2009). Obesity and elevated markers of cardiovascular disease increase the risk for incidence of dementia later in life (Fitzpatrick et al., 2009; Whitmer, Gunderson, Barrett-Connor, Quesenberry, & Yaffe, 2005). The evidence for the negative role of obesity in cognitive decline is compelling. However, knowledge of how obesity affects cognition during childhood has only emerged over the last decade, and as such is limited.

COGNITIVE IMPLICATIONS OF OBESITY IN CHILDHOOD

Studies assessing the impact of obesity on cognition vary in the age of children studied (prepubertal or pubertal) and outcomes evaluated (neuro-electric or academic achievement). Most have relied on BMI as the primary measure of obesity, neglecting the influence of body composition or fat distribution. This is a significant limitation, as body composition in children differs by age, gender, and stage of sexual maturity (Ahmed, Ong, & Dunger, 2009; Bacha, Saad, Gungor, Janosky, & Arslanian, 2003; Heyward & Wagner, 2004). Additionally, individuals with excess central adiposity have a substantially higher risk for developing insulin resistance and metabolic syndrome (Després, 2006). To our knowledge, only one study has assessed event-related brain potentials (ERPs; see Chapter 3) among children with or without insulin resistance (Tascilar et al., 2011). Tascilar et al. (2011) investigated alterations in the P3-ERP among 10- to 11-year-olds. The P3 is a positive-going, endogenous ERP component that occurs approximately 300–800 ms after stimulus onset (Hillman, Kamijo, & Pontifex, 2012). In contrast to their healthy weight counterparts, the obese group of children had smaller P3 amplitude and longer P3 latency indicating a decrease in the allocation of attentional resources, and slower cognitive processing/stimulus evaluation speed, respectively. Furthermore, the obese group of children with insulin resistance had smaller P3 amplitude and longer latency compared to the obese group of children without insulin resistance. Kamijo, Khan et al. (2012) assessed cross-sectional relationships between direct measures of adiposity (percent fat mass and central adiposity), cognitive control, and scores on the Wide Range Achievement Test 3rd edition (WRAT3). Following adjustment of confounding variables (age, gender, IQ, SES, VO_{2max}) percent body fat negatively predicted reading and spelling, but not arithmetic.

However, central adiposity negatively predicted performance on all three WRAT3 components. These findings suggest that insulin resistance and fat distribution are associated with cognitive ability in prepubertal children.

Obesity, assessed using BMI-for-age, has been found to be negatively related to cognitive control in children as well (Kamijo, Pontifex et al., 2012a, 2012b; Li, Dai, Jackson, & Zhang, 2008). Using ERPs, Kamijo, Pontifex et al. (2012a) showed that obese children exhibit lower response accuracy in a NoGo task requiring inhibitory control. Specifically, overweight children failed to display the typical frontal distribution for the NoGo P3 relative to the Go P3, indicating that obese status in childhood is negatively and selectively associated with prefrontal inhibitory control. Another aspect of cognitive control, action monitoring, has recently been investigated in relation to obesity. The error-related negativity (ERN) is a neuroelectric measure used to reflect the action monitoring system and larger ERN amplitude and longer reaction time following error detection is indicative of improved cognitive control (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Gehring, Goss, Coles, Meyer, & Donchin, 1993). It was recently demonstrated that obese children exhibit smaller ERN amplitude and lower post-error response accuracy compared to their healthy weight counterparts Kamijo, Pontifex et al. (2012b). Such a finding points to a maladaptive relationship between obesity and aspects of cognitive control and action monitoring processes. Among adolescents, extreme obesity (i.e., BMI-for-age >99th percentile) was related to impairments in attention, mental flexibility, and disinhibition (Lokken, Boeka, Austin, Gunstad, & Harmon, 2009). Li et al. (2008) assessed relationships between academic performance, cognitive functioning, and BMI among a nationally representative sample of 2,519 children aged 8–16 years. Visuospatial organization and general mental ability was negatively related to BMI after controlling for demographics, lifestyle factors, and lipid profiles. Although BMI was not related to academic achievement, overweight children had lower working memory performance as well as lower average scores of the series of four tests (block-design and digit-span subtests of the Wechsler Intelligence Scale for Children, and the reading and arithmetic sections of the Wide Range Achievement Test). Collectively, the aforementioned studies suggest that obesity is implicated in lower performance on cognitive control tasks. However, the impact of obesity on academic achievement has been a controversial topic, and on this front, the evidence has been inconclusive.

