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Pediatric obesity. An introduction ⋆

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Abstract

The prevalence of child and adolescent obesity in the United States increased dramatically between 1970 and 2000, and there are few indications that the rates of childhood obesity are decreasing. Obesity is associated with myriad medical, psychological, and neurocognitive abnormalities that impact children's health and quality of life. Genotypic variation is important in determining the susceptibility of individual children to undue gains in adiposity; however, the rapid increase in pediatric obesity prevalence suggests that changes to children's environments and/or to their learned behaviors may dramatically affect body weight regulation. This paper presents an overview of the epidemiology, consequences, and etiopathogenesis of pediatric obesity, serving as a general introduction to the subsequent papers in this Special Issue that address aspects of childhood obesity and cognition in detail.

Keywords

Children; Adolescents; Hyperphagia; Overeating; Etiology

Introduction

Among children in the US, the percentage of children classified as obese, according to the U.S. Centers for Disease Control growth standards, has more than tripled since the 1970s (Ogden, Carroll, Curtin, Lamb, & Flegal, 2010; Ogden et al., 2006; Ogden, Carroll, Kit, & Flegal, 2014; Ogden, Flegal, Carroll, & Johnson, 2002). Obesity-related diseases rarely seen in children previously, including obesity-associated sleep apnea (Muzumdar & Rao, 2006), non-alcoholic fatty liver disease with resultant cirrhosis (Molleston, White, Teckman, & Fitzgerald, 2002), and type 2 diabetes (Dabelea et al., 2014; Pettitt et al., 2014), are increasingly diagnosed in children and adolescents. Because childhood onset obesity frequently persists into adulthood, it is also associated with increased long-term morbidity and mortality (Must, Jacques, Dallal, Bajema, & Dietz, 1992). For all these reasons, it is

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crucial to understand the causes and consequences of childhood obesity. This paper serves as a general introduction to the subsequent papers in this Special Issue that more specifically address childhood obesity and cognition by presenting an overview of the epidemiology, consequences, and etiopathogenesis of pediatric obesity.

Body mass index-based definitions and the epidemiology of pediatric obesity

"Obesity" is defined as the accumulation and storage of excess body fat, while "overweight" is weight in excess of a weight reference standard (Ogden & Flegal, 2010). Because there are no consensus criteria defining childhood obesity on the basis of excessive body adipose tissue, weight-based classification based on body mass index (BMI, kg/m^2) has been routinely used for both epidemiological and clinical purposes.

The BMI typically decreases immediately after birth, increases through the first 6–8 months (WHO Multicentre Growth Reference Study Group, 2006), decreases until age 5–7 years, with corresponding decreases in percentage body fat (Garn & Clark, 1976) and then increases for the reminder of childhood up to adult levels. Because the distribution of BMI changes dramatically with age and differs by sex in children and adolescents, age- and sex-specific BMI percentiles rather than raw BMI values are used for BMI-based classification (Rolland-Cachera et al., 1982). The reference standards most commonly used in the United States for evaluating children's BMI are the 2000 Centers for Disease Control and Prevention (CDC, 2000) growth charts that provide age- and sex-specific standards for ages 2 to 18 (Kuczmarski et al., 2000, 2002). These charts supply smoothed percentiles for BMI that were constructed using a modified LMS (lambda, mu, and sigma) estimation procedure (Kuczmarski et al., 2002) from data obtained in nationally representative U.S. surveys conducted between 1963 and 1980 (Kuczmarski et al., 2000). More recent data were not included because of the marked increases in BMI that were seen in subsequent U.S. surveys (Flegal, Ogden, Wei, Kuczmarski, & Johnson, 2001; Troiano & Flegal, 1998). Because of the paucity of data for children at the greatest BMIs in the data sets used, the top percentile defined by the CDC 2000 growth charts is the 97th percentile.

Before 2010, CDC 2000 growth charts for ages 2 to 18 years demarcated the 85th to 94.99th percentiles for BMI as "at risk for overweight" and ≥95th BMI percentile as "overweight" (Himes & Dietz, 1994). These cut points were subsequently renamed "overweight" for the 85th to 94.99th BMI percentiles and "obese" for ≥95th BMI percentile, to be consistent with recommendations by other groups (Barlow, 2007; Barlow & Dietz, 1998; Himes & Dietz, 1994; Koplan, Liverman, & Kraak, 2005; Krebs et al., 2007; Obesity: preventing and managing the global epidemic, report of a WHO consultation, 2000; Ogden & Flegal, 2010; Physical status: The use and interpretation of anthropometry, 1995; Koplan, Liverman, & Kraak, 2004).

