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Is the Energy Demand of the Developing Brain Related to Lifetime Obesity Risk?

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ABSTRACT

The causes of obesity are complex and multi-factorial. The researchers propose that one unconsidered but likely important factor is an energetic trade-off between brain development and fat deposition. Humans are leanest during early childhood and regain body fat in later childhood and adolescence. Children reaching this "adiposity rebound" (AR) early, or at higher body mass index (BMI), are at risk for adult obesity. In aggregate data, the energy demands of the developing brain reach a lifetime peak of 66% of resting energy expenditure in the years preceding the AR and are tightly, inversely related to body weight gain from infancy until puberty. Building on this finding, the authors hypothesize that individual variation in childhood brain energy expenditure will help explain variation in the timing of the AR and subsequent obesity risk. This hypothesis is consistent with evidence that genes that elevate BMI are expressed in the brain and mediate a tradeoff between the size of energetically costly brain structures and BMI. Variability in energy expended on brain development and function could also help explain widely documented inverse relationships between BMI and cognitive abilities associated with prefrontal cortex. The researchers estimate that variability in brain energetics could explain the weight differential separating children at the 50th and 70th BMI-for-age centiles immediately prior to the AR. Our model proposes a role for brain energetics as a driver of variation within a population's BMI distribution, and suggests that early educational interventions that boost global brain energy use during childhood could help reduce the burden of obesity.

Introduction

As rates of overweight and obesity continue to rise globally, the burden of these conditions among children has risen at an alarming rate (1). In 2016, it was estimated that more than 250 million children were overweight or obese worldwide, with the rate of increase most rapid in lower- and middle-income countries. Childhood obesity imposes social and emotional costs, while increasing the likelihood of being an obese adult who develops disorders that shorten healthy lifespan, including the metabolic syndrome encompassing hypertension, diabetes and altered lipid profiles. The rising global burden of obesity, and the severe mental and physical health impacts of these trends, underscore the need for additional work aimed at clarifying the origins of excess weight gain during infancy and childhood. Why are some children at greater risk of gaining excess weight than their peers, and what underlies this heterogeneity?

One potential contributor that has not been considered in the nutrition and obesity literature, but that we think could be important, is brain metabolism. The oft-quoted statistic is that the brain accounts for 2% of the body's mass but 20% of daily energy expenditure. Although correct, this estimate is specific to adults. A recent study has shown that the brain accounts for a lifetime peak of 66% of the resting metabolic rate (RMR) or 43% of daily energy requirements (DER) at 4-5 years of age (2). This rate of energy use is 2-3 times higher than that of the adult brain. This study also reported evidence for a trade-off between brain energetics and the rate of weight gain throughout childhood: there is a close inverse linear relationship between brain metabolism and the rate of weight gain between infancy and puberty, with peak brain energetic demands corresponding with the age of slowest body weight gain - which is also known to be an age of low body fat stores (2). These findings thus suggest that the energy requirements of the developing brain constrain energy devoted to fat deposition during childhood, and are likely an important influence on the developmental timing of the adiposity rebound and consequently, later obesity risk.

Here we explore possible links between the energetic costs of brain development and risk for excess weight gain, as a complement to the more widely-appreciated role of conventional lifestyle factors like diet and physical activity. We begin by briefly reviewing the developmental pattern of body composition changes during childhood, and show that the timing of the adiposity rebound roughly coincides with, and therefore may be driven by, developmental declines in the brain's energy requirements. Following from this observation, we propose that factors that shift the developmental timing, height or duration of the peak in childhood brain energy use could alter age-trends in energy balance and body composition. Second, we review genetic evidence for pleiotropic trade-offs between the volume and surface area of a number of cortical and subcortical brain structures, on the one hand, and body fat deposition and the body mass index (BMI) on the other. Recent genome wide association studies (GWAS) predicting BMI identify a prominent role for genes associated with, and expressed in, the central nervous system, including genes associated with energetically costly processes like synaptic function, long-term potentiation, and neurotransmitter signaling (3). Third, because development of the prefrontal cortex (PFC) is an important contributor to the energy demand of the developing brain in early childhood, we review research that has identified deficits in executive function abilities as a

common comorbidity of obesity, in childhood and across the lifespan, as further evidence in support of a biological brain-body energetic tradeoff. Finally, we quantify the potential impact that variability in cerebral metabolism could have on the body's energy balance and body weight across development. Viewed together, available evidence converges on the idea that variation in the pattern and magnitude of the energy demand of the developing brain in early childhood will have direct effects on weight gain and obesity risk during childhood by impacting the body's energy balance, thus likely helping explain individual variability in BMI within a population.

Developmental changes in body composition and the adiposity rebound

Clues into potential influences on childhood overweight are revealed by the developmental timing of changes in body composition. Healthy infants are born with a large quantity of "baby fat", and fat deposition accounts for the majority of the energetic costs of growth during the first 6-9 months of life (4). The percentage of body weight that is fat usually starts to decline during infancy and eventually reaches a lifetime nadir by early childhood. Normatively, net fat deposition and an increase in adiposity typically ensues by 5-7 years of age (5-8), and the timing of this inflection point is called the adiposity rebound (AR). As shown in Figure 1 for a French study, children who experience the inflection earlier, and who thus start regaining body fat at a younger age (the dashed line), tend to follow a higher body fat trajectory than their peers and are at increased risk of becoming overweight and obese later in childhood, adolescence and adulthood (6, 8-10). Early rebounders also tend to have a higher BMI, and thus experience higher adiposity at the AR. The importance of the timing and height of the AR to obesity risk raises questions about the causes that underlie this variation across children.

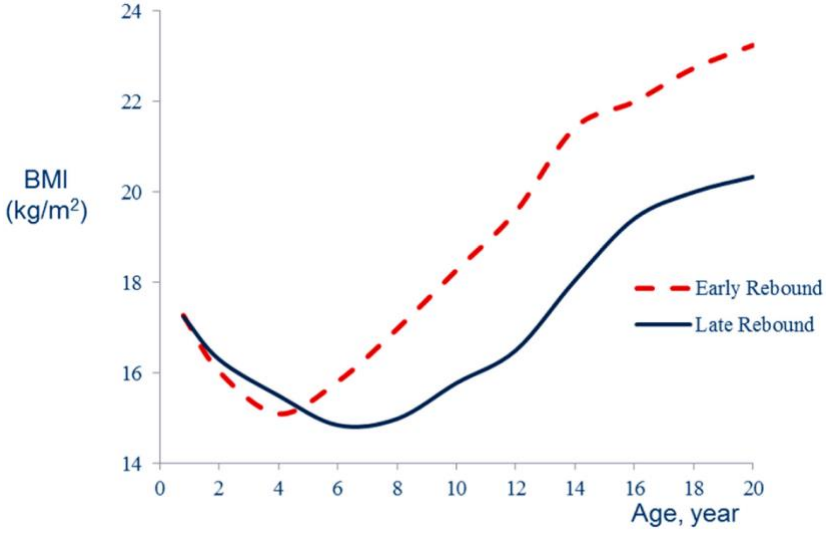

Figure 1. Developmental changes in body mass index (BMI; kg/m^2) related to age at adiposity rebound in a French study (from 11 with permission).