Scholastic Outcomes and Obesity in Childhood

There is a paucity of representative datasets that evaluate obesity along with a wide range of school outcomes. The Early Childhood Longitudinal Study—Kindergarten Class (ECLS-K) examined the link between change in

overweight status and school outcomes among a national sample of U.S. elementary school children (Datar & Sturm, 2006). Datar and coworkers assessed changes in weight status over the first 4 years of schooling (kindergarten to 3rd grade). Their findings indicated that girls who moved from normal to overweight status were likely to score lower on standardized mathematics and reading tests, higher on teacher-reported externalizing behavior problems, and lower on teacher ratings of self-control compared to girls who were never overweight. However, there were no differences between girls who were never overweight and those who remained overweight. Additionally, there were no significant findings for boys on the measure of academic performance. A follow-up cross-sectional analysis at 3rd grade showed that the differences between overweight and non-overweight children on math and reading disappeared when individual characteristics were adjusted for (SES, mother's education, etc.) (Judge & Jahns, 2007). The most recent study related to the ECLS-K (kindergarten to 5th grade) considered all five waves of the study and their findings differed by BMI group (never obese, later onset, and persistent), time point (kindergarten, 1st, 3rd, and 5th grades), and gender (Gable, Krull, & Chang, 2012). Girls who displayed later onset of obesity performed more poorly on math assessments at first and third grade. These effects were mediated by interpersonal skills and were accompanied with higher internalizing behaviors. Considering the work by Li et al. (2008), it appears that weight status has a cross-sectional relationship with lower academic performance. However, longitudinal data remain limited and the results from the ECLS-K studies do not implicate obesity as a causal factor in diminished academic outcomes in children.

Recent evidence suggests that the relationship between obesity and cognition may not be unidirectional. In other words, aspects of cognition may instead determine obesity. Graziano, Calkins, and Keane (2010) investigated the role of emotion regulation and sustained attention and inhibitory control in development of obesity among 2-year-olds. Poorer inhibitory control at 2 years was predictive of obese status at 5.5 years. This relationship persisted even after controlling for BMI at 2 years, suggesting that poorly developed self-regulation skills may contribute to the development of pediatric obesity. Guxens et al. (2009) conducted a longitudinal study among 421 Spanish preschool children to assess whether cognition at age 4 would predict changes in BMI at age 6. Children with higher scores of general cognition at age 4 were less likely to be overweight at 6 years of age. After adjusting for maternal education and BMI, children with higher general cognition at 4 years were more likely to maintain a healthy weight status between ages 4 and 6 years. Interestingly, Guxens et al. (2009) did not observe cross-sectional relationships between cognitive function scores and BMI at age 4. An MRI study among 83 young females (18–19 years) showed that weight gain was related to low gray matter (GM) volume in regions implicated in inhibitory control. The

authors concluded that abnormalities in regional GM volumes, but not WM volumes, increase the risk for future weight gain (Yokum, Ng, & Stice, 2011). However, it should be noted that other studies suggest no relationship between weight status and cognitive performance (Gunstad et al., 2008; LeBlanc et al., 2012). Gunstad et al. (2008) failed to find any association between weight status and several markers of cognitive performance (including cognitive control, verbal memory, and attention) among a healthy sample of 6- to 19-year-olds ($N = 478$). Similarly, Leblanc et al. (2012) found no impact of obesity on standardized academic tests among 1963 fourth to sixth graders.

Overall, the evidence for the negative influence of childhood obesity on cognitive function remains equivocal and thus controversial. However, it is recognized that obesity in adulthood is associated with poorer cognitive outcomes later in life including increased risk for dementia (Fitzpatrick et al., 2009; Whitmer et al., 2005). Although the mechanism remains unknown, insulin resistance appears to play a significant role in this pathology (Hildreth et al., 2012). Given that the majority of overweight or obese individuals are insulin resistant (Stefan et al., 2008), identification of modifiable risk factors in childhood could reduce the incidence of cognitive impairment later in life. Most studies in children utilize cross-sectional designs, lack adjustment of key covariates, and rely exclusively on BMI. These limitations notwithstanding, there is growing cross-sectional evidence suggesting that obesity has a weak negative association with cognitive health. Additional research is needed to determine which cognitive processes have greater susceptibility to the effects of overall adiposity and fat distribution.

