Social Science & Medicine xxx (2014) 1–9

Contents lists available at ScienceDirect

Social Science & Medicine

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

Genetic vulnerability to diabetes and obesity: Does education offset the risk?

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ARTICLE INFO

Article history:
Available online xxx

Keywords:
Genetic risk
Education
Diabetes
Obesity
Older adults

ABSTRACT

The prevalence of type 2 diabetes (T2D) and obesity has recently increased dramatically. These common diseases are likely to arise from the interaction of multiple genetic, socio-demographic and environmental risk factors. While previous research has found genetic risk and education to be strong predictors of these diseases, few studies to date have examined their joint effects. This study investigates whether education modifies the association between genetic background and risk for type 2 diabetes (T2D) and obesity. Using data from non-Hispanic Whites in the Health and Retirement Study (HRS, $n = 8398$), we tested whether education modifies genetic risk for obesity and T2D, offsetting genetic effects; whether this effect is larger for individuals who have high risk for other (unobserved) reasons, i.e., at higher quantiles of HbA1c and BMI; and whether effects differ by gender. We measured T2D risk using Hemoglobin A1c (HbA1c) level, and obesity risk using body-mass index (BMI). We constructed separate genetic risk scores (GRS) for obesity and diabetes respectively based on the most current available information on the single nucleotide polymorphism (SNPs) confirmed as genome-wide significant predictors for BMI (29 SNPs) and diabetes risk (39 SNPs). Linear regression models with years of schooling indicate that the effect of genetic risk on HbA1c is smaller among people with more years of schooling and larger among those with less than a high school (HS) degree compared to HS degree-holders. Quantile regression models show that the GRS × education effect systematically increased along the HbA1c outcome distribution; for example the GRS × years of education interaction coefficient was −0.01 (95% CI = −0.03, 0.00) at the 10th percentile compared to −0.03 (95% CI = −0.07, 0.00) at the 90th percentile. These results suggest that education may be an important socioeconomic source of heterogeneity in responses to genetic vulnerability to T2D.

1. Introduction

Type 2 diabetes (T2D) and obesity are two largely preventable chronic conditions. Despite targeted public health interventions, the prevalence of both conditions has increased in recent years. These dual epidemics will likely continue to contribute to substantial morbidity and mortality and greater healthcare costs in the future (Dall et al., 2010; Dieren et al., 2010; Tobias et al., 2014; Wang et al., 2011; Withrow and Alter, 2011; Zhang et al., 2010).

Obesity and T2D both have strong genetic bases (Apovian, 2010; Das and Elbein, 2006; Lin and Sun, 2010; Walley et al., 2009). Environmental and lifestyle factors, such as diet and physical inactivity, are also critical to the pathogenesis of these conditions (Hu et al., 2001; Maes et al., 1997). Previous research investigating the complex interplay of factors contributing to risk has focused on interactions between genetic predisposition and health behaviors. For example, physical activity attenuates genetic vulnerability to obesity and T2D (Ahmad et al., 2013; Brito et al., 2009; Kilpelainen, 2009; Li et al., 2010), and eating foods associated with a Western dietary pattern exacerbates genetic risk on T2D (Cornelis and Hu, 2012). Our study extends this focus to education, a more upstream factor that is likely to moderate the effect of hereditary

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http://dx.doi.org/10.1016/j.socscimed.2014.09.009
0277-9536/

predispositions towards diabetes risk and obesity through several possible mechanisms.

As a fundamental cause of disease, education acts through multiple pathways to affect health and disease risks (Cutler and Lleras-Muney, 2008) related to differential access to resources (Johnson et al., 2011; Link and Phelan, 1995; Phelan et al., 2010). On an individual-level, education leads to increases in a person's general capabilities, skills, knowledge, money and prestige (Becker, 1964). Education also increases a person's ability to access societal resources such as healthy built environments and high-quality medical care (Fig. 1). It is this differential access to resources that individuals use to avoid disease risks or minimize the consequences of disease risks that cannot be directly modified, such as genetic background.

In this study, we investigate whether education modifies genetic propensity for obesity or T2D. Under the social trigger framework, the presence or absence of contextual variable affects the phenotypic expression of a specific genotype (Shanahan and Hofer, 2005; Reiss et al., 2013). Educational attainment has consistently been shown to be inversely associated with obesity and T2D (Borrell et al., 2006; Cohen et al., 2013; McLaren, 2007). As a fundamental cause of disease, greater educational attainment may trigger mechanisms (e.g. increased psychosocial skills) and be used to attain tangible resources (e.g. high-quality medical care, higher income) that mitigate the impact of inherent genetic risks for these conditions. We hypothesize that attaining more education may enable individuals with higher genetic risk to overcome innate susceptibility to obesity and T2D. Although both obesity and T2D are affected by genetic risk, they are also highly influenced by modifiable risk factors. Education plays a major role in determining access to individual- and environmental-level factors that are protective against obesity and T2D (e.g. healthy food, less stressful occupational environments, residential neighborhoods more conducive to physical activity). Low educational attainment and the subsequent low socioeconomic status and psychological characteristics associated with it may act as a triggering mechanism that affects the expression of inherent genetic risk. For example, a person with high genetic risk for obesity and a college degree may never experience the individual-level and environmental conditions that will lead to greater BMI. However, if the same high-risk individual has less than a high school degree, he/she may have lower access to resources and, as a result, have a greater BMI. In this example, obesity may be "triggered" under the conditions of a high genetic risk and low educational attainment. We expect to find significant effect measure modification of inherent risk by education for T2D and obesity because these conditions have well-known prevention and disease management strategies that are associated with access to socioeconomic resources and more education. The links between HbA1c and BMI and health are not monotonic. Thus, we would expect that education should be associated with the largest *reductions* in BMI at high ends of the distribution.

