Social Science & Medicine 148 (2016) 102–109

Contents lists available at ScienceDirect

Social Science & Medicine

journal homepage: www.elsevier.com/locate/socscimed

Birth weight, early life course BMI, and body size change: Chains of risk to adult inflammation?

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ARTICLE INFO

Article history:
Received 4 August 2015
Received in revised form
22 October 2015
Accepted 24 November 2015
Available online 28 November 2015

Keywords:
C-reactive protein
Inflammation
Birth weight
Obesity
Fetal origins
Chains of risk
Sensitive periods

ABSTRACT

This paper examines how body size changes over the early life course to predict high sensitivity C-reactive protein in a U.S. based sample. Using three waves of the National Longitudinal Study of Adolescent Health (Add Health), we test the chronic disease epidemiological models of fetal origins, sensitive periods, and chains of risk from birth into adulthood. Few studies link birth weight and changes in obesity status over adolescence and early adulthood to adult obesity and inflammation. Consistent with fetal origins and sensitive periods hypotheses, body size and obesity status at each developmental period, along with increasing body size between periods, are highly correlated with adult CRP. However, the predictive power of earlier life course periods is mediated by body size and body size change at later periods in a pattern consistent with the chains of risk model. Adult increases in obesity had effect sizes of nearly 0.3 sd, and effect sizes from overweight to the largest obesity categories were between 0.3 and 1 sd. There was also evidence that risk can be offset by weight loss, which suggests that interventions can reduce inflammation and cardiovascular risk, that females are more sensitive to body size changes, and that body size trajectories over the early life course account for African American- and Hispanic-white disparities in adult inflammation.

Although a great deal of attention has been devoted to both the etiology and pathogenic consequences of obesity (Guh et al., 2009; Zeyda and Stulnig, 2009), understanding how patterns of body size stability and change over the early life course contribute to adult cardiovascular disease remains an important public health issue (Biro and Wien, 2010). Obesity is closely linked to comorbid conditions such as Type 2 diabetes, cardiovascular disease, and is a major contributor to lower U.S. life expectancy (Juonala et al., 2011; Kahn et al., 2006; Olshansky et al., 2005). Evidence suggests that chronic low-grade inflammation is a key pathway linking obesity to metabolic and CVD risk (de Heredia et al., 2012). Obesity-related inflammation increases pro-inflammatory cytokine production (i.e., IL-6 and TNFα) in adipose tissue, elevating acute phase inflammatory responses by way of C-reactive protein (CRP) produced in the liver (Tilg and Moschen, 2006). Moreover, chronically elevated CRP is associated with insulin resistance, Type 2 diabetes, and CVD (Van Gaal et al., 2006; Yudkin et al., 1999). Though links between harmful comorbid conditions and obesity are well documented (Guh et al., 2009), how body size across early life course periods predicts inflammatory markers linked to subsequent CVD outcomes remains largely unaddressed (though see Attard et al., 2013; Nazmi et al., 2009).

We assess four pathways by which body size over the early life course increases inflammation using the representative U.S.-based National Longitudinal Study of Adolescent Health (Add Health). The fetal origins hypothesis (or thrifty phenotype) proposes that insults during the biologically *sensitive period* in utero (e.g. growth restriction) alters offspring metabolic processes that shape long-term risk (Hales and Barker, 2001). Adolescence, a time of rapid physiological change via pubertal development intersecting with dramatic social change in the lives of youth (Crosnoe, 2011) creates an additional biologically sensitive period. In early adulthood, the acquisition of new social roles and environmental stressors can increase or solidify obesogenic health risk behaviors coupled with declines in overall self-rated health (Bauldry et al., 2012; Crosnoe and Elder, 2004) that marks an important *socially sensitive* period. These periods may also string together into "chains of risk" to shape current health as a consequence of correlated risks over time (Kuh

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http://dx.doi.org/10.1016/j.socscimed.2015.11.040
0277-9536/

et al., 2003; Lynch and Smith, 2004). We assess the contributions of these different pathways to adult inflammation among a cohort of youth first measured as adolescents in 1993-94 during a period of rising obesity and obesogenic morbidity (Lee, H. E., Lee, D., Guo, G., & Harris, K. M. 2011).

1. Literature review

We examine the consequences of birth weight, obesity, and weight gain over the early life course for adult systemic inflammation as measured by high sensitivity CRP levels at ages 24 to 34. Obesity and adiposity are associated with elevated chronic inflammatory markers such as CRP (de Heredia et al., 2012) and may be tied to the accompanying risk of other obesity related conditions including metabolic dysregulation and cardiovascular disease (Hotamisligil, 2006; Zeyda and Stulnig, 2009). Given the dramatic weight gain trends in the U.S. at all age groups in recent years (Olshansky et al., 2005), and the generally poor birth weight profile of the U.S. relative to other developed nations, there are multiple hypothesized pathways for how body size is linked to health over the early life course. Fig. 1 presents the pathways we assess. These pathways are denoted with *fetal origins* (birth) and adolescent *sensitive periods*, the socially disruptive transition to adulthood, and the *chains of risk* model capturing correlated risks over time.