NUTRITIONAL EFFECTS ON COGNITION

In vitro studies demonstrate that nutrients function as substrates for energy, form precursors for neurotransmitters, and serve in pathways involved in cell signaling and gene transcription in the brain. However, much of what is known *in vivo* is based on animal studies assessing cognitive decline. This focus on aged models has limited the knowledge on the role of nutrition in cognitive function in childhood. Nutritional effects on brain health may involve the composition of the gut microbiota, as well as dietary components.

The Gut Microbiota

The bidirectional signaling between the gastrointestinal tract and the brain is vital for maintaining homeostasis and is regulated by the neural [both central (CNS) and enteric nervous systems (ENS)], hormonal and immunological components. The human gut is home to trillions of microorganisms that

influence host health and disease, including, among others, diet and nutrition, obesity, intestinal diseases, and cancer (Flint, Scott, Louis, & Duncan, 2012). Pertinent to this review, growing evidence supports a key role for the gut microbiota in childhood obesity (Karlsson et al., 2012) and in brain development, including learning and anxiety (Manco, 2012), suggesting that the gut microbiota could be a central mediator, although to date this has not been directly investigated. A recent study demonstrated that the gut microbial species differed between preschool children (age 4–5 years) with excessive body weight ($n = 20$) versus normal weight ($n = 20$). The amount of *Enterobacteriaceae* was significantly higher in those with excessive body weight. In contrast, *A. muciniphila*-like bacteria and *Desulfovibrio* were more abundant in children with healthy BMI. Further, there was a trend for decreased bacterial diversity in children with excessive body weight (Karlsson et al., 2012).

Evidence from animal models provides further insight into the link between gut microbiota and brain development. An essential role for the microbiota in brain development was demonstrated by comparing mice with a conventional microbiota to germ-free mice, which displayed increased motor activity and reduced anxiety and altered expression of genes involved in long-term potentiation in brain regions implicated in motor control and anxiety-like behavior (Bravo et al., 2011; Heijtz et al., 2011; Neufeld, Kang, Bienenstock, & Foster, 2011). Importantly, a critical window exists after which microbial colonization did not reverse the abnormal behavioral phenotype (Heijtz et al., 2011). Additionally, provision of a single lactobacillus species (*L. rhamnosus JB-1*) reduced anxiety- and depression-related behaviors in mice, which did not occur in vagotomized mice, identifying the vagus as a major modulator of communication between gut microbes and the brain (Bravo et al., 2011). Thus, future investigations are needed to define whether differences in the microbiome between lean and obese children impacts brain development and cognitive function.

Neurodevelopment and Nutrient Deficiencies

The development of the brain occurs through several overlapping processes (migration, myelination, and synaptogenesis) that proceed at varying velocities from early gestation into childhood (Lenroot & Giedd, 2006). Over the first 2 years of life, the brain achieves 80% of its adult weight (Dekaban & Sadowsky, 1978). This rapid early development of the brain in relation to the rest of the body emphasizes the need for optimal nutritional intake during pregnancy and early postnatal life. Extensive reviews on nutrients necessary for healthy neurodevelopment have been presented elsewhere (Benton, 2010; Bryan et al., 2004; Georgieff & Innis, 2005; Rao & Georgieff, 2007). However, some micronutrients play especially crucial roles in hippocampal and prefrontal growth and function (Georgieff, 2007).

Neurodevelopment processes provide critical periods of growth during which the brain is especially sensitive to nutritional insult. For example, the closing of the neural tube, which occurs 21–28 days into gestation, requires adequate levels of folate—an essential B vitamin (Benton, 2010). Approximately 300,000 newborns worldwide are affected by neural tube defects (NTDs) often manifesting in the form of spina bifida and anencephaly (Gardiner et al., 2008). Epidemiological evidence shows a decline in the prevalence of NTDs since the U.S. food supply was fortified with folic acid in 1998 (Williams et al., 2002). Maternal intake of folate during early pregnancy has been linked to higher scores on the Peabody Picture Vocabulary Test III (PPVT-III), a test of receptive language that predicts overall intelligence, in children at 3 years (Villamor, Rifas-Shiman, Gillman, & Oken, 2012). However, additional studies are needed to determine whether folate supplementation in childhood enhances performance on specific aspects of cognition and memory.