There are limitations to the use of BMI-based standards to define obesity (Barlow & Dietz, 1998; Barlow, 2007; Flegal, Ogden et al., 2010; Himes & Dietz, 1994; Krebs et al., 2007) because BMI cannot discriminate between lean and fat mass (Wellens et al., 1996) and thus excess body fatness cannot be measured directly from weight and height (Himes & Dietz,

1994). However, there is a high correlation between fat mass and BMI among children (Field et al., 2003; Mei et al., 2002), and the majority of children with BMI ≥95th percentile have high adiposity (Freedman, Mei, Srinivasan, Berenson, & Dietz, 2007). Nevertheless, about 25% of U.S. children with BMI ≥95th percentile do not appear to have particularly high amounts of body fat (Flegal, Ogden et al., 2010); thus BMI is a first screening tool to identify children who may be overfat. BMI percentiles may be particularly inaccurate for children belonging to some racial and ethnic minorities (Flegal, Ogden et al., 2010).

An expert committee convened by the American Medical Association proposed recognition of the 99th BMI percentile as a cut point to classify children with severe obesity who are likely to be at increased risk for cardiovascular risk factors (Barlow, 2007). However, estimates of the cut points for the 99th percentile for age and sex are considered unstable. Extreme percentiles extrapolated from the CDC-supplied LMS parameters do not match well to the empirical data for the 99th percentile. A statistically defensible cut point for severe (sometimes called “extreme”) obesity based on available U.S. data is 120% of the smoothed 95th percentile (Flegal et al., 2009). Many investigators also include all adolescents with BMI ≥35 kg/m^2 in the severe/extreme obesity group (Kelly et al., 2013; Koebnick et al., 2010). Children with extreme/severe obesity are at even higher risk for the complications of obesity detailed below (Kelly et al., 2013).

Over the past 50 years, global trends suggest that the prevalence of obesity among children (using BMI-based criteria) has increased significantly (Lobstein, 2010; Wang & Lobstein, 2006). Since the 1960s, prevalence rates have quadrupled in many countries (Lobstein, Baur, & Uauy, 2004). Based on the CDC 2000 BMI standards, among those ages 2–19 years, in 2012, 31.8% had BMI ≥85th percentile, 16.9% (approximately 12.7 million children) had BMI ≥95th percentile (Ogden et al., 2014) and in 2010, 12.3% had BMI ≥97th percentile (Ogden, Carroll, Kit, & Flegal, 2012). Certain racial and ethnic minority populations, especially African Americans, Hispanics, and American Indians, are at particular risk for obesity, while Asian children appear to have lower BMI-based risk of obesity (Flegal, Carroll, Ogden, & Curtin, 2010; Ogden et al., 2014; Spiegel & Alving, 2005). Although some recent data suggest obesity rates have stabilized in children and may even have decreased in those ages 2–5 years (Flegal, Carroll, Kit, & Ogden, 2012; Flegal, Carroll et al., 2010; Ogden et al., 2010, 2012, 2014; Yanovski & Yanovski, 2011), the obesity prevalence among children and adolescents remains alarmingly high.

Consequences of pediatric obesity

Pediatric overweight and obesity are of concern because of both immediate and later onset health consequences (Daniels, 2009). Children at the highest levels of BMI are usually at the greatest risk of obesity-associated adverse health outcomes (Koplan et al., 2004). Obesity in childhood is more likely to lead to adult obesity (Freedman et al., 2007) and to the tracking of poor health throughout adulthood; thus obesity appears to be a major contributor to many preventable causes of morbidity. The risk of adult obesity appears higher for older obese children, for those with more severe obesity, and for those with obese parents. (Whitaker, Wright, Pepe, Seidel, & Dietz, 1997). Some data suggest that those with extremely high BMI percentiles (significantly above the 97th percentile) are even more likely to have

tracking of obesity into adulthood (Freedman et al., 2007). Although there is variation in the estimates among studies examining the question of persistence, it appears that approximately 40% of obese children become obese adults (Freedman et al., 2004; Must & Strauss, 1999; Power, Lake, & Cole, 1997). The appearance of obesity-associated conditions in childhood has been shown to lead to an earlier onset of related medical complications (Pavkov et al., 2006). Some (Jeffreys, McCarron, Gunnell, McEwen, & Smith, 2003; Must et al., 1992) but not all (Gray, Lee, Sesso, & Batty, 2011; Juonala et al., 2011) studies suggest that pediatric obesity itself has a unique impact on later health independent of adult weight; regardless, there is unanimity that pediatric obesity is a strong risk factor for adult obesity and its complications. The current U.S. childhood obesity epidemic thus has the potential to reverse the improvements in life-expectancy that occurred during the 20th century in the U.S. (Olshansky et al., 2005) and to cause more functional disability in those who survive to old age (Alley & Chang, 2007).

