Early in the Life Course: Time for Obesity Prevention

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1 Introduction

Although the dramatic rise in obesity in the USA experienced in recent decades (Wang and Beydoun 2007) may have now stabilized (Ogden et al. 2014; Wen et al. 2012), the prevalence of obesity remains high. The most recent nationally representative data collected in 2012 showed that 17% of children ages 2–19 years were obese (Ogden et al. 2014). From 2003 through 2010, the prevalence of obesity in low-income children aged 2–4 years remained at approximately 15% (Pan et al. 2012), while one regional study suggested that from 2004 through 2008, obesity prevalence started to drop among 0 to 6-year-olds from non-low-income families (Wen et al. 2012). The reasons for this potential slowing or slight reversal of the trend among some subgroups in the USA remain unknown. However, obesity has not affected all segments of the population equally (Wang and Beydoun 2007; Wang et al. 2011), and racial/ethnic differences in obesity are already evident by the preschool years (Ogden et al. 2014).

The short- and long-term consequences of obesity include conditions involving nearly every organ system, such as asthma, type 2 diabetes, high blood pressure, cardiovascular disease, depression, and orthopedic problems, starting in childhood and escalating among adults (Han et al. 2010; Lobstein et al. 2004). Children who are obese are much more likely to be obese adults, and obesity at any age is very difficult to treat (Lobstein et al. 2004). Furthermore, the population-level effects of obesity are substantial. Nationwide, 9.1% of annual medical spending is attributable to adult obesity, representing a cost of $147 billion per year (Finkelstein et al. 2009). This combination of evidence on the epidemiology, health consequences, and public health impact of obesity suggests that prevention is essential.

2 Conceptual Framework

One of the reasons for the intractability of childhood obesity is the failure to take into account the complexity and interconnectedness of contributing factors ranging from the social, built, and economic environments to behavior, physiology, and epigenetics. These factors may also interact with each other creating a self-perpetuating cycle

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N. Halfon et al. (eds.), *Handbook of Life Course Health Development*,
DOI 10.1007/978-3-319-47143-3_9

of obesity, as we illustrate using gestational diabetes mellitus (Sect. 4.3; Gillman 2016). Based on the life course health development approach to chronic disease epidemiology, biological, behavioral, and psychosocial exposures that occur at particular stages in the life course may have differential and/or lasting effects on later outcomes (Ben-Shlomo and Kuh 2002; Halfon and Forrest 2017).

The effects of these exposures can be cumulative across an individual's life as well as operate across generations to influence future generation's risk for chronic disease. Factors can also interact with each other over the life course and be more or less important at particular stages. These periods of particular influence are often termed critical or sensitive (Ben-Shlomo and Kuh 2002). Throughout the chapter, we demonstrate that multiple critical and sensitive periods for obesity risk exist across the life course, although practically they may be hard to identify. Given the plasticity inherent in early human development, the pre- and perinatal periods may present the most important opportunity for critical or sensitive period effects. Added to the fact that treatment of obesity is impeded by cultural, behavioral, and physiological feedback loops, modifying environment, behaviors, and physiology early in life is likely an especially effective strategy for preventing obesity and its consequences.

Consistent with LCHD principles (see Halfon and Forrest 2017), Glass and McAtee (2006) propose that the multilevel approach shown in Fig. 1 places obesity prevention in a complex system with individual risk factors being influenced by multiple "above-water" levels (families, neighborhood, policies) as well as by the interaction with biology and "underwater" levels (genes, epigenetics, physiology) over time. This framework adds to a life course health development approach by emphasizing feedback loops and cross-level influences, such as gene-environment interactions, thus highlighting the need for methodology that takes into account these complex relationships to help identify the important and modifiable levers of change (Huang and Glass 2008).

We have organized this chapter to reflect the current thinking on periods in the life course that appear to be most important for the development of obesity. We focus primarily on the early portion of the life course, but also discuss later periods that may be key time points for intervening. These periods often represent times of active growth or turning points when the primary sources of influence change.

At each stage of the life course, we discuss specific macro-level factors if they are directly relevant to that time period. Most macro-level factors, however, either indirectly or directly influence all age groups, so we present them together after reviewing each life course stage individually. While this chapter does not represent a systematic review of the literature, we present key examples at each stage of the life course to illustrate important risk factors, mechanisms, and gaps in research. We conclude with recommendations for future work on methodology, research in emerging areas, and implications for practice and policy.

3 Measurement of Overweight and Obesity

Body mass index (BMI; weight/height^2) is the most commonly used indirect measure of adiposity, or fatness, at the population level. The US Centers for Disease Control and Prevention (CDC) recommends monitoring growth in children aged 0–2 years using the World Health Organization weight for recumbent length growth standards and defines excess weight as at or above the 97.7th percentile (Grummer-Strawn et al. 2010). The CDC defines obesity in children aged 2–19 years as a BMI at or above the 95th percentile for age and sex, with overweight between the 85th and 95th percentiles, using the CDC sex-specific BMI-for-age growth charts from 2000 (Kuczmarski et al. 2002; Ogden and Flegal 2010).

4 Prenatal Period

4.1 Birth Weight

Numerous studies have confirmed the associations of higher birth weight with risk of later obesity and type 2 diabetes mellitus; lower birth

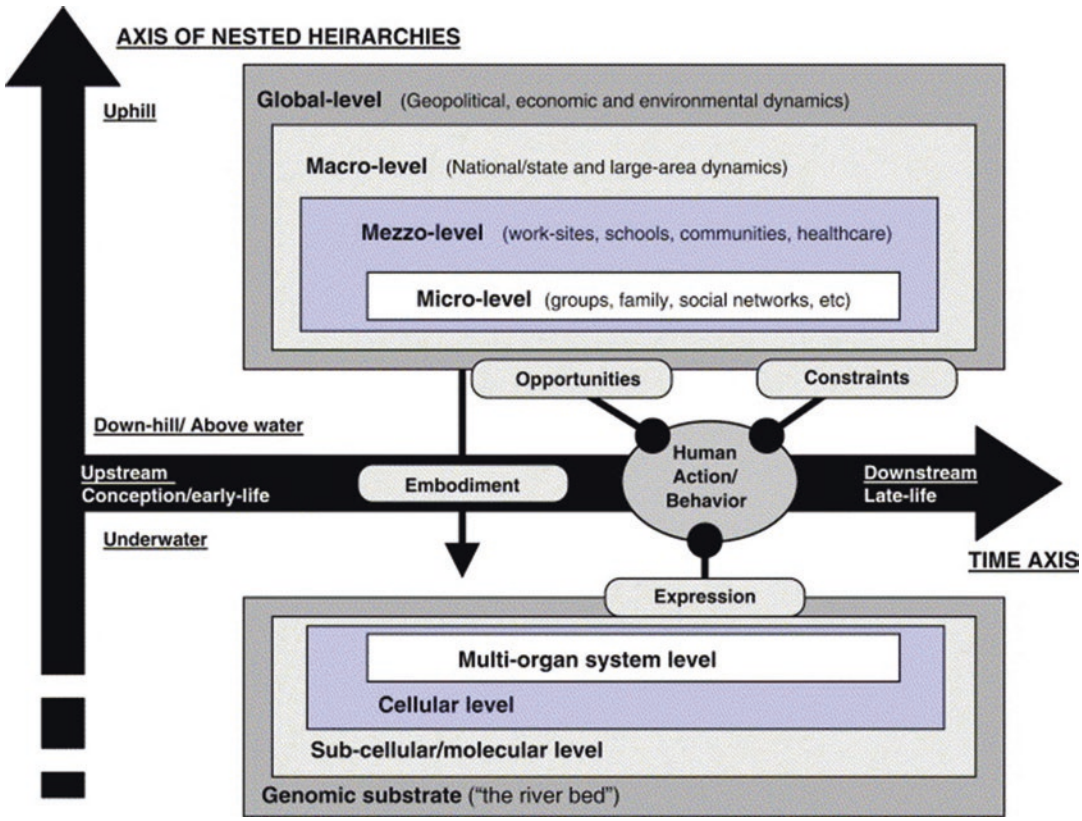

Fig. 1 Conceptual framework for etiology of childhood obesity (Reproduced from Glass and McAtee (2006))

weight is consistently associated with increased risk for central adiposity and its metabolic correlates, including type 2 diabetes mellitus and cardiovascular disease (Parsons et al. 1999; Yu et al. 2011). Birth weight, however, is not an etiologic factor in itself. Some have used birth weight as a marker of in utero programming during sensitive periods of development (Gillman 2005). However, many factors could explain the relationship between birth weight and later obesity. For example, maternal obesity, a risk factor for higher birth weight, is also highly related to childhood obesity (Perng et al. 2014). This association may be due to genomic inheritance and shared postnatal environment of eating habits and physical activity or inactivity in addition to in utero effects (Gillman and Poston 2012). However, even after controlling for maternal obesity, sociodemographic characteristics, and other risk factors, the birth weight-obesity association remains, raising the possibility of a lasting effect of fetal programming on later health (Gillman 2004; Oken and Gillman 2003).