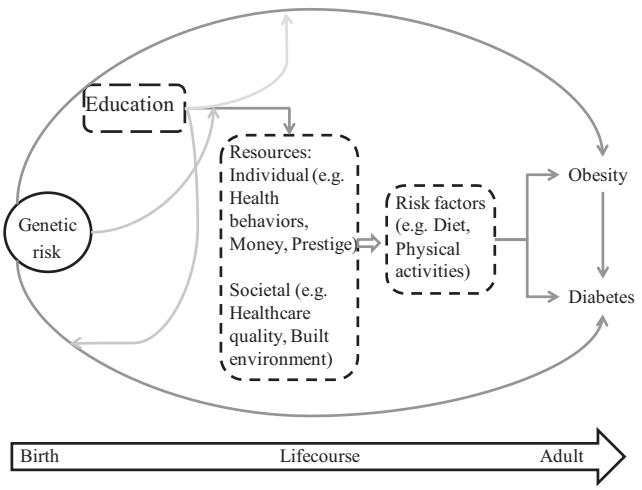

Fig. 1. Conceptual framework illustrating the potential pathways linking genetic risk, education and obesity and Type 2 diabetes in later life. Circles indicated fixed risk factors present at birth and boxes with dashed lines indicate modifiable factors throughout the lifecourse.

Furthermore, we expect the relative contribution of genetic and environmental risk factors for T2D and obesity and their interaction to vary at higher versus lower points in the outcome distribution. Variation in the effects may reflect possible differences within the population that are not readily identifiable. Interaction effects of education and genetic risk score might be larger and negative at the high end of the HbA1c and BMI distribution, as these individuals may be at especially high risk for disease because of other unidentified characteristics. Differences in effects along the outcome distribution may thus reflect unmeasured sub-groupings in the population. Extreme BMI and HbA1c values, the underlying clinical indicators corresponding with risk of obesity and T2D respectively, are associated with elevated mortality risks (Aggarwal et al., 2012; Carson et al., 2010; Flegal et al., 2005) although the exact mechanisms are not always known. Estimates from standard models assuming uniform response will likely understate benefits of education and potentially entirely miss the interaction of education and genetic risk.

Finally, systematic inequalities in resources may also lead to gender-specific interaction effects between education and genetic risk of obesity and T2D. Gene-environment interactions differ by gender when the "environment" reflects gender inequality (Perry et al., 2013). Education differentially shapes the resources of men and women because of their differential access to resources. According to resource substitution theory (Ross and Mirowsky, 2006), females may be more reliant on education because they lack alternative resources to obtain comparable levels of socioeconomic status. Men in the US may have access to more alternative resources than women. For men, more education may not convey substantial additional benefits, because they already have other resources deriving from their physical capacity, inherited wealth, broader range of socially acceptable occupations and activities, and position in the social hierarchy. Women may have more limited options so higher education is necessary to be able to attain such benefits as high occupational prestige and socioeconomic status. Previous research has found stronger effects of education among women compared to men in health conditions as varied as disability, depression, and obesity (Brunello et al., 2013; Ross and Mirowsky, 2006, 2010). We extend this to investigate whether moderation of genetic risk by education is also stronger among women compared to men. In our study, this would imply that education has a stronger moderation effect for women, since females have fewer socioeconomic resources to plausibly offset genetic risk when compared with men. Men with low education levels may still have more opportunities than women with similar educational levels for maintaining a healthy weight or low diabetes risk.

In summary, little work has considered the simultaneous effects of genetic risk and education. Previous research has found that education reduces expression of genetic susceptibilities to health, but these studies used self-reported health outcomes and classical twin study designs (Johnson et al., 2011, 2010). The aim of this study is to investigate whether education can modify the consequences of genetic risk for diabetes and obesity as indicated by HbA1c and BMI. We hypothesize that highly educated individuals are better positioned to overcome genetic vulnerability to obesity and T2D,

Please cite this article in press as: Liu, S.Y., et al., Genetic vulnerability to diabetes and obesity: Does education offset the risk?, Social Science & Medicine (2014), http://dx.doi.org/10.1016/j.socscimed.2014.09.009