Cardiovascular disease

Obese and overweight youth are more likely to have cardiovascular risk factors resulting in cardiac structural and hemodynamic alterations (Freedman et al., 2007) including hypertension (Speiser et al., 2005), increases in ventricular mass (Daniels, 2009) endothelial dysfunction, with carotid artery intimal medial thickening, and early coronary and aortic fatty streaks and fibrous plaque (Freedman et al., 2004; Tounian et al., 2001), as well as atherosclerosis (Berenson et al., 1998; Daniels, 2009; McGill et al., 2002). Analyses have suggested, however, that there is little evidence that childhood BMI is an independent risk factor for adult cardiovascular risk once adult BMI is taken into consideration (Lloyd, Langley-Evans, & McMullen, 2010).

Dyslipidemia

Childhood obesity is associated with dyslipidemia, with the most common abnormality being elevated triglycerides and decreased high-density lipoprotein (HDL) cholesterol (Daniels, 2009). Elevated low-density lipoprotein (LDL)-cholesterol is also seen in obese children; however, the association between adiposity and LDL-cholesterol is weaker than that of adiposity with triglycerides and HDL-cholesterol (Daniels, 2011). BMI is also positively associated with likelihood for LDL particle size <25.5 nm (Shimabukuro, Sunagawa, & Ohta, 2004). Childhood dyslipidemia has been shown to persist and to be a predictor of adult dyslipidemia, adult carotid intimal media thickness, and other cardiovascular disease risks (Nadeau, Maahs, Daniels, & Eckel, 2011) (Lauer, Lee, & Clarke, 1988).

Impaired glucose homeostasis

Obesity is commonly accompanied by insulin resistance and hyperinsulinemia, which precede and play a major role in the development of type 2 diabetes mellitus (T2DM) (Shulman, 2000). In children, total body fat and visceral fat are positively associated with fasting insulin (Caprio et al., 1995; Freedman et al., 1987; Gutin et al., 1994), and impaired insulin sensitivity may worsen with duration of obesity (Le Stunff & Bougneres, 1994). Some data suggest as many as 21% of obese adolescents and 25% of obese children may have impaired glucose tolerance (Sinha et al., 2002), although most studies report much

lower prevalence (Uwaifo, Elberg, & Yanovski, 2002). The increasing incidence of pediatric T2DM has paralleled the increasing prevalence of obesity. It has been estimated that more than 20% of all new cases of pediatric-onset diabetes among adolescents are now T2DM (Dabelea et al., 2014) and the overall prevalence of T2DM in children ages ≥10 years is 0.46 per 1000 children, a 30% increase since 2001 (Dabelea et al., 2014; Liese et al., 2006). Development of T2DM adds on higher risk for cardiovascular disease than obesity alone. Among Pima Indians, the onset of T2DM during childhood or adolescence has been associated with a markedly earlier age for development of end-stage renal disease and a significant increase in mortality rate before age 55 years (Pavkov et al., 2006).

Metabolic syndrome

The metabolic syndrome refers to the clustering of insulin resistance, hypertension, dyslipidemia, and obesity, and this condition has been associated with increased risk of cardiovascular disease and T2DM in adults. There is no consensus definition for the metabolic syndrome in pediatrics, but there are sets of criteria derived from the adult criteria that use percentile-based cut points for children (Daniels, 2009). Increasing BMI and insulin resistance during childhood are strong predictors of the metabolic syndrome (Shaibi & Goran, 2008; Srinivasan, Myers, & Berenson, 2002). In the NHANES 1999–2002 survey data, the overall prevalence of metabolic syndrome among U.S. adolescents ages 12 to 19 years ranged from 2.0% to 9.4% depending on the definition used, whereas among obese adolescents, the prevalence ranged from 12.4% to 44.2% (Cook, Auinger, Li, & Ford, 2008). However, the clinical utility of the metabolic syndrome in pediatrics remains unclear (Daniels, 2009). There is also quite limited stability for the diagnosis of metabolic syndrome among children and adolescents (Goodman, Daniels, Meigs, & Dolan, 2007; Goodman et al., 2009; Gustafson et al., 2009; Stanley, Chen, & Goodman, 2014). A detailed scientific statement appraising the evidence for utility of the metabolic syndrome in pediatrics is available from the American Heart Association (Steinberger et al., 2009).