In addition to folate, lower intake of choline during pregnancy has also been suggested to affect risk for NTDs (Shaw et al., 2009). Choline has wide-ranging functions including neurotransmitter synthesis, cell structure integrity, and conversion to methyl donor betaine (Benton, 2010; Zeisel & Da Costa, 2009). Deficiency of choline during the final stages of gestation in rodents results in poorer memory as an adult (Zeisel & Niculescu, 2006). However, among pregnant women, supplementing with phosphatidyl choline, the main dietary source of choline, from 18 weeks to 90 days postpartum did not result in enhanced cognitive abilities (short-term visuospatial memory, long-term episodic memory, language development, and global development) in their children at 10–12 months of age (Cheatham et al., 2012). Given that 80% of the women supplemented in this study already met their daily choline recommendation at time of supplementation, it remains unknown whether supplementing pregnant women with chronically lower intake of choline would enhance infant brain development. In addition, it is possible that a longer follow-up period would have revealed late-emerging effects. Therefore, additional supplementation studies are needed to elucidate the role of choline in cognitive development in infancy and childhood.

Vitamin B12 plays an important role in fatty acid metabolism and its deficiency causes impaired myelination and demyelination of the spinal cord and the brain (Dror & Allen, 2008; Healton, Savage, Brust, Garrett, & Lindenbaum, 1991). Several mechanisms have been proposed for this effect including reduced phosphatidylcholine synthesis, elevated homocysteine, imbalance of neurotrophic and neurotoxic cytokines, and accumulation of lactate in brain cells (Dror & Allen, 2008). Given that myelination is most active in the first 6 months of life, the brain may be especially susceptible to B12 deficiencies early in life (Lövblad et al., 1997). However, the evidence

for impaired neurological development due to vitamin B12 deficiency in humans is largely based on case studies, and thus the long-term impact of suboptimal intake of vitamin B12 on cognitive development remains unknown.

The role of vitamin D in brain development and function has also been gaining support over the past decade. Early life deficiency has been linked to neuropsychiatric disorders, such as schizophrenia, and deficiencies in adulthood are known to exacerbate Parkinson's disease, Alzheimer's disease, depression, and cognitive decline (Cui, Groves, Burne, Eyles, & McGrath, 2013). The discovery that the brain synthesizes the active form of vitamin D, and expression of vitamin D receptors in the hippocampus suggests it may modulate proteins involved in learning and memory (Langub, Herman, Malluche, & Koszewski, 2001). Although the evidence in early life is limited to rodent models, gestational vitamin D deficiency appears to cause permanent damage by altering the ratio of neural stem cell proliferation to programmed cell death in the brain (Levenson & Figueirôa, 2008). Considering the surprisingly high prevalence of vitamin D deficiency among pregnant women (5% among white and 29% among black women) and newborns (10% and white and 47% among black neonates) in the United States (Bodnar et al., 2007), it is crucial that researchers elucidate whether vitamin D deficiency alters cognitive function in childhood.

Among minerals, iron deficiency is the most common gestational micronutrient deficiency (Rao & Georgieff, 2007; Stoltzfus, 2001). Perinatal iron deficiency has been shown to alter the neurochemical profile of the rat hippocampus resulting in impairments in energy status, neurotransmission, and myelination (Rao, Tkac, Townsend, Gruetter, & Georgieff, 2003). Decrements in memory and learning have also been observed as a function of iron deficiency. Neonatal piglets consuming an iron deficient diet displayed lower acquisition on a hippocampal-dependent spatial T-maze task (Rytych et al., 2012). Among humans, newborns with low amounts of cord ferritin exhibit lower performance on mental and psychomotor tests at 5 years of age (Tamura et al., 2002). Another key mineral, Zinc, is a co-factor in enzymes that mediate protein and nucleic acid synthesis (Sandstead, 1985). Children born to zinc deficient mothers show decreased preferential looking behavior suggesting that zinc deficiency selectively affects hippocampal function (Merialdi et al., 2004).