4.2 Maternal Prepregnancy Obesity

Many women start their pregnancy already overweight or obese. In 2009, a representative survey from 20 states found that 21% of women were obese prepregnancy and an additional 25% were overweight (Fisher et al. 2013). Mothers who are overweight or obese prepregnancy are more likely to have infants with higher birth weight and an increased risk for being large-for-gestational age (LGA; >90th percentile of weight-for-gestational age) or macrosomic (birth weight > 4000 g) (Institute of Medicine 2009).

Women who are overweight or obese going into pregnancy are at higher risk for developing gestational diabetes mellitus (Torloni et al. 2009) and more likely to gain excessive amounts of weight during pregnancy (Battista et al. 2011; Dalenius et al. 2012). Studies must take into account these related factors to tease apart the roles of potentially modifiable risk factors. Furthermore, these risk factors may also be markers for shared genes and/or the postnatal environment (including lifestyle behaviors), which could also influence children's risk for obesity. This issue of interrelated factors—which may serve as mediators, moderators, or confounders of each other—is applicable not just to the prenatal period, but also to all stages of life course health development.

4.3 Gestational Diabetes Mellitus (GDM)

GDM is defined as diabetes first diagnosed in pregnancy, typically between 24 and 28 weeks gestation. Data on 59 million births from the National Hospital Discharge Survey showed that GDM increased from 1.9% to 4.2% from 1989 through 2004 (Getahun et al. 2008). Over this time period, the relative increase in GDM was 94% for white women (from 2.2% to 4.2%), but 260% for black women (from 0.6% to 2.1%) (Getahun et al. 2008).

GDM may be fueling the obesity epidemic (Battista et al. 2011; Herring and Oken 2011). Figure 2 shows the interrelationships of maternal, fetal, and child factors across the life course that may propagate the intergenerational transmission of obesity and diabetes (Gillman 2016). Both maternal prepregnancy obesity and excessive gestational weight gain (GWG) independently increase mothers' risk for developing GDM. A systematic review found that higher maternal prepregnancy BMI was associated with an increase in risk for GDM, such that overweight, moderately obese, and morbidly obese women were 2, 3, and 5.5 times more likely to develop GDM compared to women with normal BMI (Torloni et al. 2009). Excess GWG during pregnancy may also increase mothers' risk for GDM, independent of women's prepregnancy weight (Hedderson et al. 2010). Compared to women with adequate levels of weight gain, women with excessive GWG are also more likely to have greater postpartum weight retention (Nehring et al. 2011). All of these factors increase women's risk for subsequent health problems. Women with a history of GDM are more likely to develop type 2 diabetes mellitus, particularly within the first decade after delivery (Kim et al. 2002). Developing GDM in one pregnancy increases mothers' risk for the recurrence of GDM in subsequent pregnancies (Kim et al. 2007). If women do not lose the excess weight they gained before they become pregnant again, this increased adiposity reinforces the cycle in the subsequent pregnancy.

Prepregnancy obesity, excessive GWG, and GDM are associated with higher fetal growth and subsequent increases in children's adiposity and risk for obesity (Fig. 2) (Gillman 2016). Infants born to mothers with prepregnancy obesity or GDM are more likely to be of higher birth weight or be macrosomic (Battista et al. 2011; Institute of Medicine 2009), and trials of GDM treatment show reductions in macrosomia (Crowther et al. 2005; Gillman et al. 2010; Landon et al. 2009). A study found that children born to mothers with GDM had higher levels of adiposity and insulin secretion at age 5–10 years, independent of current BMI (Chandler-Laney et al. 2012). Boney et al. (2005) found that children who were LGA at birth and exposed to either GDM or maternal obesity in utero were at an increased risk for developing metabolic syndrome. The cycle continues when girls who are obese mature and have children of their own.

Plausible developmental mechanisms exist for the influence of GDM on childhood obesity. Pancreatic β-cells normally increase their insulin secretion to compensate for the insulin resistance during pregnancy. Glucose intolerance results when the β-cells are not able to respond to this increasing demand (Battista et al. 2011). Since glucose crosses the placenta but insulin does not, the fetus is exposed to greater levels of glucose (Freinkel 1980). The developing fetal pancreas

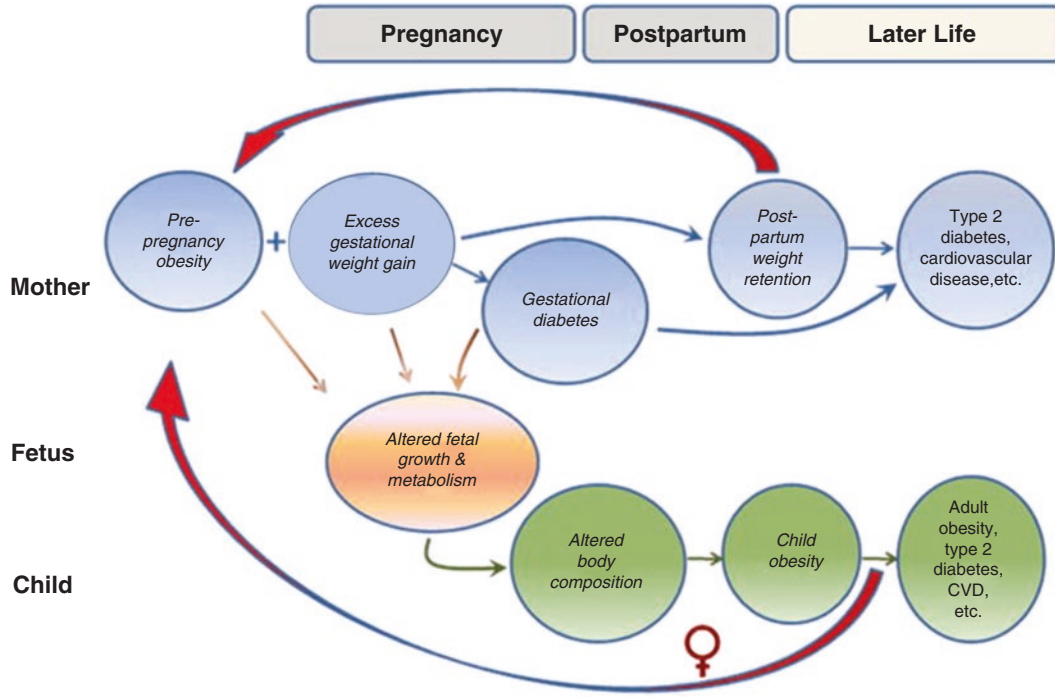

Fig. 2 Intergenerational transmission of obesity and gestational diabetes mellitus (Reproduced from Gillman (2016))

responds to the additional glucose by producing insulin, which can increase fetal adiposity (Freinkel 1980). Current research on the mechanisms of GDM is focusing on the areas of genetics, glucose, amino acid, lipid transport, and adipokines (Harlev and Wiznitzer 2010).