Pulmonary comorbidities

It is estimated that up to 33% of obese children have obstructive sleep apnea (OSA) (Marcus et al., 1996; Tauman & Gozal, 2006; Wing et al., 2003). Among severely obese adolescents, 55% have polysomnographic findings consistent with OSA (Tauman & Gozal, 2006). Central hypoventilation syndrome also has been described in obese children (Tauman & Gozal, 2006). Pediatric studies have also documented an association between obesity and asthma (Jensen, Collins, Gibson, & Wood, 2011).

Gastrointestinal comorbidities

Gastroesophageal reflux, nonalcoholic fatty liver disease (NAFLD), cholelithiasis, and gallstones are increased among obese pediatric patients. A 13% prevalence of gastroesophageal reflux has been observed in obese children (Pashankar, Corbin, Shah, & Caprio, 2009). NAFLD has been shown to occur in 2.6–25% of obese children and adolescents from small epidemiological studies using indirect diagnosis tests such as liver enzymes or ultrasound (Socha et al., 2009), while an autopsy study reported a 9.6% prevalence in children ages 2–19 years and a higher prevalence among obese children (38%) (Schwimmer, Deutsch et al., 2003). NAFLD can potentially progress to nonalcoholic

steatohepatitis (NASH) or to hepatic fibrosis and cirrhosis (Socha et al., 2009). NAFLD histology shows more fibrosis in children than adults (Schwimmer et al., 2006). Gallstones also have been shown to be more common in obese adolescents, with a higher prevalence observed in obese girls (Koebnick et al., 2012).

Orthopedic complications

A higher frequency of musculoskeletal discomfort and/or impairment of mobility (Taylor et al., 2006) and eased risk of fractures (Goulding, Grant, & Williams, 2005) has been documented in obese children and adolescents. Tibia vara (Blount's disease) and slipped capital femoral epiphysis (SCFE) are the most common orthopedic problems in obese children (Daniels, 2009), resulting from mechanical stress on the developing skeletal system. Blount's disease usually occurs in severely obese boys age 9 years or older and presents with bowing of the tibia and abnormal gait. SCFE presents with a waddling gait, limitation of hip movement, and/or pain in the hip or knee joints. SCFE occurs more commonly among obese African-American than non-African American males (Loder, Aronson, & Greenfield, 1993).

Psychosocial and neurocognitive issues

Obese children are more likely to have psychological distress including low self-esteem, higher rates of anxiety disorders, body image disturbance, and depressive symptoms (Hesketh, Wake, & Waters, 2004; Reeves, Postolache, & Snitker, 2008). There is also evidence suggesting increased risk for obesity among depressed youth (Richardson et al., 2003). Obese children and adolescents reported significantly lower health-related quality of life compared to their normal-weight peers, and they rated their health-related quality of life as low (Fallon et al., 2005), in some studies as low as that of children being treated for cancer (Schwimmer, Burwinkle, & Varni, 2003). Experiences of teasing and bullying have been shown to be higher among obese children and adolescents (Griffiths, Wolke, Page, & Horwood, 2006; Neumark-Sztainer et al., 2002; Young-Hyman et al., 2006). Weight-related teasing may result in unhealthy weight-control behaviors such as binge- or loss of control eating, which could cause further weight gain among overweight and obese youth (Tanofsky-Kraff et al., 2006; Tanofsky-Kraff, Yanovski et al., 2009).

With regard to neurocognitive function, many manuscripts have documented cross-sectional associations between body weight and neurocognitive dysfunction among children (Cserjesi, Molnar, Luminet, & Lenard, 2007; Kamijo et al., 2012, 2014; Li, Dai, Jackson, & Zhang, 2008; Verdejo-Garcia et al., 2010). A recent critical review of the literature found support for an inverse relationship between body weight/adiposity and executive functioning, attention, visuospatial performance, and motor skill (Liang, Matheson, Kaye, & Boutelle, 2014). Several of the genetic syndromes associated with obesity (reviewed below) are also associated with significant neurocognitive defects. It is possible that neurocognitive defects are etiologic factors causing or worsening obesity; it is also likely that at least some of the observed issues in obese children are the result of obesity and its medical complications. These concepts, as well as the possibility that specific macro- and micro-nutrients in the diet may change neurocognitive function in a fashion that worsens the predisposition toward obesity, are explored in some of the subsequent papers in this Special Issue.