Given the importance of age at the AR to long-term risk for overweight and obesity, much research has focused on explaining individual variation in the timing of this event. Research has demonstrated relationships between the timing of the AR and a range of conventional lifestyle and environmental factors, including physical activity (12), diet (13), and the mother's pre-pregnancy BMI (14). This work has generally supported the idea that lifestyle factors during and prior to the AR, including the gestational environment, can influence the timing of this transition, with long-term impacts on body composition development. Here we expand this argument by

suggesting that individual variation in the brain's energy requirements is another important factor with direct impacts on age changes in energy balance and body composition development.

Early attempts to measure brain energetics across development

The potential importance of the brain as an influence on energy balance during childhood is underscored by the organ's high, and developmentally dynamic, energy costs. The majority of the brain's energy expenditure is related to glucose metabolism for neuronal signaling, synapse formation, and information processing (15, 16). The energy requirements of neuronal activity are dominated by action potentials (neuronal "spikes"), which account for roughly half of the brain's adenosine triphosphate (ATP) consumption, with postsynaptic receptors and resting potentials also important consumers of energy (17). Although most work on the energetic costs of the brain have focused on the adult brain, here we are specifically concerned with how those costs change across early development, when synaptic densities and other parameters shaping brain energy requirements reach their lifetime peak.

Several methods have been used to measure cerebral metabolic rate (CMR), reflecting the brain's global metabolic expenditure. The first direct quantification of the energy costs of the human brain were conducted among adults in the mid-20th century using the nitrous oxide method (18). This method is invasive as it involves measuring the gradient of an inert gas (nitrous oxide, NO_2) between the arteries and veins servicing the brain, which allows estimation of oxygen extraction by the brain. This method led to the frequently cited estimate that the brain consumes 20% of the body's oxygen uptake at rest, which is a value far higher than in most other mammals, for which 2-4% would be more typical (4).

It was widely noted by anthropologists interested in the evolutionary implications of human brain energetics that the brain is even more costly in a relative sense early in life, given the much higher brain-to-body size ratio, which is maximal at birth (19-21). It was further proposed that the large energy requirements of human brain development might help explain why, during childhood, humans gain body weight at a rate that is 30-100 times slower than other non-primate mammals of our size. This places human growth on the growth allometry of reptiles, which have very low energy expenditure as a result of being cold-blooded (21). Efforts to characterize the evolutionary impacts of human brain development have been hampered by the lack of direct measures of the brain's energetic costs across human development. Although the NO_2 method has been used in children, and yielded estimates of $CMRO_2$ considerably higher than adults (22), relatively few data points are available and with incomplete coverage across development. Until recently, the one attempt to calculate developmental changes in brain energetics across different ages of human development assumed that brain metabolism was a proportion of brain mass during infancy and early childhood, and estimated brain expenditure was divided by estimates of the body's resting metabolic rate (RMR e.g. kcal expended per day) at that age (23). The limitation with this approach is that it assumed that the per-gram metabolic expenditure of the brain is stable across early development, which direct measures of glucose uptake rates using positron emission tomography (PET) has shown is not the case (24). Although the sample size is modest (n=29 children, 7 adults), the one published age series of PET glucose uptake data

spanning birth to adulthood shows that the per-gram rate of cortical glucose uptake is roughly 30% less than the adult level at birth, but rapidly rises to twice the adult level by early childhood (24).

These dynamics in the per-gram metabolic cost of the brain reflect several processes, some of which were already alluded to above. The first and likely primary influence is changes in the density of synapses in early childhood, which account for much of the metabolic expenditure of neuronal tissue (17). Synaptic densities (synaptogenesis), increase in many cortical regions early in the postnatal period and reach their peak during childhood before being gradually pruned to adult levels as an integral part of learning (synaptic pruning; 25, 26). A second contributor to these energy dynamics is a process called aerobic glycolysis in which glucose enters into non-metabolic processes affecting synaptic growth and other functions (27 although see, 28).

Using PET and MRI to quantify the energy costs of the brain

Prior work shows that estimating developmental changes in the brain's energetic drain on the body would need to account not only for changes in the brain's size with age (grams of brain), but also its marked changes in the rate of glucose usage (grams of glucose/gram of brain tissue/unit time). PET data in children, however, are very rare due to the requirement that participants be exposed to radiation. As such, only one study to data, based upon individuals referred for scans for medical reasons but who showed no obvious abnormalities, reports a compilation of PET data across development (24). A recent study used these and MRI data to estimate the total energy expenditure of the brain and how this changes developmentally (2). These estimates showed that the costs of the human brain reach a peak in both relative and absolute terms around 4-5 years of age (Figs. 2A & 2B), when the brain accounts for 66.3% and 65.0% of RMR, in males and females respectively, and ~43% of total daily energy expenditure in both sexes. Notably, this is an age when brain growth is nearly complete, but when synaptic densities are at or near their lifetime maxima in PFC and other regions, as executive function abilities that support higher-order thinking, and that organize and regulate behavior, are developing (29).

A similar developmental pattern of brain metabolism was recently replicated using data on total cerebral blood flow and aortic blood flow in individuals spanning early infancy to adulthood (30). The ratio of these two measures can be interpreted as reflecting the percentage of cardiac output destined for the brain, and is thus a second metric reflecting the brain's relative dominance of the body's metabolism. This approach yielded a similar curve to the findings of the PET and MRI-based study, and most notably confirmed that the brain reaches a peak in relative metabolism during early childhood, followed by a gradual decline to adult levels that are about one-third those of the childhood peak. Finally, another recent study compiled published data on glucose uptake rates, cerebral metabolic rate of oxygen and cerebral blood flow by age, and again demonstrated a similar peak in brain energy requirements during childhood (27).