Methodological challenges abound in studying the association between GDM and later obesity. Kim et al. (2011) have argued that many studies combine pregestational diabetes mellitus and GDM into one category, examine only exposed or high-risk infants without an appropriate control group, and fail to control for potential confounding factors, most notably BMI. Their systematic review identified 12 studies of children exposed prenatally to GDM (excluding pregestational diabetes), with resulting crude odds ratios of 0.7–6.3 for offspring obesity. However, in many studies, it is not possible to distinguish women with GDM with true onset during pregnancy from undiagnosed pregestational diabetes (Herring and Oken 2011; Kim et al. 2011). In the two studies that adjusted for maternal prepregnancy BMI, results attenuated and were no longer significant after the covariate was included (Kim et al. 2011), which suggests that GDM may be a marker for preexisting maternal factors.

Randomized controlled trials (RCTs) of risk factor manipulation in pregnancy with childhood follow-up are especially valuable because they minimize the effect of confounding and thus are the most direct assessment of in utero programming in humans. In a US-based RCT of the treatment for mild GDM on pregnancy-related outcomes, Landon et al. (2009) found reduction in LGA and macrosomia; however, no childhood follow-up has been done. Gillman et al. (2010) followed up a subset of children who participated in an Australian-based multicenter RCT of treatment for mild GDM. Although the parent trial showed halving of macrosomia at birth, there were no differences in child BMI at age 4–5 years. One possible explanation for the null result is that offspring of mothers with GDM appear to lose their excess fat in the first year of life and do not again begin to diverge from their unexposed

peers until school age; thus, continued follow-up of these children may be needed to demonstrate a longer-lasting effect of prenatal GDM treatment. Furthermore, as this study included women with mild GDM only, a more dramatic benefit of treatment may be experienced among offspring of women with more extreme hyperglycemia (Gillman et al. 2010).

Another method for minimizing confounding is sibling-pair designs, which partially control for differences in the pre- and postnatal environment (Brion 2010). This method relies on discrepant in utero exposure between siblings, such that the mother experienced GDM during her pregnancy with one sibling but not the other. Lawlor and colleagues (2011b) conducted a sibling-pair study of over 280,000 Swedish men through a record linkage study of their military conscription medical examination with birth information. They found that BMI at age 18 was higher in men whose mothers had GDM during pregnancy than those who did not; these differences were still evident in the within-sibling analyses and independent of maternal BMI. The authors concluded that GDM may influence later obesity risk through intrauterine mechanisms (Lawlor et al. 2011b).

4.4 Gestational Weight Gain (GWG)

In 1990, the Institute of Medicine (IOM) (1990) issued guidelines for the appropriate amount of weight women should gain during pregnancy. However, over the last two decades, excessive GWG has been common and increasing. In 2010, based on the Pregnancy Nutrition Surveillance System (PNSS) from 29 states and the District of Columbia, approximately 48% of low-income women gained more weight than recommended (Dalenius et al. 2012). Excessive weight gain is associated with adverse infant outcomes, including macrosomia and LGA infants, as well as postpartum weight retention in mothers (Siega-Riz et al. 2009). In 2009, the IOM published new guidelines, which for the first time include a weight gain range for obese women that recommends lower gains than for women with lower weight status (Institute of Medicine 2009).

GWG may also have a lasting effect on body size across the life course through in utero conditioning. Although some evidence suggests that extreme undernutrition during pregnancy may be associated with higher obesity risk in offspring, the more common occurrence is overnutrition during pregnancy (Herring et al. 2012). Recent systematic reviews found that excessive GWG was associated with an increased risk for offspring obesity compared to adequate GWG (Lau et al. 2014; Mamun Mamun et al. 2014; Nehring et al. 2013), with an overall pooled odds ratio of 1.4 (Mamun et al. 2014; Nehring et al. 2013). For example, Perng et al. (2014) found that every 5 kilograms of GWG was associated with greater adiposity (measured total fat and trunk fat) and higher leptin in children at ages 6–10 years, independent of maternal prepregnancy BMI.

GWG may influence childhood obesity through several potential developmental pathways. Mothers who are more prone to gain weight through genetic risk, poor diet, or other behavioral factors may have children who are also themselves exposed to these same risks. However, associations still remain after adjustment for maternal and paternal BMI, reducing some influence of shared genes and the postnatal environment. An alternative explanation may be through fetal conditioning (Gillman 2005), similar to that proposed for GDM. In animal models, overnutrition during pregnancy has resulted in insulin resistance, increased adiposity, and hypertension in offspring (Alfaradhi and Ozanne 2011).

One methodology to test causality is through an intervention aimed at influencing maternal weight gain during pregnancy through positive lifestyle changes. Three recent meta-analyses summarized the evidence on RCTs for prenatal dietary, physical activity, and behavioral or lifestyle interventions on maternal weight gain and infant outcomes (Agha et al. 2014; Oteng-Ntim et al. 2012; Thangaratinam et al. 2012). The reviews found that dietary and lifestyle interventions resulted in a small reduction in GWG (1.42–2.21 kg), but together the interventions did

not appear to influence birth weight or LGA (Agha et al. 2014; Oteng-Ntim et al. 2012; Thangaratinam et al. 2012). However, none of the trials to date have looked at longer-term outcomes of child adiposity. Several ongoing RCTs targeted at changing GWG will follow offspring for development of obesity and its consequences (Dodd et al. 2011; Moholdt et al. 2011; Vesco et al. 2012). Vesco et al. (2014) found that obese women randomized to a dietary intervention gained less weight during pregnancy and had a lower proportion of babies born LGA, with further follow-up planned.

Two separate sibling-pair analyses have examined GWG and offspring obesity. Lawlor and colleagues (2011a) examined the association of maternal weight gain during pregnancy with obesity in men at age 18 years. They found that among mothers with a normal BMI, there was no relationship between GWG and later obesity. However, among mothers who were already overweight or obese, GWG was associated with an increased risk for later obesity, even in the within-sibling analyses, suggesting an influence of the intrauterine environment (Lawlor et al. 2011a). Although Branum et al. (2011) found that women with higher prepregnancy BMI and gestational weight gain had children with a higher BMI at age 4, differences were no longer significant in the sibling fixed-effects analysis. The interaction between maternal prepregnancy BMI and GWG on childhood obesity risk is an area of active investigation (Institute of Medicine 2009).

4.5 Maternal Smoking During Pregnancy

In 2010, approximately 9% of US women smoked during pregnancy, with white mothers and mothers with lower education more likely to smoke during pregnancy (Hawkins and Baum 2014). Many short- and long-term health effects of smoking during pregnancy on mothers and infants are well known, including lower fetal growth (U.S. Department of Health and Human Services 2004). It may seem paradoxical then that numerous studies, as summarized in recent meta-analyses, have shown that prenatal smoking exposure is associated with an increased risk for later obesity, even in studies that adjusted for potential confounding factors (Oken et al. 2008; Weng et al. 2012). Although mechanisms for the relationship between maternal smoking during pregnancy and childhood obesity are not fully understood, animal studies have shown an association between prenatal nicotine exposure and increased adiposity in offspring (Gao et al. 2005).

However, the extent to which this association, seen mainly in observational studies, is causal remains uncertain, especially since smoking is so strongly socially patterned. Several approaches have been used to minimize confounding, including accounting for paternal smoking, a proxy for sociodemographic risk that is likely to provide little direct exposure to the fetus. One study with information on both maternal smoking during pregnancy and paternal smoking status postpartum found that the association remained after adjustment for sociodemographic characteristics and paternal smoking (von Kries et al. 2008), while in another study the association was no longer evident after adjustment (Fleten et al. 2012).

Others have used alternative study designs to test whether the association may be causal. Although RCTs have demonstrated that smoking cessation during pregnancy reduces rates of low birth weight and preterm birth (Lumley et al. 2009), none have examined later child obesity risk. Two studies have used sibling-pair designs to examine smoking during pregnancy (Gilman et al. 2008; Iliadou et al. 2010). Although both found a relationship between smoking and later obesity, the association was no longer evident after including the sibling fixed-effect. These results raise the possibility that the association may be confounded by unmeasured factors that are shared within families rather than being causal.