Puberty

Obesity is associated with early onset of the larche (Crocker et al., 2014; Juul et al., 2006; Kaplowitz, Slora, Wasserman, Pedlow, & Herman-Giddens, 2001) and slightly earlier menarche among girls (Anderson, Dallal, & Must, 2003; de Ridder et al., 1992; Freedman et al., 2002; Garn & Haskell, 1959; Jaruratanasirikul, Mo-suwan, & Lebel, 1997; St George, Williams, & Silva, 1994; Wattigney, Srinivasan, Chen, Greenlund, & Berenson, 1999). In contrast, obese boys are more likely to have delayed onset of gonadarche (Crocker et al., 2014; Lee et al., 2010; Wang, 2002). Excess adipose tissue results in elevated estrogenic effects because of several factors, including greater aromatase expression in adipose tissue, low levels of sex hormone-binding globulin, and possibly other contributors such as high-fat diets (Jasik & Lustig, 2008).

Hyperandrogenism and polycystic ovary syndrome

Among girls, peripubertal obesity is associated with significant hyperandrogenism, which is particularly marked in the pre- and early pubertal period (McCartney et al., 2007). Elevated insulin levels are thought to be the mechanism leading to hyperandrogenism (McCartney et al., 2007). Excess adiposity may thus cause polycystic ovary syndrome and may be associated with anovulation resulting in irregular menses (oligomenorrhea or amenorrhea), elevated androgens with or without clinical hyperandrogenism (hirsutism, acne, and male-pattern hair loss), and cystic ovaries. In adults, 30% to 75% of women with polycystic ovary syndrome have obesity (Ehrmann, 2005).

Mortality

Some (Jeffreys et al., 2003; Must et al., 1992) but not all (Gray et al., 2011) studies have suggested that pediatric obesity has a unique impact on subsequent mortality. For example, in 1992, investigators (Must et al., 1992) reported that adolescent obesity was independently associated with an increased risk of mortality among 508 men in the Harvard Growth Study, but a subsequent analysis (Gray et al., 2011) found no evidence for an independent effect of high BMI in early adulthood on cardiovascular mortality risk in a study of 18,995 participants in the Harvard Alumni Study. Nevertheless, projection analysis by Olshansky and colleagues (2005) predicted a shorter life span for the current generation of U.S. children, largely because of obesity and all its related comorbidities.

Etiopathogenesis of pediatric obesity

Obesity is clearly an environmentally-induced disorder; our genetic endowments have changed minimally during the last 40 years, yet the prevalence of abnormally high BMI in US children has tripled – an observation that can only be explained by changes in external factors affecting children's energy economy (Fig. 1). Obesity is also just as clearly a genetic disease, because all available data suggest that 60–80% of the observed variance in human body weight can be accounted for by inherited factors (Wardle, Carnell, Haworth, & Plomin, 2008). Finally, there is good evidence for gene × environment interactions for obesity risk alleles (Ahmad et al., 2011; Andreasen et al., 2008; Demerath et al., 2013; Garver et al., 2013; Qi et al., 2012; Rampersaud et al., 2008; Rosenquist et al., 2015). Thus, for obesity, "genetic background loads the gun, but the environment pulls the trigger" (Bray, 2004).

More than 300 genetic loci that are potentially involved in human body weight regulation have been identified through analyses in humans, rodents, and *Caenorhabditis elegans* (Ashrafi et al., 2003; Rankinen et al., 2006), and at least 32 have genome-wide significance (Speliotes et al., 2010). Some exceedingly rare gene variants affect gene function and behavior to such an extent that obesity results even without a particularly "obesogenic" environment, but the vast majority of genetic differences are presumed to affect body weight enough to cause obesity only in a permissive environment. Conditions known to influence body weight include:

Classical endocrine disorders associated with weight gain

Children with identifiable endocrinopathies are believed to comprise only a small minority of children referred for evaluation of overweight, on the order of 2–3% (Crino et al., 2003). Hypothyroidism is associated with a BMI increase in children of 1–2 BMI units (i.e., only a few kg) (Ning & Yanovski, 2006). Because children with hypothyroidism usually have diminished linear growth, BMI may be high even though weight does not exceed the 95th percentile (Abbassi, Rigterink, & Cancellieri, 1980). Growth hormone (GH) deficiency is also associated with diminished linear growth that is accompanied by continued increase in body weight. GH deficiency leads to increased fat mass, especially in a central distribution, along with decreased lean mass. Cushing's Syndrome usually causes central obesity, although weight gain may be more global in children, and it is also associated with markedly diminished height velocity (Greening et al., 2006; Magiakou et al., 1994). Insulinomas are quite rare in children, with an incidence rate of ~4 per 50,000,000 per year. Elevated insulin production leads to increased food intake to counter lower blood sugars and therefore leads to obesity (Bonfig, Kann, Rothmund, & Schwarz, 2007; Dizon, Kowalyk, & Hoogwerf, 1999).