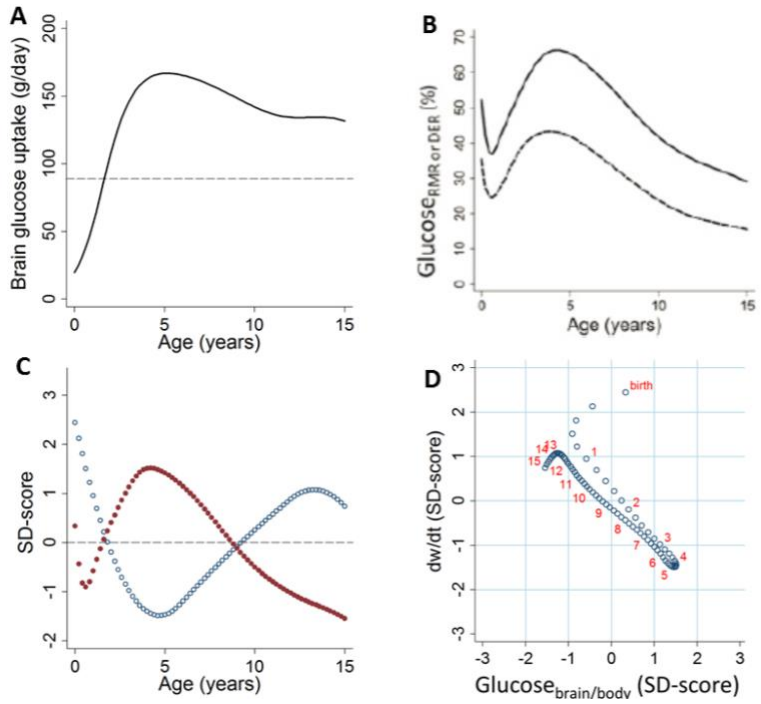

Figure 2. Glucose use by age and trade-offs with body weight growth rate (all males): A) daily grams of glucose used by brain; B) brain glucose use as a fraction of RMR (upper line) and daily energy requirements (lower line); C) Z-scores of %RMR to the brain and body weight velocity by age; D) body weight velocity vs. % RMR to the brain (both Z-scores) showing linear trade-off between the two. Weight velocity and glucose uptake values are predicted at intervals of one-fifth of a year, with red numbers marking each birthday for reference.

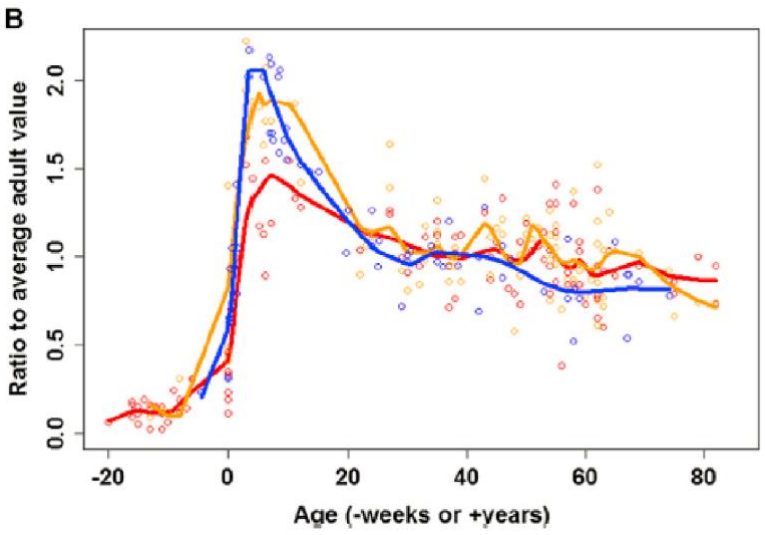

Figure 3. CMR_{gluc} (blue), $CMRO_2$ (red), and CBF (orange) plotted across the lifespan as normalized proportions of average adult values (from 27 with permission)

Linking brain energetics, weight gain and body composition

The studies described above use several methods to show that the brain does not have greatest impacts on the body's metabolism at birth, when relative brain size is largest, but in early childhood, when synaptic densities (25) and associated energetics costs are greatest (24). This

finding is of strong interest for research on obesity risk because it shows that the brain's peak demand for energy coincides developmentally with the age of slowest weight gain, which also roughly corresponds with lifetime lowest body fat stores and the AR (9). The study of Kuzawa and colleagues (2), discussed above, explicitly addressed the links between brain energetics and weight gain and found strong evidence for a trade-off between them (Figs. 2C & 2D). The authors reported that the age of peak brain energetics is also the age of slowest weight gain, and with a clear inverse linear relationship between the percentage of resting metabolic rate (RMR) accounted for by the brain and weight velocity between infancy and puberty.

This finding confirmed the long-standing hypothesis posed by anthropologists that the unusually slow pace of body growth during human childhood evolved in part to help free up energy to subsidize the brain's high energy costs (20, 21, 31). Both the extended postnatal period of brain development and the slow pace of physical growth are atypical aspects of development in our species (19-21) that this recent work shows are tightly linked. As we explain next, we feel that these population-level observations may also provide new insights into the causes of individual risk for gaining excess body weight.

Hypothesis: Individual variation in brain developmental energetics will be inversely related to individual variation in obesity risk

The foregoing findings have potentially important but as yet unexplored implications for understanding the rate and pattern of weight gain during infancy and childhood. Although there are abundant data on individual variability in weight gain and change in BMI, little is presently known about variability in the energy demand of the developing brain between children. Obesity is a complex condition in which factors like diet and physical activity are clearly implicated. However, several observations lead us to propose that variation in the energy demands of the developing brain is likely an important additional influence on individual variation in patterns of weight gain and changes in BMI during childhood, thereby influencing long-term weight trajectories and risk for overweight and obesity.

First, and perhaps most obviously, the brain accounts for a large fraction of energy expenditure during childhood, whether measured at rest or in relation to total expenditure. During early childhood, the proportion of the brain accounted for by grey matter, as opposed to white matter, is high, and grey matter consumes three times more energy than white matter (17). Also, glucose use in excess of $CMRO_2$, indicating aerobic glycolysis, closely tracks the trajectory for CMR_{gluc} (Fig 3) and is highly associated with gene expression related to energetically costly synapse formation and growth, throughout the brain but particularly strongly in PFC (27). In light of these high costs, any factors that modify patterns of synaptic proliferation could alter the timing, height or duration of the brain energetics peak, thereby impacting patterns of energy expenditure, energy balance and fat deposition.

Second, the timing of the adiposity rebound—when the body begins depositing excess energy in fat deposits—roughly coincides developmentally with the age of decreasing brain energy demand. As indicated in Fig 2, the Kuzawa et al. (2) paper shows clearly that, in the pooled data

used in that analysis, the average rate of weight gain is increasing at ages when brain developmental energetics are on the decline. Further, we know that the weight gain that occurs at this age includes fat as part of the adiposity rebound. Thus, children's bodies begin to accrue excess fat at an age when the brain's energy requirements are decreasing with development. Given that fat tissue is literally stored energy, we feel it unlikely that this correspondence is a coincidence.

The above considerations suggest that any changes in brain developmental energetics – whether in peak energy demands, or their developmental timing – could impact energy balance, and thereby, the rate, composition and timing of weight gain. The absolute magnitude of expenditure could be important, as could the timing – if children experience the peak early or late, this presumably reflects age-specific patterns of metabolic expenditure, and thereby, the likelihood that there are excess calories to be laid down as fat. The changing energy demand of the brain in early childhood might vary in a) the timing of onset, b) the rate (slope) of rise, c) the height of the peak, d) the duration of the peak, and e) rate of the decline.