4.6 Hormonal Influences: Leptin

In 1973, Douglas L. Coleman published his seminal work in two papers, discussing an unknown circulating factor responsible for the obese/diabetic

state in the *ob/ob* mouse, later called leptin (Grayson and Seeley 2012). Leptin is a hormone primarily produced by adipose tissue known to be responsible for the regulation of appetite, energy expenditure, and neuroendocrine function (Hauguel-de Mouzon et al. 2006). It is sometimes called the satiety hormone because of its effects on inducing a sense of fullness.

The developmental role of leptin in the perinatal period may differ from that later in the life course. The placenta releases leptin into maternal and fetal circulation, which may influence appetite and weight regulation. Maternal plasma leptin concentrations during gestation are two times higher than during non-gravid periods (Hauguel-de Mouzon et al. 2006). Fetuses born to obese mothers and mothers with GDM have higher cord leptin levels than fetuses of lean mothers or mothers without GDM, respectively (Catalano et al. 2009; Okereke et al. 2002). Umbilical cord leptin levels are positively associated with fetal fat mass, percent body fat, and birth weight (Okereke et al. 2002).

Sensitive period(s) may exist for the role of leptin in later obesity risk. A series of studies from Project Viva, a US pre-birth cohort, has examined relationships of leptin with early growth. Lower cord blood leptin levels were associated with smaller size at birth, but higher weight gain from birth to 6 months and higher BMI at age 3 years (Mantzoros et al. 2009; Parker et al. 2011). In a follow-up study, Boeke et al. (2013) found that lower leptin levels during pregnancy and in cord blood were associated with more adiposity at age 3 years; however, higher leptin levels at age 3 were associated with greater weight gain and higher adiposity through age 7. These findings were independent of maternal BMI and birth weight. The authors concluded there may be a sensitive period of leptin influence during the prenatal period followed by accumulation of leptin tolerance during early childhood, with different effects of leptin exposure by timing (Boeke et al. 2013). These observations are consistent with animal studies showing conditioning impact of heightened leptin sensitivity on later obesity, with differences evident across the life course (Bouret et al. 2004). There is great interest in identifying the correct sensitive period(s) for leptin to influence fetal development and reduce later obesity risk. To date, however, little is known about modifiable factors influencing fetal leptin regulation in humans (Boeke et al. 2013).

5 Infancy

5.1 Rapid Weight Gain

Infants grow in both length and weight, and weight changes include growth in both fat-free mass and fat mass. Many studies have used change in weight as a proxy for gain in adiposity, which may or may not be a valid assumption. There are many different definitions of rapid growth, which are often based on country- or population-specific references (Monteiro and Victora 2005).

Several meta-analyses have demonstrated that infants who gain weight more quickly than average during the first 2 years of life are at higher risk for later obesity (Baird et al. 2005; Monteiro and Victora 2005; Weng et al. 2012). Taveras and colleagues (2011c) examined the number of major weight-for-length percentiles crossed on the CDC 2000 growth chart during each of the 6-month periods from birth to 2 years with outcomes of obesity at ages 5 and 10 years. They found that crossing upward 2 or more percentiles in the first 2 years was associated with an increased risk for obesity at both ages. The highest prevalence of later obesity was seen in children with the crossing upward of 2 or more weight-for-length percentiles within the first 6 months of life (Taveras et al. 2011c).

Debate continues as to the exact time frame that rapid weight gain matters the most for later obesity risk. A major limitation of current research is the lack of repeated measurements at small intervals during infancy. Studies with repeat detailed measurements often include small, homogeneous samples of children, and thus their generalizability is limited. An important area of future research is to more precisely define the critical window for rapid gain in adiposity (or length) as well as modifiable determinants of rapid weight gain.

Although based on the research we summarize here a potential conclusion might be to limit rapid weight gain in infants to prevent later obesity, an important consideration is the potential detrimental effects of restricting weight gain for other organ systems. For infants born preterm, more rapid postnatal weight gain has an important benefit for neurodevelopment and attained size (Ehrenkranz et al. 2006) Although no association was seen between slower infant weight gain and poorer neurodevelopmental outcomes in a study of healthy, term infants (Belfort et al. 2008), this area requires more study to help determine optimal length and BMI patterns to promote healthy neurodevelopment as well as reduce childhood obesity.

One important modifiable determinant of the rate of infant weight gain is infant feeding, both the type and the approach. Although exclusively breastfed infants gain weight more rapidly in the early postnatal period, infants who are formula fed or fed a combination of breast milk and formula gain BMI more rapidly during the latter half of the first year of life (Kramer et al. 2004). In an Australian RCT promoting positive feeding practices, Mihrshahi et al. (2011) found that formula feeding and feeding on a schedule were independently associated with rapid weight gain between birth and age 4–7 months. Although the association between breastfeeding and childhood obesity is discussed in the next section, infant gain in length or adiposity and nutrition are closely linked and, in fact, may be challenging to tease apart.

5.2 Breastfeeding

Despite the numerous demonstrated health benefits of breastfeeding (Section on Breastfeeding 2012), according to the CDC's 2014 Breastfeeding Report Card, only 79% of US mothers initiated breastfeeding and only 49% breastfed for at least 6 months (Centers for Disease Control and Prevention 2014). Moreover, racial/ethnic disparities in breastfeeding are substantial. Using national data from 2004 to 2008, there was a 20% point differential between black and white mothers for both breastfeeding initiation (54% versus 74%) and breastfeeding for at least 6 months (27% versus 43%) (Centers for Disease Control and Prevention 2010).

Systematic reviews and meta-analyses of observational studies have demonstrated an inverse association of breastfeeding initiation or duration with later obesity (Arenz et al. 2004; Harder et al. 2005; Owen et al. 2005b). Two reviews found that an inverse relationship still remained after adjusting for confounding factors, such as parental obesity or social class (Arenz et al. 2004; Owen et al. 2005b). However, a third showed attenuation of the association with BMI to null after such adjustment (Owen et al. 2005a). There was also evidence for a dose-response relationship, such that a longer duration of breastfeeding conferred a greater reduction in obesity risk (Harder et al. 2005; Owen et al. 2005b). As the majority of study samples were often homogeneous with children of mostly white European descent, there is debate about the extent to which these relationships apply to all racial/ethnic groups (Gillman 2011; Harder et al. 2005).

Plausible mechanisms abound for the relationship between breastfeeding and childhood obesity (Bartok and Ventura 2009). Breastfed infants may be better at self-regulation than bottle-fed infants because they come off the breast when they are full, which may help them learn to regulate energy intake (Li et al. 2010). Breast milk contains hormones, such as leptin, involved in regulating growth and development during infancy (Savino and Liguori 2008). After the first 3 months of life, breastfed infants have slower weight gain for the remainder of the year than formula-fed infants (Savino and Liguori 2008).

Nevertheless, evidence is mounting to question the extent to which this relationship is causal (Gillman 2011). The majority of research has been based on observational studies, and associations may still be due to unmeasured factors. The few studies using a sibling-pair design showed that breastfeeding duration reduced risk for later obesity, but because mothers often breastfeed similarly across siblings, there are a limited number of discordant pairs to detect effects (Gillman et al. 2006; Metzger and McDade 2010; Nelson et al.

2005; O'Tierney et al. 2009). Furthermore, these designs may not eliminate the role of infant growth and behavior as a predictor—rather than result—of breastfeeding intensity and duration.

Another methodological design to infer causality is to examine the association in a context with different social gradients for both the exposure and outcome measures (Brion 2010; Gillman 2011). Brion et al. (2011) compared the association between breastfeeding duration and BMI from two cohorts—in England where breastfeeding is associated with more advantaged social circumstances and in Brazil where there is little social patterning. There was an inverse association between breastfeeding duration and obesity risk for children in England, but no such association for children in Brazil, from which the authors concluded the effects are likely due to residual confounding (Brion et al. 2011). Similarly, a study in Hong Kong also found no association between breastfeeding and childhood obesity, where breastfeeding and obesity follow different social patterns (Kwok et al. 2010).