Structural disorders of the hypothalamus associated with weight gain

Hypothalamic obesity may arise after injury to, or congenital malformation of, the hypothalamus. For example, loss of function of the hypothalamic developmental factor Sim1 leads to obesity in humans (Holder, Butte, & Zinn, 2000; Hung et al., 2007). Obesity occurs in approximately 50% of children treated surgically for craniopharyngioma (Hoffman et al., 1992; Muller et al., 2001; Srinivasan et al., 2004).

Leptin signaling pathway genes

Rare inactivating mutations affecting genes in the leptin signaling pathway may account for as much as 3 or 4% of severe, early-onset obesity. Inactivating mutations affecting both alleles of the genes coding for leptin (Montague et al., 1997; Strobel, Issad, Camoin, Ozata, & Strosberg, 1998), the leptin receptor (Clement et al., 1998; Farooqi, Wangensteen et al., 2007), pro-opiomelanocortin (POMC) (Challis et al., 2002; Creemers et al., 2008; Farooqi et al., 2006; Krude et al., 1998, 2003; Lee et al., 2006), and enzymes that process POMC, such as prohormone convertase 1 (Farooqi, Volders et al., 2007; Jackson et al., 1997, 2003) have also been found in pediatric patients. Abnormalities causing inactivation in genes affecting leptin receptor signal transduction, such as SH2B1 are also associated with obesity and neurocognitive defects (Bochukova et al., 2010; Doche et al., 2012). Some data suggest that

ciliopathies such as those causing Bardet Biedl Syndromes may disrupt leptin signaling (Feuillan et al., 2011; Seo et al., 2009). Homozygous and heterozygous inactivating mutations in the melanocortin 4 receptor (MC4R) cause obesity and hyperphagia during childhood (Farooqi et al., 2003) and are the most common known cause of severe, early onset obesity accounting for, in some series, as many as 3% of such children (Farooqi et al., 2000). Rare mutations in MRAP2, a protein essential for MC4R function, are also associated with pediatric obesity (Asai et al., 2013). Some data also support a role for polymorphisms in the MC3R for regulation of body weight, particularly in African American children (Feng et al., 2005; Savastano et al., 2009). Brain derived neurotrophic factor (BDNF) is believed to function downstream from MC4R in the leptin signaling pathway. Haploinsufficiency for BDNF has been suggested to be the cause of pediatric-onset obesity and contribute to neurocognitive problems in patients with WAGR syndrome (Han et al., 2008, 2013). A heterozygous inactivating mutation in the gene coding for the BDNF receptor has also been found to be associated with obesity, seizures, and developmental delay (Yeo et al., 2004).

Syndromic obesity

Many genetic syndromes (Table 1) involve obesity as part of their presentation but only a small fraction of obese children have one of these etiologies. Importantly, developmental delay or neurocognitive defects are reported in the majority of these syndromes. It is possible that some individuals with non-syndromic obesity have less-damaging mutations in one or more of these genes that may in part account for the greater incidence of developmental delay among obese individuals.

Common allelic variation in genes that may affect energy balance

Single Nucleotide Polymorphisms (SNPs) and copy number variation in many genes and chromosomal regions have been found to be associated with body weight or body composition (Meyre et al., 2009; Scherag et al., 2010; Speliotes et al., 2010; Thorleifsson et al., 2009; Wheeler et al., 2013; Willer et al., 2009). The mechanisms explaining how identified gene regions might change energy balance are often not fully understood. The most widely replicated finding is linkage of the *FTO* gene locus with body weight (Dina et al., 2007; Frayling et al., 2007; Hinney et al., 2007; Hunt et al., 2008; Scuteri et al., 2007). *FTO* mRNA is highly expressed in brain areas important for regulation of energy- and reward-driven consumption (Fredriksson et al., 2008). Some limited data also suggest that children with less common alleles in *FTO* may have greater food intake (Cecil, Tavendale, Watt, Hetherington, & Palmer, 2008; Wardle, Llewellyn, Sanderson, & Plomin, 2008), reduced satiety (Wardle, Carnell, Haworth, Farooqi et al., 2008) and greater prevalence of loss of control over their eating (Tanofsky-Kraff, Han et al., 2009). It remains unclear whether the protein coded by *FTO* itself (Church et al., 2010) or other genes regulated by the *FTO* locus (Smemo et al., 2014; Stratigopoulos et al., 2008) account for these associations.