In addition to micronutrient inadequacies, protein/energy malnutrition between the third trimester and 2 months of postnatal life has enduring detrimental effects on global deficits in motor control and language development (Grantham-McGregor & Baker-Henningham, 2005). In summary, brain structures displaying rapid growth during early childhood such as the hippocampus and cortex appear especially vulnerable to nutritional insult (Georgieff, 2007; Gotlieb, Biasini, & Bray, 1988; Pollitt & Gorman, 1994).

Nutrients and Cognitive Function in Children

Children in developed countries rarely present with gross nutritional inadequacies, and supplementation in the absence of clinical deficiency remains a controversial topic. Nevertheless, the search for nutrients that enhance cognitive performance during growth is important because functional development of the hippocampus and frontal lobe continues throughout childhood (Bryan et al., 2004; Johnson, 2001; Lenroot & Giedd, 2006; Thatcher, 1991). Breast milk is the optimal form of nutrition for the infant and its nutrient profile provides the basis for current nutrient recommendations for children younger than 2 years (IOM (US), Panel on Macronutrients, 2005). However, by 6 months of age, half of infants are consuming fortified infant formula (Li, Darling, Maurice, Barker, & Grummer-Strawn, 2005). Furthermore, most studies of breastfed infants lack cognitive assessment of the child or mother. Few randomized controlled trials have been conducted and much of the evidence is based on observational studies. According to a meta-analysis, breast-fed infants may score 2–5 points higher on cognitive developmental tests compared to their non-breast-fed counterparts (Anderson, Johnstone, & Remley, 1999). This difference may be even higher for children who are born preterm (Lucas, Morley, Cole, Lister, & Leeson-Payne, 1992). After stratifying children based on breastfeeding duration and gestation status, preterm infants who were breast-fed performed better on naming vocabulary, pattern recognition, and picture similarities subscales at 5 years of age (Quigley et al., 2012). It remains unclear whether these positive effects can be attributed to specific nutrients in breast milk since maternal and lifestyle characteristics often confound the findings (Qawasmi, Landeros-Weisenberger, Leckman, & Bloch, 2012; Von Kries, Koletzko, Sauerwald, & Von Mutius, 2002).

Long chain polyunsaturated fatty acids (LCPUFAs) have been extensively studied for their role in brain development and cognitive function (Eilander, Hundscheid, Osendarp, Transler, & Zock, 2007; Georgieff & Innis, 2005). Among LCPUFAs, both DHA and arachidonic acid (AA) are preferentially accumulated in the forebrain during the third trimester and first 2 years of life (Lauritzen, Jorgensen, Olsen, Straarup, & Michaelsen, 2005; Martinez, 1992). Docosahexaenoic acid (DHA), in particular, plays a crucial role in maintaining cortical neuronal integrity (Joardar, Sen, & Das, 2006; McNamara et al., 2010). Deficiency in DHA results in abnormalities in neurons, glial cells, oligodendrocytes, myelin, and nerve endings (Bourre, 2006). Although DHA and AA can be derived from their essential fatty acid precursors, α-linolenic (ALA) and linoleic acid (LA), this conversion is not efficient in the human fetus and breast milk varies in its concentration of LCPUFA (Cetin & Koletzko, 2008; Hoffman, Boettcher, & Diersen-Schade, 2009; Jensen & Lapillonne, 2009; Uauy, Mena, Wegher, Nieto, & Salem, 2000). Therefore, it

was hypothesized that supplementing infant formula with DHA and AA would improve cognitive function in children. Supplementation of preterm infants with DHA improved visual acuity and short-term global development (O'Connor et al., 2001; SanGiovanni, Parra-Cabrera, Colditz, Berkey, & Dwyer, 2000). However, the overall results thus far have been inconclusive and a recent meta-analysis concluded that LCPUFA supplementation did not significantly improve early cognition (Campoy, Escolano-Margarit, Anjos, Szajewska, & Uauy, 2012; Qawasmi et al., 2012). Interestingly, among school children with learning disabilities and developmental disorders, supplementation with DHA has been shown to improve cognitive function (Kirby, Woodward, & Jackson, 2010), indicating the potential benefits of supplementation during school-aged years.