Figure 4 overlays hypothetical curves for the changing energy demand of the brain in early childhood on CDC growth curves for BMI in individuals at the 97^{th}, 85^{th}, and 50^{th} percentiles (32). It is important to acknowledge that the brain is only one potential influence on energy balance and body composition change, and we do not mean to imply that it is the sole or even primary driver of this variation in BMI. Most obviously, variation in diet and physical activity are also important influences on the balance between intake and expenditure. This caveat aside, we hypothesize that, all other influences on BMI being equal, the child with lower peak brain energy demand in early childhood, or for whom the brain energy demand peaks earlier or is of shorter duration, will experience an earlier AR and thus be at a higher BMI for age relative to a child with greater peak brain energy demand or for whom brain energy demand peaks later and is of longer duration.

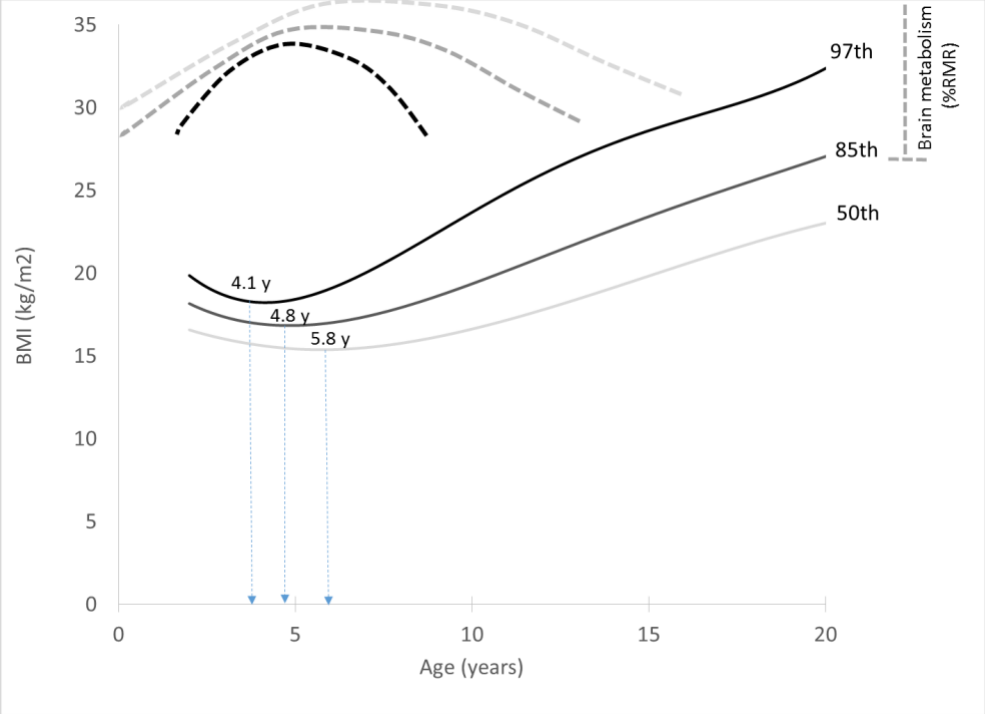

Figure 4. Hypothesized role of variation in brain developmental energetics as an influence on the timing and pattern of body fat gain during childhood. Solid lines show age percentiles for BMI, and with age of adiposity rebound noted for each. Dotted lines show hypothesized pattern of brain developmental energetics that correspond with each BMI growth pattern.

It is important to emphasize that essentially no data are available to address the hypothesis graphically depicted in Fig. 4. Data with which to address it could readily be acquired using several non-invasive proxies (CBF and MRI-based $CMRO_2$, discussed below) but acquisition of data on variability in brain energy demand has not been a scientific priority, possibly on the assumption that this variability is unrelated to other aspects of child development. Several literatures reviewed below, however, are independently revealing relationships that are consistent with an energetic trade-off between the brain and body weight, providing complementary insights into the plausibility of our model.

Anatomic evidence for a trade-off between the brain and body weight

A first line of evidence linking brain energetics and body weight gain, or the BMI, come from a growing list of neuroimaging studies that document reductions in energetically costly aspects of the brain, notably including the proportion of the brain that is grey matter, across the range of BMI in healthy adults, adolescents and children (33-36). Reduced grey matter volume in relation to BMI in children is consistently observed in frontal cortex but associations have been demonstrated in most cortical regions and in whole brain grey matter volume as well as the volume of subcortical structures, including the hippocampus. These findings are generally consistent with neuroimaging studies comparing obese vs. normal weight controls in which reductions in cortical thickness and surface area are found to be specific to orbitofrontal cortex,

anterior cingulate cortex and hippocampus, and correlated with performance on measures of executive function abilities (37-39). Two other studies, which included large independent samples for internal replication, examined variation in brain structure as a function of variation in BMI within the typical range (40, 41). These studies indicated incremental reductions in brain structure with incremental increases in BMI, including inverse associations of prefrontal grey matter volume in orbital frontal cortex (40) and reduced white matter integrity with BMI (41). These observations were not limited to overweight or obese individuals or to individuals suffering from the metabolic dysregulations that often accompany obesity (the metabolic syndrome).

Evidence from GWAS and the genetic architecture of BMI

Related work is showing that inverse relationships between the brain and body weight have at least a partial genetic basis, with genes mediating pleitropic trade-offs between the size of brain structures and body weight or fat deposition. Genome-wide association studies (GWAS) identify the genetic architecture of complex traits, like BMI, by measuring single nucleotide polymorphisms (SNPs) sampled across the genome in large samples of human populations. These studies have identified a growing list of gene variants associated with excess body weight in humans. A recent meta-analysis of the largest sample analyzed up to that time (N=339,224) indicated a dominant role for genes associated with CNS function and neuronal development, as much or more so than genes associated with energy homeostasis and the regulation of appetite (3). The intention in the analysis was to capitalize on the large sample size to identify biological pathways and mechanisms through which identified genes affect BMI. Using a variety of approaches to identify cell types and tissues in which genes near SNPs associated with BMI are highly expressed, this analysis found converging evidence indicating that BMI-associated genes are largely expressed in the CNS (Fig. 5). Using publically available gene expression microarray data, enrichment was observed in brain areas associated with appetite regulation, hypothalamus and pituitary, but was even stronger in brain areas associated with learning and memory, the hippocampus and limbic structures. Further, by examining BMI-associated variants with 5 regulatory marks found in most of the selected cell types, strongest enrichment was found in mid-frontal lobe, anterior caudate, astrocytes and substantia nigra. Secondly, using predefined gene sets reconstituted from coexpression data, enriched gene sets were identified relating to synaptic function, long-term potentiation, and neurotransmitter signaling, glutamate most prominently but also monoamines and GABA. Finally, by conducting manual review of all 405 genes within 500 kb of BMI-associated SNPs and identifying biological categories associated with those genes, this analysis found that the largest category comprised genes involved in neuronal processes, including genes involved in hypothalamic function and energy homeostasis and also neuronal transmission and development.