The Promotion of Breastfeeding Intervention Trial (PROBIT) in Belarus is a cluster-randomized trial of breastfeeding promotion (Kramer et al. 2001). Mothers who started breastfeeding were randomly assigned to an intervention group that provided additional breastfeeding support or a standard care control group. Although mothers in the breastfeeding promotion group showed increases in duration and exclusivity of breastfeeding, there was no evidence for a protective effect of breastfeeding on skinfold thickness or obesity in children at age 6.5 or 11 years (Kramer et al. 2007; Martin et al. 2013). Based on the existing evidence, breastfeeding may only confer modest protection against obesity rather than being a major determinant (Gillman 2011).

5.3 Disparities in Obesity Partially Explained by Early-Life Factors

Beyond breastfeeding, many other early-life obesogenic exposures may be socially patterned (Dixon et al. 2012). Several investigators have attempted to investigate whether observed racial/ethnic disparities in obesity rates (Ogden et al. 2014) are related to early-life factors. Taveras and colleagues (2010) have shown that compared to white children, black and Hispanic children were more likely to have risk factors for childhood obesity including excessive weight gain during infancy and early introduction of solid foods, while after 2 years, they were more likely to have a television in their bedrooms, shorter sleep duration, and higher intake of sugar-sweetened beverages and fast food (Taveras et al. 2010). In contrast, they were less likely to be exposed to factors associated with protection against obesity, including exclusive breastfeeding (Taveras et al. 2010). The same investigators more recently examined whether racial/ethnic differences in childhood obesity at age 7 were explained by these early risk factors (Taveras et al. 2013). Although black and Hispanic children had higher BMI z-scores than white children, there were no longer differences in BMI after adjustment for infancy- and childhood-related risk factors. The authors conclude that racial/ethnic disparities in obesity may be determined by modifiable factors in early life (Taveras et al. 2013).

6 Early to Mid-childhood

6.1 Family

Although family members have similar levels of adiposity, meaning that children are more likely to have a high BMI if their parents have a high BMI (Patel et al. 2011), the influence of parents on child adiposity almost certainly extends beyond shared genes. Parents (including caregivers) also share a similar family, neighborhood, and social environment. During the early years, parents are the primary influence on children's dietary and physical activity/inactivity choices. Parents not only physically provide children with food and opportunities for physical activity, but they also influence children's preferences through modeling or other experiences (Birch and Davison 2001; Van Der Horst et al. 2007). In the next two sections on early childhood to mid-childhood and adolescence, we focus on "above-

water" macro-level factors where there is potential for population-level interventions and public health impact.

6.2 Diet, Physical Activity, and Inactivity

In the simplest terms, excessive weight gain occurs when there is more "energy in" than "energy out." The dietary and physical activity patterns of children and adolescents in the USA have changed substantially over the last few decades. Total energy intake and portion sizes from energy-dense, nutrient-poor foods have increased, and more meals are being eaten away from home (Duffey and Popkin 2013; Piernas and Popkin 2011). Among school-aged children, daily calories from sugar-sweetened beverages have increased from 130 to 212 kcal/day over the last 20 years (Lasater et al. 2011). Although children and adolescents are recommended to participate in 60 min or more of physical activity daily (U.S. Department of Health and Human Services 2008), many children are not achieving this goal. In 2013, nationwide, 15% of students did not engage in at least 60 min of physical activity on any of the prior 7 days (Kann et al. 2014). As children transition from childhood through adolescence, physical activity levels decrease (Kahn et al. 2008), and media exposure and sedentary behaviors increase (Kann et al. 2014; Rideout and Hamel 2006). In recent decades, screen time and media use have increased. Currently, 41% of students play video or computer games 3 or more hours per day, and an additional 33% watch television 3 or more hours per day (Kann et al. 2014). Even by age 1, children are using approximately 50 min of screen media daily, which increases to nearly 2 hours by age 4–6 years (Rideout and Hamel 2006).

As media use has increased, so has children's exposure to advertisements and food marketing. Food advertising has been linked to influencing children's food preferences, purchasing requests, and consumption patterns (McGinnis et al. 2006), suggesting a potential mechanism by which television and media use may increase children's risk for obesity. US guidelines for the responsible advertising to children are voluntary self-regulatory initiatives, and the Rudd Center for Food Policy and Obesity (2013) suggested that loopholes in industry pledges may provide for more public relations benefits than health benefits.

6.3 Food Insecurity

In 2013, 14% of US households with children were food insecure at least once during the year, meaning they were unable to provide adequate food for one or more household members due to insufficient means (Coleman-Jensen et al. 2014). Black and Hispanic households, low-income households, and single-parent households with children had rates of food insecurity higher than the national average (Coleman-Jensen et al. 2014). Since children from lower-income families are at higher risk for obesity, the challenge for many families is to dependably provide nutritious and high-quality food rather than obtaining enough food (Ludwig et al. 2012). The Supplemental Nutrition Assistance Program (SNAP) has no regulations on the quality of foods purchased (US Department of Agriculture, 2013b), and families may be spending their limited food budget on foods that are high in calories but with low nutrient quality such as sugar-sweetened beverages.

Three systematic reviews found that although food insecurity was associated with an increased risk for obesity in adults, particularly women, the evidence was mixed for children (Dinour et al. 2007; Eisenmann et al. 2011; Franklin et al. 2012). A challenge for studies is identifying whether the measure of food insecurity is at the family or child level as parents may protect children from being food insecure. Echoing the conclusion from a review by Eisenmann et al. (2011), even if the association is not causal, both food insecurity and obesity exist in low-income households. It is essential, therefore, to learn more about purchasing patterns, diet, and physical activity in these families to learn why food insecurity and obesity coexist and identify areas for intervention.

6.4 Child Care and School

Policies and programs in child care and school can influence children's dietary intake, physical activity patterns, and risk for obesity. Approximately 30% of children are in center-based programs by age 2 and 40% of children by age 3, spending nearly 30 hours in nonparental care each week (National Center for Education Statistics 2005). Thus, child care is a setting in which obesogenic behaviors can be allowed or prevented (Larson et al. 2011a). A review by Larson and colleagues (2011b) identified 18 obesity prevention interventions that take place in child care centers/preschools and 2 of the 5 interventions that used weight status as an outcome found evidence for reduced weight.

In 2007, Benjamin et al. (2008) reviewed state child care regulations for policies related to nutrition and physical activity that may contribute to childhood obesity. They found that 80% of states had regulations to ensure that water is freely available in child care centers, 33% regulated screen time, 18% had regulations for the provision of breast milk, 14% restricted sugar-sweetened beverages, and only three states required a specified number of minutes of physical activity. Four states had no policies related to obesogenic practices in child care. The proportion of states with these regulations for family child care homes—as opposed to centers—was either the same or less. As of 2013, up to one quarter of states did not comply with any of the five recommendations from the IOM to promote physical activity among infants in child care centers or family child care homes (Slining et al. 2014). Benjamin et al. (2009) showed that infants who attended home-based child care early in life had an increased weight for length at 1 year and BMI at 3 years, suggesting that more research is needed into the food and physical activity policies of family child care homes. Additional studies in Denmark (Neelon et al. 2015) and Finland (Lehto et al. 2015) have demonstrated an association between starting child care before age 1 and an increased risk for later obesity. In 2011, the White House Task Force on Childhood Obesity supported the development of new national standards for healthy eating, encouraging breastfeeding, promoting physical activity, and limiting screen time in early-care settings (American Academy of Pediatrics, American Public Health Association, and National Resource Center for Health and Safety in Child Care and Early Education 2012).

Since children spend most of their time in school and may eat two daily meals there, the school environment can play an important role in shaping health behaviors (Institute of Medicine 2007; Story et al. 2009). A systematic review and meta-analysis by Waters et al. (2011) identified 55 interventions for preventing obesity in children aged 0–18 years, with 5 of the 6 most promising strategies related to the school environment: school curricula that include healthy eating and physical activity, increases in opportunities for physical activity throughout the school week, improvements in the nutritional quality of the food served in schools, environments and cultural practices that support children eating healthier foods and being active throughout the day, and support for teachers and staff to implement health promotion strategies and activities. They also concluded that interventions did not increase disparities. There have been a number of reviews that examined the impact of school-based interventions overall or school food and physical activity, separately, on obesity risk (Gonzalez-Suarez et al. 2009; Katz et al. 2008; Kropski et al. 2008).