Supplementing infant formula with micronutrients (e.g., iron) has yielded mixed results as well. Among infants without iron deficiency, supplementing with iron does not improve and may even be related to lower cognitive function in those with elevated hemoglobin levels at 10 years of age (Lozoff, Castillo, Clark, & Smith, 2012). Conversely, providing a cocktail of micronutrients along with DHA has been shown to improve verbal learning but not general intelligence or attention (Osendarp et al., 2007). Therefore, current findings suggest that nutritional status of the child (deficient or adequate) may play an important role in determining cognitive outcomes as a function of supplementation. In addition, future research should examine the efficacy of supplementation of combinations of nutrients rather than provision of a single nutrient for cognitive and brain health.

Dietary components such as high saturated fats and sugars may also have a detrimental impact on brain function (Das, 2010), although much of this evidence is derived from animal models. Brain derived neurotrophin factor (BDNF) appears to function at the crossroads of cognitive and metabolic regulation (Gómez-Pinilla, 2008). BDNF modulates insulin resistance and glucose metabolism and deletion or polymorphisms of BDNF are related to abnormal hippocampal function among rodent and human studies (Egan et al., 2003; Gómez-Pinilla, 2008; Nakagawa et al., 2002; Tonra et al., 1999). Exposure to a diet high in saturated fat and sucrose, independent of obesity, was related to decreased BDNF in the hippocampus and poorer learning and memory performance (Molteni, Barnard, Ying, Roberts, & Gomez-Pinilla, 2002).

However, conclusive evidence for specific nutrients that can enhance cognitive function in children has been elusive thus far. Some studies have considered nutrition composition of meals and cognitive function. Breakfast omission has been linked to poorer performance on learning and memory among school-aged children and adolescents (Pollitt & Mathews, 1998; Rampersaud, 2009). Modifying nutritional composition of meals may also affect short-term cognitive performance. School-aged children consuming

breakfasts with low glycemic index (GI) may perform better on attentional tasks when compared to no breakfast or breakfast with high GI (Cooper, Bandelow, Nute, Morris, & Nevill, 2012; Ingwersen, Defeyter, Kennedy, Wesnes, & Scholey, 2007).

CONCLUSION

Emerging evidence suggests that cognitive and brain health may be profoundly affected by weight status and nutritional intake. Obese children have been shown to exhibit lower performance on cognitive control tasks and findings from ERP studies indicate that overweight and nonoverweight children have differential underlying brain activity during task performance. In addition to weight status, central adiposity and insulin resistance are associated with lower cognitive control in children (Kamijo, Khan et al. 2012; Tascilar et al., 2011). Insulin resistance has already been implicated in adult cognitive impairment; however, additional work in children is needed to elucidate insulin's role in brain function through the lifespan. Regarding academic achievement, there are no definitive prospective studies demonstrating a causal relationship between weight status and diminished academic achievement in children. However, cross-sectional studies indicate a negative association with obesity and academic achievement (Li et al., 2008). Therefore, additional longitudinal studies are needed to determine whether obesity is a determinant of lower academic achievement.

The rapid development of the brain over the first 2 years of life makes it particularly susceptible to nutrient deficiencies (Georgieff, 2007). This is evident from observations of decrements in brain development and function among animals and humans following perinatal or early nutrient deficiencies. However, there remains remarkably little known about the effects of overall diet or particular nutrients on specific aspects of cognitive control among children without nutrient deficiencies. Emerging data suggest the potential for the gut microbiome to mediate brain development and childhood obesity risk. Considering that the gut microbiota is highly susceptible to nutrient intake as well, future studies should investigate how nutrients targeting the microbiome may modulate both obesity and cognition.

Despite wide-scale intervention efforts, childhood obesity remains a major public health threat in much of the developed world (De Onis, Blössner, & Borghi, 2010; Ogden et al., 2012). Given that this trend may persist for the foreseeable future (Wang et al., 2008), it is essential that researchers develop a comprehensive understanding of the cognitive implications of nutrition and obesity.

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