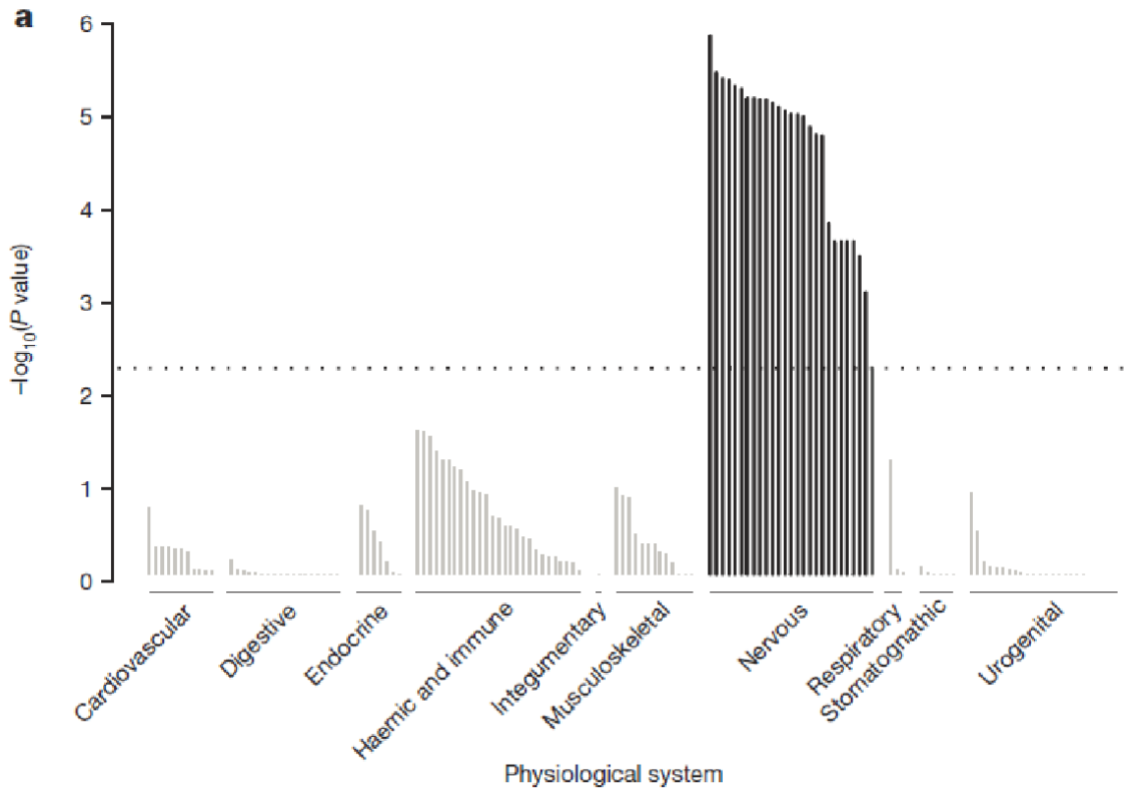

Figure 5. Genes associated with BMI-related loci are enriched for expression in the brain and central nervous system. Tissues are organized by biological system and those exhibiting significant enrichment are in black, with the dotted line representing the threshold for statistically significant enrichment (from3 with permission).

The authors hypothesize that these findings reflect the importance of functions like neuronal plasticity to obesity-relevant behaviors like impulse control and appetite regulation (3). Although by no means mutually exclusive, we hypothesize that there are also direct effects of these polymorphisms on obesity risk operating through their impact on energetically costly processes of neuronal development, which in turn will moderate the brain's contribution to the body's total energy use. It is particularly notable that the list of significant identified genes included many involved with energetically costly synaptic processes that are thought to account for a sizeable fraction of cerebral metabolic rate, including those that drive the large childhood increase in cerebral metabolism over that of the adult that coincides with the nadir in childhood weight gain, and that precedes onset of the adiposity rebound.

Indeed, the analysis (40) that identified an association between reduced grey matter volume in PFC and BMI in two large independent samples, discussed above, also found that the polygenic risk score for obesity, based upon the analysis of Locke and colleagues (3), was strongly positively related to BMI, as expected, but equally strongly and inversely related to prefrontal grey matter volume, thus providing evidence of individual variation in a genetically-mediated tradeoff between cortical volume in PFC and BMI. Another study reported that each 1 kg/m^2

increase in the BMI predicted a 1-1.5% volume reduction throughout the frontal, temporal, parietal and occipital lobes, with additional reductions in subcortical structures like the brain stem and cerebellum (42). This analysis also found that carriers of a common obesity-risk polymorphism at the FTO gene were heavier, but also had 8% and 12% reductions, respectively, in the frontal and occipital lobes.

Further evidence for genetic pleiotropy linking increased BMI with reduced brain structures comes from a large family-based Mexican American study (N=839) of adults that identified negative genetic correlations between BMI and the size of structures throughout the brain (43). Specifically, the authors found evidence for strong negative genetic correlations between the BMI and cortical surface area in parietal (inferior parietal, supramarginal gyrus), temporal (middle temporal gyrus), occipital (cuneus), and frontal cortex (orbitofrontal, middle frontal, inferior frontal). BMI was also inversely correlated with volumes of subcortical structures including the accumbens area and ventral diencephalon.

Evidence linking BMI and obesity with cognitive development and executive function abilities
An association between individual variation in the energy requirement of the developing brain and change in BMI in early childhood, and later obesity risk, is also supported by research on cognitive development in early childhood. Changes in cognitive ability, primarily the development of executive functions, the emergence of which coincide with steep increases in brain energy demand and the timing of the adiposity rebound, represent a key developmental transition that marks the end of early childhood (44). In high income societies, by the age of approximately 5-7 years children are typically expected to regulate behavior and reason and think abstractly in ways that allow for engagement in formal learning activities, such as schooling (45).

The area of the brain primarily associated with these changes in cognitive ability – the PFC – is characterized by high energy demand during the child's first 4 to 6 years. A period of synaptic proliferation in early childhood is followed by synaptic pruning that is particularly rapid during late childhood, but continues into the third decade of life (26, 46). Available data suggest that peak synaptic spine density in pyramidal neurons in layers III and V of PFC is reached at approximately age 5 years (26), thus corresponding with the peak in brain energetics. Given that white matter has few synapses which collectively account for $\leq$0.5% of the energy required by grey matter synapses (17, 47), the timing of peak gray matter thickness during childhood is one factor that likely helps explain why the brain is far more energetically costly in early childhood than at any other time in the lifespan.