Food and beverages available in schools are either part of the federal school lunch and breakfast programs or are competitive foods sold outside the federal programs. Meals served in the National School Lunch Program and School Breakfast Program must adhere to federally defined nutrition standards in order for schools to be eligible for federal subsidies (Institute of Medicine 2007). In 2013, the US Department of Agriculture issued the new "Smart Snacks in Schools" nutrition standards for competitive foods and beverages, which limit calories, fat, sugar, and sodium (U.S. Department of Agriculture 2013a). A study by Masse et al. (2013) found that between 2003 and 2008, states significantly strengthened their school nutrition-related laws, particularly those related to the sale

of competitive foods. Overall, laws for competitive food policies were stronger for elementary schools than for middle and high schools. As of 2008, 7 states had no school nutrition laws across the 16 categories they examined (Masse et al. 2013).

The National Association for Sport and Physical Education (NASPE) sets standards for physical education, including time allotment, curriculum, and staffing (National Association for Sport and Physical Education 2004). Perna et al. (2012) found that public schools in states with specific and stringent physical education laws reported more weekly time for physical education: specifically, elementary schools reported 40 more minutes and middle schools reported 60 more minutes than schools within states with no laws. There were no differences between high schools. However, overall, only 8.5% of schools fully met the NASPE guidelines for physical education time (Perna et al. 2012). Without federal legislation for physical education, policies vary widely by state and even by schools themselves.

7 Adolescence

7.1 Social Influences

Adolescence is a developmental period characterized by hormonal changes and a period of rapid growth both physically and psychologically (Viner et al. 2012). As children become more independent, their sphere of influence moves from parents to peers with increasing autonomy in making choices. Although influences of dietary and physical activity habits on obesity risk are similar to those described during the early- to mid-childhood periods, these habits are often influenced by peer norms. Strong peer relationships are an important developmental change during adolescence, and peer groups can influence health behaviors both positively and negatively (Viner et al. 2012).

Using social network theory and analysis, Christakis and colleagues (2007) found that weight gain in one person spread through social ties and influenced risk of obesity in a friend, sibling, or spouse among adults in the Framingham Study. Trogdon et al. (2008) used the National Longitudinal Study of Adolescent Health (Add Health) to examine the influence of peer effects on adolescents' own BMI by constructing a detailed definition of peer groups based on nominated friendship relationships. They found that mean peer BMI was associated with adolescent BMI, females were more sensitive to peer BMI and overweight status than males, and peer weight was more influential among adolescents with the highest BMI (Trogdon et al. 2008).

Ali et al. (2011) also used data from the Add Health study to understand potential mechanisms of peer effects on obesity-related health behaviors. They found evidence for the influence of peers on adolescents pursuing an active sport, regular exercise, and eating in fast-food restaurants, but no consistent relationships with television viewing, short sleep duration, or other dietary factors (Ali et al. 2011). Although additional research is needed to confirm these findings, the potential implications are that obesity prevention programs aimed at adolescents will need to consider the influence of peer groups.

8 Macro-level Factors

Although we have touched upon policies and social issues that have their strongest influence in particular age groups, this section presents macro-level factors that either indirectly or directly influence obesity risk across all stages in life course health development.

8.1 Environment

The term "obesogenic environment" often refers to features of the built and natural environments that limit healthful behaviors related to eating, sleeping, screen time, and physical activity. The definition used to study the built environment varies widely across studies (Dunton et al. 2009; Lovasi et al. 2009; Papas et al. 2007). The most common measures of access to food are distances to the nearest fast-food restaurants or grocery

stores or density of food outlets within a defined area. The most common measures of access to physical activity resources are measured distance to facilities for physical activity such as parks, density of such facilities, walkability, or aspects of community design. Related measures included assessments of aesthetics or neighborhood safety. Papas et al. (2007) found that 17 of the 20 studies identified found a significant association between some aspect of the built environment and risk for obesity across the life course, with the majority of studies looking at features of the environment related to physical activity. Dunton et al. (2009) examined aspects of the built environment related to physical activity and childhood obesity. While they found few consistent findings in children, in adolescents obesity was associated with access to equipment and facilities, neighborhood type (urban/rural), and urban sprawl. Lovasi et al. (2009) examined how the built environment may be contributing to disparities in obesity and its risk factors. They focused on studies that included individuals who were poor or of low socioeconomic status, black, or Hispanic. The authors found that lack of access to supermarkets, exercise facilities or places to be active, and safety because of crime or traffic was all associated with BMI or related behaviors, and they concluded that prevention strategies should focus on these areas (Lovasi et al. 2009).

There are many methodological challenges to understanding the effects of the neighborhood environment on children because of the diversity of populations, measures, and outcomes across studies (Dunton et al. 2009; Lovasi et al. 2009; Papas et al. 2007). A further limitation is that nearly all of the studies have been cross-sectional, so the temporality of associations is not clear. Effects of the built environment on health vary across the life course because exposure to and interaction with the environment change by age. For example, distance to playgrounds matters more for children than adolescents, whereas walkability may have less impact on young children. While subjective measures of the built environment are often from parents or children themselves, more studies are using objective measures of the environment, such as geographic information system (GIS) mapping or even personal devices to determine time, place, and activity simultaneously. The most important aspect is the definition of the built environment. Studies that examine the same construct, such as walkability, may be using different definitions and measurements, which limit the ability to synthesize the evidence. As Dunton et al. (2009) conclude, it is imperative to identify "modifiable and specific" features of the built environment to inform the development of interventions.

Neighborhoods vary in many ways, most of which are unmeasured but likely interrelated; observed associations that remain after adjustment are still subject to residual confounding. RCTs, which balance both measured and unmeasured confounders, are uncommon in this area primarily due to the feasibility of manipulating aspects of the built environment. The Department of Housing and Urban Development conducted a unique social experiment from 1994 through 1998 to better understand the effects of neighborhood characteristics on health and social outcomes (Sanbonmatsu et al. 2011). Women with children living in public housing in high-poverty areas were randomly assigned to one of three groups: experimental housing vouchers redeemable only if they moved to a low-poverty area, unrestricted traditional vouchers, and a control group that offered neither opportunity (Ludwig et al. 2011). Ludwig et al. (2011) followed up the participants from 2008 to 2010 and found that women assigned to the experimental group had lower levels of extreme obesity and diabetes than women in the control group, although there were no baseline measures of these outcomes. However, among youth, there were no differences in physical health outcomes, including obesity (Sanbonmatsu et al. 2011). The authors concluded that although the mechanisms for these reductions were unknown, the intervention provides some causal evidence for the impact of the neighborhood environment on health (Ludwig et al. 2011).

A methodology for future research in this area is quasi-experimental designs that evaluate a clearly defined change—often a wide-ranging

policy—that are referred to as natural experiments. Taking measurements of residents before and after this change, or using secondary measures such as data from electronic medical records, especially in comparison with an unexposed control group, can help assess the impact of neighborhood factors on obesity itself or related health behaviors. Such alternative study designs are needed to identify important levers of change to help inform the development of interventions conducted at the neighborhood or community levels.

8.2 Local and State

In recent years, city and state governments have taken bold actions to change the environment and encourage healthy choices. New York City (NYC) has been a pioneer in this effort by using a multiagency approach to tackle obesity and its risk factors (Mello 2009). In 2006, NYC passed the first regulation in the USA banning trans fat use in restaurants. An evaluation comparing food purchase data before and after the ban found a significant decrease in the trans fat content of purchases from fast-food chains after the law, with benefits for patrons from both high- and low-poverty neighborhoods (Angell et al. 2012). In 2008, NYC required chain restaurants to post calorie information prominently on menu boards and menus. Although children and adolescents' reported they noticed the posted information, there were no differences in calories purchased after versus before the introduction of calorie postings (Elbel et al. 2011). NYC initiatives have also extended to schools and the built environment (Office of the Mayor 2012). NYC established nutritional standards for every city agency that purchases or serves meals to clients, including the 1.1 million students that attend city schools, as well as standards for city vending machines. The most controversial proposal was to limit the size of sugar-sweetened beverages sold in food service establishments to 16 ounces, which caused much debate both for and against this measure and was ultimately blocked (Grynbaum 2012).