Pre-conception, maternal, and intrauterine factors

Beyond straightforward genetic links between parent and child body weight, there is evidence that the maternal environment can have great consequences for subsequent risks

for both obesity and its metabolic complications (Ludwig & Currie, 2010; Whitaker & Dietz, 1998). For example, high pre-pregnancy maternal weight and pregnancy weight gain are risk factors for infants to be born large for their gestational age (Whitaker & Dietz, 1998; Yu et al., 2013) and for subsequent development of metabolic abnormalities including impaired glucose homeostasis. Maternal diabetes also has an unquestioned role in predisposing infants to large size and subsequent type 2 diabetes (Dabelea et al., 2000, 2008; Gillman, Rifas-Shiman, Berkey, Field, & Colditz, 2003). Inadequate intrauterine growth also appears associated with childhood obesity, type 2 diabetes, and coronary heart disease (Barker, 2007; Hales & Barker, 1992). The notion that the intrauterine environment may be of paramount importance for subsequent child health is sometimes referred to as the "Developmental Origins of Health and Disease" model, but is also known as the Barker Hypothesis, after David Barker, who reinvigorated this area of research and carried out many studies documenting that fetal re-programming by the intrauterine environment can have lasting impact on children's health (Bateson et al., 2004).

Acquired obesity

Many medications may lead to weight gain, including insulin secretagogues, glucocorticoids, antipsychotics, mood stabilizers, antidepressants, anticonvulsants, antihypertensives, antihistamines, and chemotherapeutic agents (Maayan & Correll, 2011; Malone, 2005). An avian form of adenovirus, AD36, has been found to cause increased adiposity in infected chickens (Dhurandhar, Kulkarni, Ajinkya, & Sherikar, 1992) and some studies suggest that humans with antibodies to AD36 (indicating past infection) also tend to have higher rates of obesity (Atkinson et al., 2005; Dhurandhar, Kulkarni, Ajinkya, Sherikar, & Atkinson, 1997).

As outlined in Fig. 1, and as suggested by the recent increases in the prevalence of obesity, the sociocultural and ecological environment plays a major role in determining who becomes obese (Hawkins, Cole, & Law, 2009; Keith et al., 2006; Lang & Rayner, 2007). Arizona Pima Indians who live on a reservation have much higher rates of obesity and diabetes than their genetically-related counterparts in an isolated Mexican village (Ravussin, Valencia, Esparza, Bennett, & Schulz, 1994). Asian and Hispanic adolescents born in the United States have a higher prevalence of obesity than immigrant members of the same community (Popkin & Udry, 1998). Finally, the differential response of some people to environmental conditions that lead to obesity may be the result of epigenetic changes – alterations in gene expression related to disease risk that are modified by the environment during development (Almen et al., 2014; van Dijk, Molloy, Varinli, Morrison, & Muhlhausler, 2015). Some of the papers included in this Special Issue will address mechanisms through which the environment may predispose susceptible individuals to develop obesity.

Conclusion

Pediatric obesity is a complex disorder, with myriad contributing environmental, biopsychosocial, genetic, and epigenetic factors. It causes significant medical, psychosocial, and neurocognitive abnormalities during childhood. The persistence of obesity into

adulthood makes understanding the causes of excessive adiposity during childhood of paramount importance to prevent its impact on long-term health and quality of life.

The subsequent papers in this Special Issue discuss one of the most interesting proposed mechanisms for the establishment and maintenance of pediatric obesity; these manuscripts examine the potential effects of obesity and diet composition on brain substrates for cognition, elucidate the cognitive processes influenced by childhood weight and nutritional status, and provide data from intervention studies aimed at improving cognition to affect body weight in children. It is hoped that this Special Issue will promote future research in this area that will ultimately aid efforts to prevent and treat pediatric obesity.