The dominance of the body's energy budget by brain development suggests that individual differences in the energy demand of brain development could make substantial contributions to variation in energy balance and thus affect the pattern of fat deposition and the timing of the adiposity rebound. In this light, it is notable that a recent meta-analysis (48) as well as systematic reviews of the literature (49, 50) comparing cognitive abilities of obese versus healthy weight individuals indicate deficits in learning and memory and executive function in children and

adults in a majority of studies across a variety of assessments. Overall, a recent meta-analysis (48) found deficits in performance of moderate effect size (0.33-0.44, e.g. explaining 10-20% of variance) in obese vs. normal weight comparisons for each aspect of executive function examined, including inhibitory control, working memory, cognitive flexibility, decision making, verbal fluency, and planning. However, relatively few studies included child participants exclusively and many used BMI as the sole indicator of obesity. Notably, one of the methodologically stronger studies in the meta-analysis that included child participants found that BMI, as well as fat mass measured by dual-energy X-ray absorptiometry (DXA), were both inversely related to measures of executive function and academic achievement in a sample of 126 children spanning 7 to 9 years of age (51). Further, a follow-up to this study with a larger sample (N=233) of 7 to 9 year olds, also using DXA, found that whole body adiposity was negatively related to executive function even when controlling for aerobic fitness relative to fat-free mass (52).

As perhaps even more direct evidence for an energetic trade-off between cognitive development and body fat gain, follow-ups of two longitudinal samples have demonstrated in very young children that deficits in executive function and the ability to delay gratification are associated with an earlier timing and steeper trajectory of adiposity change in childhood. In one sample (N=1061), children exhibiting difficulty with delay of gratification tasks at ages 3 and 5 had a steeper trajectory of BMI increase between 3 and 12 years of age (53). In a second longitudinal study (N=195), children exhibiting difficulty with self-regulation at age 2 had higher BMI at age 10 and were more likely to be obese (54).

Conventional non-energetic explanations for links between BMI and executive functions
Traditional explanations for findings of executive function deficits in relation to higher BMI have focused on several pathways, and consider the potential for bidirectional links between the brain and excess body fat. First, deficits in the size, surface area, or synaptic connectivity of PFC with other brain regions and subcortical structures will lead to executive function deficits that impair behaviors like appetite regulation and delay of gratification, thereby potentially increasing weight gain through effects on dietary intake. In addition, excess body fat deposition, whether diet-induced or otherwise, can result in low-grade inflammation and alter production of hormones that have reciprocal impacts on neuronal structure and function, potentially further eroding appetite control. For instance, a number of metabolic and immunological changes precipitated by excess adiposity, or the often correlated behavior of high fat intake, have downstream deleterious impacts on neuronal function (55, 56). Adipocytes produce pro-inflammatory cytokines and other factors that stimulate systemic as well as central inflammation. One well-studied target of central inflammation is the hypothalamus (57), which plays a key role in regulating eating behavior and executive functions among many other aspects of psychological and physiological function. For instance, the hypothalamus regulates the production of stress-related hormones such as glucocorticoids and norepinephrine that are associated with executive function abilities (58, 59), as well as appetite regulating hormones, like leptin and ghrelin, that also affect executive function abilities in addition to the control of appetite (60). Inflammatory damage to the hypothalamus would thus be expected to interfere

with the production of hormones related to both EF and appetite, which could lead to further weight gain.

Evidence that BMI relates inversely to executive function without inflammation or metabolic dysregulation

Behavioral effects of impaired cognitive and executive function, and the reciprocal effects of excess weight gain on the brain, almost certainly help explain the tendency for measures of executive functions to decline with increasing BMI. However, many studies have now reported inverse relationships between the BMI and brain or executive function that are not contingent upon obesity itself. For instance, a particularly compelling PET study of 21 healthy adults found that resting glucose metabolism in frontal cortex was positively correlated with performance on multiple measures of executive function but negatively correlated with BMI (61). Importantly, only 3 study participants were obese, and the relationship was present across the full range of BMI. A further example in adults is seen in a study in which cortical thickness in superior frontal gyrus was inversely related to BMI and higher BMI and reduced frontal cortical thickness were associated with poor inhibitory control (62). A second example is seen in a large study (N=521) with older adults (60-80 years) in which BMI in the normal range was associated with lower default mode functional connectivity in posterior cingulate cortex and precuneus, and higher BMI and lower default mode connectivity were associated with lower performance on an executive function battery (63).

In summary, conventional explanations for the inverse relationship between BMI and cognitive abilities, executive functions in particular, have emphasized that neuronal deficits and excess weight gain can have mutually reinforcing, deleterious impacts on both cognitive development and body weight gain. Although these effects do help explain the inverse relationship between BMI and cognitive development documented in many samples, the studies reviewed above show that these are not complete explanations: trade-offs between brain anatomy and body weight are distributed throughout the brain, and not limited to regions that regulate appetite-relevant behaviors. Furthermore, these relationships are already present at an early age and before any metabolic dysregulation has been in place to alter neuronal structure/function. This work raises the important question of what explains relations between these traits in the absence of inflammatory and metabolic factors associated with obesity and the metabolic syndrome. We next return to our model, and consider the potential quantitative impact of individual variation in developmental brain energetics on weight gain.

How large of an effect might individual differences in brain energetics have on weight gain and obesity risk?

Weight gain includes both fat mass and fat free mass, and the latter contributes to an increase in total energy expenditure. As such, as rising dietary intake leads to an increase in body weight, the impact of the increment in lean mass on energy expenditure must be taken into account when calculating energy balance. The method of Swinburn et al (64) allows estimation of the impact that a sustained change in intake or expenditure will have on a new stable body weight, or "settling point". Using information on total energy expenditure and energy intake in a sampling

of population studies of children, they find that, holding age, height and sex constant, a population of children that increases its energy flux (intake in excess of expenditure) by 10% will stabilize on a body weight that is 4.5% heavier. Here we use this method to estimate the potential impacts of individual variation in brain metabolism on body weight and BMI by age.

As discussed above, the brain accounts for 66% of RMR at 4 years of age, when it is estimated to consume more than 500 kcal each day. This large level of expenditure underscores the potential for any variability in brain energetics to have important impacts on individual differences in energy balance and body weight in the years that lead up to the adiposity rebound. Estimating the magnitude of this effect is unfortunately hindered by the extreme paucity of published information on variability in cerebral metabolic rate across children of the same age and body size. Such variability will result from differences in both the size of the brain or specific brain structures and differences in the rate of energy use per unit volume or mass of that tissue. While we know almost nothing about variability in global brain energetics during development, there clearly is substantial variability in brain volume and mass and in the size and thickness of specific cortical structures by age (65, 66). PET data illustrate individual variation in the rate of glucose uptake per unit of tissue mass, which will contribute to variability in brain energetics that is independent of brain size. As one illustration from the data of Chugani and colleagues (24), the per-gram rate of glucose uptake in the cerebrum of two children with very similar ages (~7 years old) was found to be 40.6 and 51.6, the latter reflecting a 27% higher rate of glucose consumption per gram of tissue among individuals of the same age. Estimates of the percentage of total cardiac output accounted for by the brain also illustrate inter-individual variability in age-specific cerebral metabolism (30): of 3 individuals measured at roughly 3 years of age (all female), the highest value for TCBF/AAo, which reflects the fraction of cardiac output used by the brain, is nearly 40% higher than that of the lowest (0.55 vs. 0.4). Although the paucity of currently available data must be emphasized, the few data that are available point to potentially significant and biologically important variability in the degree to which brain energetics dominate the body's energy budget during childhood.