Although these policies in NYC provide assessable natural experiments to allow for evaluation of specific environmental factors that might promote weight gain (or loss), a challenge is learning what may be the critical lever(s) for change. When policies and programs are implemented simultaneously or within short time periods, it may not be possible to tease apart the individual effects of each policy. Furthermore, these efforts may not be generalizable; budgets are often limited, and other cities or states may not have the resources to implement the whole suite of policies that have been enacted in NYC. Nevertheless, these efforts provide valuable data to clinicians and policy makers to help elucidate what policies or programs will have the biggest effect on obesity levels.

A relatively new area is using legislation to financially penalize the purchase and consumption of obesogenic foods and beverages. One approach draws from the lessons of tobacco control and the success of cigarette taxes. Taxes on sugar-sweetened beverages are a prime example, although taxes have also been proposed to reduce the consumption of fast food (Powell et al. 2013). The consumption of sugar-sweetened beverages is strongly related to increased body weight (Te Morenga et al. 2012). As of January 2014, 34 states and DC had a sales tax on regular soda sold in food stores, with a mean tax rate of 5.2% (Chriqui et al. 2014). A systematic review by Powell et al. (2013) found that soda taxes had little impact on weight outcomes, but the authors argued that they were based on state-level sales taxes that were relatively low and therefore unlikely to effect substantial change in behavior.

Brownell et al. (2009) have proposed a national excise tax on sugar-sweetened beverages as a public health strategy to address the obesity epidemic. They recommended implementing an excise tax of 1 cent per ounce for beverages that have any added caloric sweetener, which would increase the cost of a 20-ounce soda by 15–20% (Brownell et al. 2009). This type of tax, which is similar to cigarette excise taxes, is preferable to a sales tax because it provides an incentive to reduce the amount of sugar per ounce of sugar-sweetened beverage (Brownell et al. 2009). Since

the cost would be passed onto retailers, they would likely increase the retail price, and consumers would be aware of the cost when they are deciding to purchase the product. Andreyeva et al. (2011) estimated that a 1 cent per ounce tax on sugar-sweetened beverages could reduce consumption by 24% and daily per capita caloric intake from sugar-sweetened beverages from current levels of 190–200 calories to 145–150 calories. Brownell et al. (2009) suggest that the public health impact could be greater for groups at higher risk for obesity, such as children and low-income groups, who consume greater amounts of sugar-sweetened beverages.

An alternative approach to promoting a healthful diet is a subsidy to reduce price and encourage the consumption of healthful foods. Unfortunately, in recent decades, just the opposite situation has occurred. The real inflation-adjusted price of fruits and vegetables has increased, while soda prices have declined and fast-food prices have remained stable (Powell et al. 2013). In the USA, subsidies on food have been designed to alleviate food insecurity for low-income families rather than increasing consumption of healthful foods by everyone. Powell et al. (2013) found that lower fruit and vegetable prices were associated with lower body weight among low-income populations; however, cohort studies are mixed when it comes to the effects of fruits and vegetables on weight gain (Casazza et al. 2013). Based on the long history of tobacco control, the area of taxes and subsidies related to obesity is still in its infancy.

8.3 National

Reducing and preventing obesity is a federal priority. At a national level, the White House Task Force on Childhood Obesity and the accompanying *Let's Move!* campaign aim to reduce childhood obesity and raise a healthier generation through an intra-agency collaboration (White House Task Force on Childhood Obesity 2010). The 70 recommendations were summarized into five themes: getting children a healthy start on life; empowering parents and caregivers; providing healthy foods in schools; improving access to healthy, affordable food; and getting children more physically active. The strategy emphasized that changes are needed at many macro levels to promote healthy behaviors, including improvements to schools and the built environment. The White House Task Force reported some progress on many of these areas after just 1 year (White House Task Force on Childhood Obesity 2011). The IOM's Standing Committee on Childhood Obesity Prevention (Institute of Medicine 2011) and the US Department of Health and Human Services' National Prevention Strategy (National Prevention Council 2011) echo these priorities.

9 Recommendations

9.1 Major Themes

A multilevel approach for obesity prevention is needed, which takes into account individual risk factors that operate at multiple levels ("above-water" and "underwater" influences) and recognizes that these factors also interact across the life course (Fig. 1). We reviewed phases of life course health development, prenatal through adolescence, that appear to be most important for the development of obesity. We also presented alternative methodological approaches to observational studies that can help disentangle causal associations. The following sections outline research priorities and data/methods development priorities, and conclude with recommendations for practice and policy.

9.2 Research Priorities

Of the many emerging risk factors for obesity, we briefly highlight sleep duration, endocrine-disrupting chemicals, epigenetic markers, and microbial colonization.

- Sleep duration and quality: Disruption of sleep may have adverse health consequences, including childhood obesity. Biologically plausible mechanisms exist for why short sleep duration

could increase children's risk for obesity: tiredness and fatigue lead to reduced physical activity; hormone changes associated with insufficient sleep, particularly lower leptin levels and higher ghrelin levels, result in increased hunger and eating; and with less sleep, there is more awake time to eat (Taheri 2006). Although most of the studies in this area have been cross-sectional, prospective cohort studies do provide some evidence for causality. Chen et al. (2008) identified 17 studies from 1980 to 2007 on sleep duration and adiposity in children, of which 3 were prospective cohort studies. Nielsen et al. (2011) reviewed the literature from 2007 to 2009 and identified an additional 13 studies in children. Of the eight prospective cohort studies, all found a significant inverse relationship between duration of sleep and adiposity (Nielsen et al. 2011). Recent studies from Project Viva have shown that chronic sleep curtailment from infancy was associated with an increase in adiposity and metabolic risk at age 7 (Cespedes et al. 2014; Taveras et al. 2014).

- Early relational environment: Two aspects of children's early relational environment—the quality of parental relationships and children's exposure to adverse experiences—have been identified as potential risk factors for child and adolescent obesity. The psychological and physiological consequences of insecure attachments and trauma are well established, including poor emotional regulation and heightened stress responses, which may directly lead to obesity through biological changes (Glaser and Kiecolt-Glaser 2005) or indirectly through emotional eating (Michopoulos et al. 2015; Torres and Nowson 2007) and sleep disturbances (Vgontzas et al. 2008). Studies in children and adolescents have found that those with poor-quality maternal-child relationships (Anderson et al. 2012) or insecure attachment (Anderson and Whitaker 2011) in early childhood were more likely to be obese compared to those with higher-quality relationships. Danese and Tan (2014) conducted a meta-analysis of 41 studies and found that childhood maltreatment was associated with an increased risk of obesity across the life course with an overall pooled odds ratio of 1.36 and associations remained after adjustment for socioeconomic status and health behaviors. An additional meta-analysis of 23 cohort studies found that adults who reported physical, emotional, sexual, or general abuse during childhood were more likely to be obese (pooled odds ratios of 1.28–1.45) and four studies reported dose-response relationships (Hemmingsson et al. 2014). While this evidence suggests a role of children's early relational environment in the development of obesity, further research is needed to better understand the mechanisms to help inform interventions.
- Endocrine-disrupting chemicals (EDCs): EDCs are compounds that mimic or interfere with the normal actions of endocrine hormones, including estrogens, androgens, and thyroid and pituitary hormones (Newbold et al. 2007). Although some EDCs are naturally occurring, man-made organic compounds pose greater risks to human health and include flame retardants, bisphenol A (BPA), pesticides, and polychlorinated biphenyls (PCBs). EDCs that are lipophilic, resistant to metabolism, and/or able to bioconcentrate up the food chain become stored in body fats and are of particular concern (Elobeid and Allison 2008). Thus, in utero exposure to environmental chemicals, including EDCs, during critical periods may play a role in the development of obesity through fetal programming (Newbold et al. 2007). Only recently has evidence been synthesized from animal models and epidemiologic studies in humans to suggest a possible link between EDCs and later obesity (Elobeid and Allison 2008). Trasande et al. (2012) found that urinary BPA concentrations were associated with obesity in children and adolescents, although alternative explanations cannot be ruled out because the study was cross-sectional.
- Epigenetics: The notion that early environmental influences, such as maternal diet, or toxic substances, like air pollution, alter offspring outcomes through epigenetic changes that influence gene regulation could unite several strands of human and animal observations about the origins of obesity. Proof of principle emanates from agouti mice (Waterland and Jirtle 2004). The epigenetic mechanism associated with dif-