1.1. Fetal origins hypothesis

Both low and high birth weight are markers of adverse fetal environments and birth weight has a U-shaped relationship to obesity, Type 2 diabetes, hypertension, and CVD (Fraser et al., 2012; Seckl and Holmes, 2007). In the case of infant microsomia (<2500 g), poor nutrition and maternal stress levels restrict growth in-utero, altering glucose-insulin metabolic regulation while shaping subsequent growth patterns (Hales and Barker, 2001). Consequently, fetal growth restriction as measured by birth weight is associated with accelerated weight gain and increased intra-abdominal adiposity. Few studies measure the relationship between microsomia and adult inflammation, though lower birth weight may be associated with adult CRP (McDade et al., 2014; Nazmi et al., 2009; Tzoulaki et al., 2008). Although the links between macrosomia (>4000 g), obesity, and Type 2 diabetes are beginning to receive attention, less is known about macrosomia and adult inflammation (Fraser et al., 2010). Infant macrosomia is linked to gestational diabetes, elevating the risk of adult obesity and Type-2 diabetes (Yessoufou and Moutairou, 2011). Moreover, macrosomic offspring have higher proinflammatory cytokine levels compared to normal birth weight offspring (Atègbo et al., 2006).

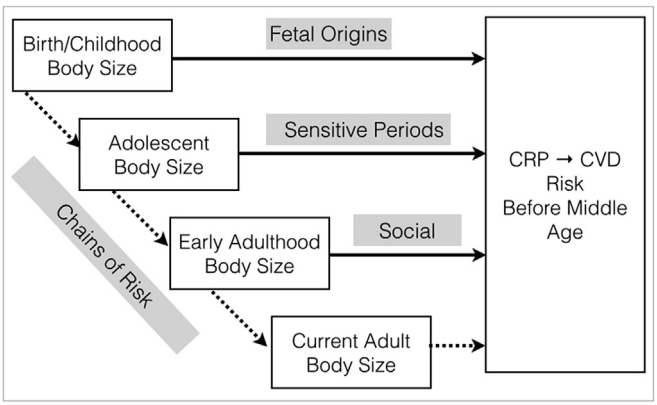

Fig. 1. Conceptual mode.

These pathways to CVD risk are shown in Fig. 1. Assessing the degree to which microsomia/macrosomia are early life course sensitive periods that influence adult inflammation is the first goal of our analysis. Because birth weight differs by race/ethnic background in the U.S. (Martin et al., 2015), birth weight may be an important pathway by which social disadvantage shapes long-term health outcomes.

1.2. Adolescence to adulthood: biological and socially sensitive periods

Later periods are also characterized by rapid physiological development and/or environmental change. As illustrated by Fig. 1, adolescence is proposed as a high-risk period for obesogenic weight gain (Frederick et al., 2014). The confluence of developmental metabolic changes coupled with increased sedentary behavior and control over diet may combine to elevate adult metabolic and cardiovascular risk (Jasik and Lustig, 2008). Such change is particularly salient among females since abnormal weight gain in adolescence is associated with earlier onset of thelarche and menarche, two established correlates of adolescent obesity and adiposity (Wang et al., 2011). Adolescent boys' obesity is associated with later puberty onset (Solorzano and McCartney, 2010) and in both cases, adolescent obesity and adiposity predict adult obesity, Type 2 diabetes, hypertension, and elevated CRP (Jasik and Lustig, 2008; May et al., 2012).

In addition to biologically sensitive periods, the transition to adulthood is a key period that may shape subsequent obesogenic risk for *social* reasons. This transition is a time of shifting demands when youth leave home, begin adopting adult roles, and acquire new stressors (Crosnoe and Elder, 2004). Consequently, there is considerable social change and physical activity further declines, fast-food intake increases, overall self-rated health declines (Bauldry et al., 2012; Jasik and Lustig, 2008; Larson et al., 2008), and BMI increases and becomes less likely to decrease (Gordon-Larsen et al., 2004a, 2004b). These trends of accumulated body size and recent weight gain are implicated in a range of adverse health conditions and life outcomes, particularly among minorities (Moore et al., 2009) who are disproportionately in poverty, face additional stressors, and are consequently at higher obesity risk (Frederick et al., 2014).

The middle-pathways in Fig. 1 show these pathways. The second goal of this study is thus to assess the sensitivity of adolescence and early adulthood for subsequent inflammation. We also assess whether minority inflammation disparities reflect differential body size trajectories and differential sensitivity by gender, while accounting for self-rated health—a key correlate of gender differences in CRP among adults aged 24–34 (Shanahan et al., 2014b).

1.3. Chains of risk

Sequential biological and social exposures that elevate the probability of subsequent insults are referred to as “chains of risks” (Kuh et al., 2003). Consequently, one period may appear especially sensitive if continuity in body size trajectories is not accurately captured. BMI during childhood is correlated with BMI in early adulthood (Deshmukh-Taskar et al., 2005), consistent with the idea that body size growth and stability are a “chain of risks” integrating sensitive periods via body size trajectory rather than period-specific sensitivity. Body size at one period may thus be a proxy for subsequent body size. The chains of risk pathway in body size is indicated in the diagonal arrows linking body size at different periods, culminating in the adult obesity pathway to CVD risk in Fig. 1. Therefore, our third goal is to assess how body size over time affects CVD risk via the CRP pathway in a multi-period model spanning