Figure 6 uses data on daily energy requirements, brain energy use and body weights in humans (2; supplemental information), and the method of Swinburn et al (64), to estimate the effect on body weight that a 40% change in brain energetics would have on weight gain by age. We assume that the energy "savings" of moving from high to low brain expenditure is the caloric equivalent of becoming more sedentary. Figs 6A and 6B show that a 40% change in brain energetics would add about 1.2 BMI (kg/m^2) units at the peak in brain energy demand at 3-4 years of age. That is, relative to the child whose brain energetic requirement is 20% above the mean, the child whose energetic requirement is 20% below the mean will have meaningfully higher BMI, holding all other aspects of the child constant, including daily energy intake.

Although this effect may appear modest, it is important to note that the age of the adiposity rebound is also a point in the lifecycle when population variability in BMI is attenuated. Thus, a 1.2 unit change in BMI would be the rough equivalent of moving between the 50^{th} and 70^{th} centile for BMI at that age (Fig. 6C and 6D). The age of maximal effect of brain metabolism on

weight status occurs in the years immediately preceding the adiposity rebound, when one's BMI centile is predictive of future obesity risk. To the extent that any effects of brain metabolism on one's BMI and population centile at this age are stable and track into adulthood, these estimates point to potentially large impacts of the energy demand of the developing brain on long-term body weight trajectories.

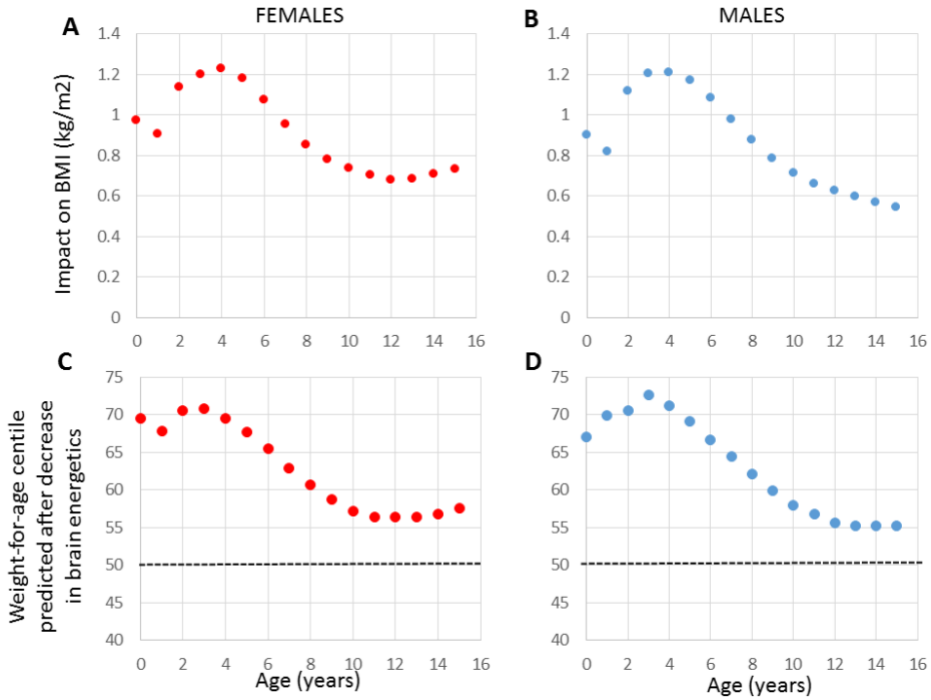

Figure 6. The predicted impact on BMI of moving from 20% above the mean for brain energy use to 20% below the mean for brain energy use. Median height and weight for age (CDC) were used to estimate the BMI. An estimate of additional weight gained with declining brain energetics was calculated using the method of Swinburn et al (64), from which a second BMI was calculated. The plotted values are the differences between the two BMI estimates in A) females and B) males. The lower figures plot the BMI predicted after that level of energetic savings in C) females and D) males.

Discussion: policy implications of links between brain energetics and fat deposition

We have argued that developmental changes in body composition during infancy and childhood, and the nadir in body fat stores called the adiposity rebound, are very likely a partial result of the shifting strength of energetic trade-offs between brain development and fat deposition. Recent work showing that average developmental changes in brain energy use are tightly, inversely linked with normative changes in the rate of childhood weight gain suggests that individual variation in the energy demand of the developing brain likely accounts for some proportion of concurrent changes in body fat deposition. In support of this idea, we reviewed evidence indicating that the energetic cost of brain development in childhood, starting in late infancy, is high (9, 15, 27). We also reviewed evidence indicating that BMI in the normal range is inversely related to surface area and/or thickness in multiple cortical and subcortical regions. Evidence is

emerging for a strong link between the genetic architecture of BMI and of brain development as seen in a suite of neuronal processes that are energetically costly, such as those governing the biology of synapse formation and neuronal transmission (10, 27). There is now substantial evidence for pleiotropically-mediated trade-offs between the BMI and the thickness or volume of structures throughout the cerebral cortex and other brain regions, pointing to the potential for direct energetic trade-offs between the brain and fat deposition (41, 42).

Additional support for the hypothesized brain-body energetic tradeoff is seen in an increasingly well-established inverse association between obesity/BMI and executive function, and also in cortical surface area and volume in energetically costly brain areas associated with executive function. These findings add support to the idea that the body's internal priorities for energy allocation—either preferentially devoted to physical growth or to brain development—have implications for later obesity risk and cognition. Without question, non-energetic links between excess fat and cognitive deficits certainly play a role. Poor inhibitory control and problems with gratification delay lead to poor appetite regulation and excess fat intake, leading to the neuro-toxic effects of resultant inflammation. Nevertheless, relations among BMI, brain and cognition are present in infancy and early childhood prior to the emergence of metabolic dysregulation, suggesting that the hypothesized brain-body energetic tradeoff can help to identify individuals at highest risk for gaining excess weight. To this end, we estimated the impact on BMI that would occur by reallocating energy from brain development to weight gain and found maximal potential for such effects in the years prior to the adiposity rebound. Specifically, plausible ranges of variability in cerebral energy expenditure are predicted to be the energetic and weight-gain equivalent of moving a child from the 50^{th} to the 70^{th} BMI-for-age centile in the years immediately preceding the adiposity rebound.