ferences in body fat and cardiometabolic disease risk of the offspring involves switching off the agouti gene by methyl groups from a dietary supplement (Waterland and Jirtle 2004). These and similar findings show, in principle, how genetically identical individuals raised in similar postnatal environments can nonetheless develop widely differing phenotypes.

- Gut microbiota: Infants get their first priming dose of microbes in utero via the placenta, followed by a more thorough colonization as they pass through the birth canal and are exposed to the mother's skin, so that by the time they are a few days or weeks old, their gastrointestinal tracts are colonized by a population of microbes notable not only for their abundance but also variety. Gut microbiota are likely to affect many organs and systems, including the regulation of energy balance and weight gain. Although research on animal models suggests a role of gut microbiota in the development of obesity, studies in humans are limited (DiBaise et al. 2008). One model system for evaluating the role of gut microbiota is the route of delivery. Microbes from the mother and the environment colonize the infant's intestinal tract during delivery (Neu and Rushing 2011). During cesarean delivery, the direct contact with maternal vaginal and intestinal flora is absent. The intestinal microbial composition of infants via cesarean delivery resembles that of the mother's skin, whereas the intestinal flora of infants born vaginally resembles the mother's vaginal flora and intestinal tract (Dominguez-Bello et al. 2010). A systematic review by Li et al. (2013) found that delivery by cesarean section was associated with an increased risk for overweight/obesity across the life course compared to vaginal delivery, with an overall pooled odds ratio of 1.33.

9.3 Data/Methods Development Priorities

There are a number of major challenges to understanding causal influences on obesity risk throughout the life course. Here, we discuss some of these challenges as well as approaches to overcoming or minimizing them.

- One recurrent issue is the extent to which associations described in observational studies are causal. One notable example is breastfeeding (Gillman 2011). Mothers who choose to breastfeed often have substantially different social and economic circumstances from mothers who do not breastfeed their infants. Furthermore, factors that predict successful initiation and long-term maintenance of breastfeeding, such as maternal obesity and cesarean delivery, are themselves putative causes of child obesity. Also, it is possible that infant characteristics themselves predict breastfeeding duration, since mothers may be more likely to supplement faster growing infants, who appear hungrier.
- In cross-sectional studies, both confounding and reverse causation are important considerations. Longitudinal cohort studies with adjustment for multiple measured characteristics can go part of the way in minimizing confounding, but other approaches such as sibling-pair design, maternal versus paternal effects, cohorts with different confounding structures, and RCTs can help control for unmeasured confounding. Others have applied Mendelian randomization, a method that takes advantage of variation in genes of known function to examine the causal effect of a modifiable exposure on disease in nonexperimental studies (Smith and Ebrahim 2003). The genotype must affect the disease status only via its effect on the exposure of interest and should be randomly distributed with respect to other covariates (Ding and Hu 2008). This approach can produce unbiased estimates of the effects of a putative causal variable without a traditional RCT. One example is the study of the maternal and offspring FTO genotype and offspring obesity risk, which suggests that maternal obesity affects childhood obesity only through pathways other than the intrauterine environment (Lawlor et al. 2008). However, many times these approaches are not feasible. For example, data may not be readily available on

large numbers of siblings with discordant exposures; RCTs are costly and may not be ethical; and the few common genes that influence obesity risk do not have strong associations and also may influence multiple metabolic pathways.

- Another challenge is that of appropriate exposure assessment, which is relevant for multiple factors of great interest including diet, physical activity, and the toxic, built, and social environments. Multiple factors may interact among each other. For example, breastfeeding may particularly affect childhood obesity risk only in the presence of an obesogenic environment, whereas two important null studies of breastfeeding and obesity (Brion et al. 2011; Kramer et al. 2007; Martin et al. 2013) were both conducted in middle-income countries with relatively low population obesity rates (Belarus and Brazil).
- Current statistical techniques typically cannot take into account the multitude of factors both hierarchically and across the life course that impact obesity. Traditional longitudinal analyses, even those that account for multiple levels of influence, are often not powerful enough to account for the complexity and interconnectedness of obesity. Systems science approaches such as agent-based and system dynamics modeling can include not only longitudinal and multiple levels but also more complex features of relationships like nonlinearity, path dependence, loops, and tipping (Hammond 2009; Huang et al. 2009). These approaches have just recently been imported into public health from disciplines such as engineering (Mani et al. 2010) and evolutionary biology (Kitano 2002) and may very well contribute to understanding and ultimately solving childhood obesity.

9.4 Translational Priorities

The key to reducing childhood obesity is finding the right level and time in the life course to intervene for the maximal effectiveness and efficiency. Many intervention studies early in the life course are getting underway or are ongoing, and will be invaluable in informing not only what factors to change but how to change them. Such interventions may be complex and costly, but ultimately may be what is required to reverse the tide of obesity.

- Interventions to modify determinants of obesity through life course health development may invoke multiple settings, e.g., medical care, homes, child care, and school (Foster et al. 2010; Taveras et al. 2011a, b, 2012); involve multiple components, e.g., system redesign and individual behavior change strategies including e-technology (Lubans et al. 2010; Taveras et al. 2012); and target single or multiple factors (Dodd et al. 2011; Taveras et al. 2011b; Vesco et al. 2012). Interventions within medical care may be especially valuable during pregnancy and infancy, when individuals see their providers more often than any other time during the life course.
- Some recommendations are already clear. For prenatal factors, smoking avoidance has been a priority for decades (U.S. Department of Health and Human Services 2004). Guidelines exist for appropriate GWG (Institute of Medicine 2009). For mild-moderate GDM, treatment with lifestyle and insulin reduces neonatal complications (Crowther et al. 2005; Landon et al. 2009); the protocol and criteria for diagnosing GDM are undergoing new scrutiny.
- Among early childhood factors, "feeding up" small-for-gestational age infants should be abandoned for most because such infants who gain weight rapidly in infancy are at higher risk of chronic disease and derive no neurocognitive benefits (Belfort and Gillman 2011). The World Health Organization recommends exclusive breastfeeding for 6 months, but in the developed world, recommendations are moving toward 4–6 months (Section on Breastfeeding 2012); that interval appears to be appropriate for introducing solid foods for obesity prevention (Huh et al. 2011; Pearce et al. 2013).
- Among dietary factors, evidence is strongest for intake of sugary beverages at many ages. Avoiding introducing these into infant diets may be especially valuable, given most

humans'—especially children's—inherent "sweet tooth" (Ventura and Mennella 2011).
- The American Academy of Pediatrics recommends zero screen time under age 2 years and no more than 2 hours/day of screen time for child age 2 years and older (Strasburger 2011). Avoiding from the outset having a TV in the room where a child sleeps appears to be key to reducing screen time (Schmidt et al. 2012).
- Among the newer risk factors, improving sleep duration and quality may be an especially effective maneuver—and preliminary studies suggest it is feasible (Taveras et al. 2011a)—because all parents want more sleep!

Funding Funded by grants from NIH R00 HD068506 to Dr. Hawkins, K24 HD069408 and P30 DK092924 to Dr. Oken, and K24 HL060841 to Dr. Gillman. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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