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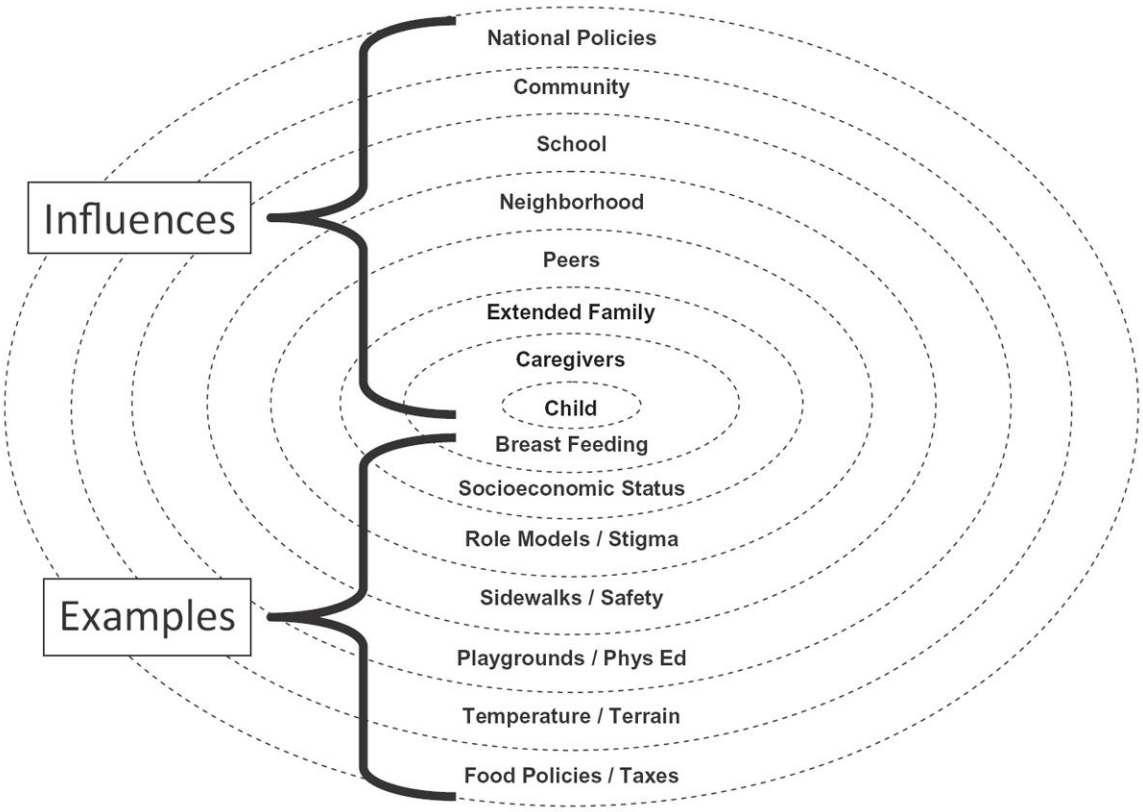

Fig. 1.

A Social–Ecological Model of Influences on pediatric obesity. Levels of environmental influence begin with the family environment and extend to larger spheres of influence and include peers, neighborhoods, schools, community, and national factors. Examples of influences within each of these spheres are also given. For example, neighborhood environment may influence children's activity if there are no sidewalks or if safe areas for play are not available. (Figure courtesy of Denise E Wilfley, PhD, St. Louis, MO; adapted with permission.)

Table 1

Genetic syndromes commonly associated with obesity or overgrowth.

Genetic syndrome	Gene(s)/chromosomal location(s)	Associated with neurocognitive deficits?
Achondroplasia	FGFR3/4p16.3	No
Alström Syndrome	ALMS1/2p13.1	Yes
Bardet Biedl Syndromes	Multiple/Multiple	Yes
Beckwith–Wiedemann Syndrome	CDKN1C, KCNQ1OT1/H19,/11p15, 11p14	Rarely
Borjeson–Forssman–Lehmann Syndrome	PHF6/Xq26.2	Yes
Carpenter syndrome	RAB23/6p11.2	Yes
Congenital disorder of glycosylation 1a	PMM2/16p13.2	Yes
Cohen Syndrome	COH1 (VPS13B)/8q22.2	Yes
Cowden syndrome	PTEN/10q23.31	Yes
Fragile X	FMR1/Xq27.3	Yes
MEHMO Syndrome	Xp22.13-p21.1	Yes
Meningomyelocele	Multiple/Multiple	Variable
MORM Syndrome	INPP5E/9q34.3	Yes
Prader Willi Syndrome	SNRPN, NDN/15q11.2	Yes
Pseudohypoparathyroidism 1a	GNAS/20q13.32	Yes
Simpson–Golabi–Behmel Syndrome	GPC3/Xq26.2	Variable
Smith–Magenis Syndrome	RAI1/17p11.2	Yes
Sotos Syndrome 1	NSD1/5q35.2-q35.3	Yes
Sotos Syndrome 2	NFIX/19p13.2	Yes
Turner Syndrome	Multiple/X	Variable
Ulnar–mammary Schinzel Syndrome	TBX3/12q24.21	Yes
WAGR Syndrome with obesity	BDNF/11p14.1	Yes
Weaver syndrome	EZH2/7q36	Yes
Wilson–Turner Syndrome	HDAC8/Xq13.1	Yes