Obesity is a complex and multi-factorial disease, and we do not see our model as competing with the focus on lifestyle factors like diet or physical activity or on more recently identified influences like the gut microbiome. We see the brain-body energetic trade-off model of obesity as complementing and augmenting a focus on these lifestyle factors. Indeed, the secular trend towards rising societal rates of overweight and obesity very likely relate to trends in intake and/or expenditure (67). Adding to this existing complexity, the brain is not only an important contributor to variation in energy expenditure in childhood, but variation in these costs could make non-trivial contributions to population variation in body weight at an age when BMI is predictive of one's future trajectory of adult overweight and obesity risk. As the societal BMI distribution shifts with lifestyle change, where individuals lie within that distribution will determine who reaches high disease risk cut points earlier. It is here—in explaining variation within a population's BMI distribution, rather than trends through time—that we feel variation in brain energetics could be most important. As discussed above, a growing literature points to reciprocal effects linking cognitive decline and weight gain. Because decreased cognitive function involves an energetic savings, thus likely enabling additional weight gain, we view energetic trade-offs between cognitive expenditure and fat deposition as potentially reinforcing the effects of these pathways.

The science that we review hints at novel intervention approaches to reducing the public health burden of overweight and obesity. On the one hand, the strong genetic linkages between neuronal function and obesity, and the pleiotropic trade-offs between these traits, could be interpreted as evidence that important components of obesity risk are inherited at birth and not likely to change. We feel that such an interpretation is not correct, because most genes, and especially those related to neuronal biology, have phenotypic effects that are highly contingent upon experience (phenotypic plasticity; 68, 69). Genetic research shows not only that many obesity-related genes influence energetically costly neuronal functions, but that they are also expressed primarily in the central nervous system (3). The functions that these genes contribute to include molecular and cellular processes that underlie the capacity and extent of neuronal plasticity, which are the quintessential examples of human phenotypic plasticity (70). Gene variants that are expressed in the brain and that alter these neuronal processes appear to modify risk for obesity, which plausibly has at least a partial energetic component. In light of this, educational or other interventions that alter the energy use of these same neuronal processes are also likely to alter obesity risk.

That early educational intervention can reduce obesity risk is seen in analyses of longitudinal follow-up data on growth and body composition in infancy, early childhood and adulthood in the intensive early intervention known as the Abecedarian Project (71). Children were randomly assigned to a full day center-based care condition or to a control condition starting at 6 months of age. Follow-up at age 35 years indicated that male treatment group participants were less likely to exhibit characteristics of the metabolic syndrome. Further, of most relevance to the present model, analysis of the early life growth data indicated that males in the control group experienced accelerated weight velocity in infancy and higher BMI at the adiposity rebound relative to participants in the treatment group (71). As such, children receiving the intensive early educational care starting in infancy were at lower risk for overweight in infancy, prior to 24 months, and were less likely to be overweight at 5 and 8 years of age. Similar findings are seen in a follow-up to a trial of an innovative program to enhance parenting practices in low-income families with preschool children (72). Children in the treatment group were less likely to be obese in preadolescence, on average five years after the intervention ended.

Such findings suggest that cognitively stimulating activities reduce the risk of obesity associated with an accelerated BMI trajectory in early childhood. Although some of the effect of high quality care on the development of obesity unquestionably occurs through treatment-related increases in self-regulation, we suggest that an energetic effect of enhanced cerebral metabolic activity on body composition is also likely. This suggestion is consistent with the underlying rationale for intensive early educational center-based interventions. That is, programmatic activities, such as an enriched language environment and opportunities for learning through play and exploration, are designed to stimulate cognitive abilities that are dependent on the development of increasingly complex and elaborated neural circuitry, primarily in PFC. The effect of the program on cognitive abilities associated with enriched development in, and connectivity between, specific brain areas would increase cerebral blood flow and the energy demand of these developing brain regions. Given associations of executive functions like self-

regulation with the functioning of the PFC, and the fact that neural development of PFC is understood to be an important driver of energy required by the developing as well as mature brain, we feel that it is plausible that some of the effects of early educational interventions on obesity risk operate by increasing brain energy use.

Although few early intervention studies include measures of brain structure, separate studies have shown sizeable gradients in energetically costly aspects of brain function and development, including cortical thickness, surface area and even brain volume, in relation to favorable early rearing environments. Multiple studies have shown that a child's cortical thickness is increased in a linear fashion in relation to the parents' level of education (73, 74), which has also been shown to positively predict cortical surface area (74). Another found that parents that were more sensitive as caregivers from 1-4 years had children with thicker cortices, increased gray matter volume and even significantly larger brain volumes (75). Although a contribution of genetic variability to these outcomes cannot be ruled out, the authors of these studies interpret these various findings as evidence that improvements in rearing environments will tend to boost brain growth and cognitive development. All of this points to higher brain energy expenditure in children experiencing high quality care in infancy and early childhood.

Future priorities

Brain energetics will only be an important predictor of energy balance and weight gain if it is variable across individuals, and at present we have almost no information on the range of this variability. The Kuzawa et al study (2) generated a composite brain energetics curve derived from PET, MRI and brain/body size data obtained from three separate populations. We know almost nothing about how this curve varies in timing, height, or duration, whether considered within or between populations, and there is currently a great scientific need to collect these data. Luckily, non-invasive MRI-based approaches to measuring cerebral blood flow (30), and cerebral metabolic rate of oxygen (76), provide opportunities to incorporate proxies of brain metabolism into longitudinal studies of normal healthy child development, which hold promise to help clarify the role of energetics *per se* in the relationships between BMI and the development of the brain and cognition.

As a second goal, we need to understand the sensitivity and responsiveness of brain developmental energetics to modifiable educational and other environmental interventions. We reviewed evidence that such interventions have had some success in reducing overweight and obesity, but a focus on brain energetics as a causal pathway could lead to additional, broader strategies not limited to boosting cognitive functions that impact behaviors like appetite regulation. According to the model outlined here, *any* boost in global brain energetics, irrespective of the underlying function, should have impacts on the body's energy balance. This may be particularly true for individuals at high genetic risk for obesity, for whom we might expect the largest effect of intensive early education.

We estimated that brain energetics have greatest potential to impact the BMI at roughly 3-4 years of age, which are the years preceding the adiposity rebound. As noted, the timing of the AR, but

also the height of the BMI curve at this age, are predictive of later obesity risk. What is less clear is whether an intervention that succeeds in boosting global brain energy use at this early age will merely lead to transient weight reductions, or potentially alter long-term trajectories of overweight and obesity risk. We know that, once gained, weight tends to be difficult to lose, and thus any weight kept off in childhood should increase the likelihood of remaining thin into later life. There is evidence that correlations between infancy and childhood BMI and adult BMI (tracking) increase with age, and in one longitudinal study the rate of weight gain between 2-6 years of age was found to be the strongest predictor of adult BMI, after which correlations with adult BMI were strengthened substantially (9). Such findings hint at the potential for interventions that increase childhood brain energy use at the peak of brain energy requirements to have not only short-term, but potentially also long-term impacts on obesity risk. The severity of the public health burden of overweight and obesity underscores the need for future research to clarify the role of brain energetics as an influence on developmental trajectories of body weight gain.

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