The genetic and cultural inheritance of obesity: Differentials in genetic penetrance by home environment

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1 Extended Abstract

1.1 Research question and theoretical framework

Obesity is a major challenge to public health in contemporary societies. It is known that adult obesity is highly correlated with early childhood and adolescent obesity and that the prevalence of the phenotype in the young population could be a predictor of future obesity. Because child and adolescent obesity has been increasing rapidly everywhere (Simmonds et al. 2016; Horesh et al. 2021), these relations call for a throrough investigation of the causes of child and adolescent obesity. One key contributing factor is the "home obesogenic environment", which refers to the summation of household conditions conducive to obesity (Swinburn et al. 1999; Davison and Birch 2001; Schrempft et al. 2015). The home environment plays a crucial role in shaping children obesity as it serves as the primary setting for early socialization (Rosenkranz and Dzewaltowski 2008), where most food consumption occurs (Kegler et al. 2021). and where children spend the majority of their time learning and copying preferences, tastes and behaviors from parents and co-resident close kin (Haddad et al. 2018). Recently, household settings have also been considered as one of the environmental factors involved in gene-environment interactions (GxE) studies. These studies show that 'healthier' household environments attenuate the effects of inherited obesity genetic risks (Schrempft et al. 2018; Tommerup et al. 2021; de Roo et al. 2023). Despite these promising insights, extant studies are limited in scope, as they focus primarily on very small set (usually one) of home environments characteristics and rely on multiple measures of disparate obesity-relared domains. Furthermore, all the studies testing for GxE interaction in children and adolescents focus exclusively on European populations (Hüls et al. 2021; de Roo et al. 2023). To our knowledge, there has been no equivalent research conducted for other populations.

This paper proposes a synthetic model that jointly considers the effects of household environments, parental characteristics and phenotypes, and genetic and indirect genetic factors. The model enables us to reduce these different domains into a one dimensional construct, the cultural risk score (CRS) that captures the weighted impact of these domains on children's body mass. We also explore the heterogeneity in BMI heritability according to different home environments. Lastly, we use two samples of children and adolescent from the US where this research question has not been fully investigated.

1.2 Data and Methods

We employ two nationally representative longitudinal datasets of US children and adolescents, namely, the National Longitudinal Study of Adolescent to Adult Health (Add Health) and the Future of Families and Child Wellbeing Study (formerly Fragile Families). Both include measures of relevant domains reflecting home environments, maternal BMI, child's BMI, child's polygenic risk score (PRS) for BMI and parental BMI and corresponding (PRS)

We use Confirmatory Factor Analysis (CFA) with a latent construct representing obesogenic environments a child is exposed through influences of parental phenotypical traits, household characteristics, and genetic markers for both parents and children. The household related factors we choose to include are all identified as highly relevant in the recent. These are: sedentarism (Prentice-Dunn and Prentice-Dunn 2012; LeBlanc et al. 2015; Haghjoo et al. 2022), diet (Roblin 2007; Ambrosini et al. 2012; Liberali et al. 2020; Pereira and Oliveira 2021), sleep atterns (Antczak et al. 2020), and stress (Kanellopoulou et al. 2022). Because of its central place in recently proposed theories about the obesogenic force (Sørensen 2023), we also include measures of food security and household poverty. Parental characteristics include maternal educational attainment (Silventoinen et al. 2019), parental BMI and parental PRS for BMI. Finally, we use a handful of indicators of neighborhood characteristics that could arguably influence household members' behaviors and exposure to stress. We compute a "Cultural Risk Score" (CRS), an analogue to the child's PGS in that it captures the weighted effects of multiple domains (diet, physical activity, sleep, stress) each related to child obesity, much as the child' PRS for BMI does with selected allelic variants instead of obese-related domains. The latent variable approach enables us to compute an integrated measure of the impact of diverse domains and helps to capture their underlying structure shared by children living in the household (Kline and Little 2023; Bollen 1989). Additionally, this approach can reduce measurement error frequently present in uncorrectd survey variables (Bollen 1989; Hair 1998).

Once optimal variables' indicators are chosen via CFA, we estimate a Structural Equation Model (SEM) to identify direct and indirect pathways between variables chosen via the CFA and the latent variables. We expect that BMI of the mother will have a significant influence on CRS, partly because maternal BMI is a product of preferences and behaviors to which children are exposed and partly because, albeit imperfectly, it may also reflect pregnancy and post-partum conditions (Williams et al. 2017). We also expect that maternal BMI will be associated with the child's obesity polygenic score (PGS) as parental genetic predispositions that influence their BMI are inherited by the child and reflected in their PGS. This association should disappear when parental PRS for BMI are included in the model. Estimates from SEM account for both the direct effect of maternal BMI on the child's BMI and the indirect effects mediated through the child's CRS and child's PGS. Figure 1 displays relations between variables and constructs of our model. We initially split the sample into two subsamples based on CRS levels, one with low CRS and one with high CRS, and estimate the model separately for each subgroup. We expect to observe important contrasts in the coefficient of child's PGS on child's BMI between these groups suggesting the existence of non-trivial GxE effects. The 'G' in this case is the obesogenic (or not) environment reflected in the CRS.

We argue that the construction of the CRS has a significant advantage over alternative ways of assessing household and parental influences commonly used in empirical research. This is that the effects of obesity-related domains reflected by the CRS are a synthetic and easily interpretable measure of what population geneticists refer to as 'cultural traits'. Because these are potentially transmitted across generations with variable fidelity, they have strategic importance as predictors of future obesity trends.

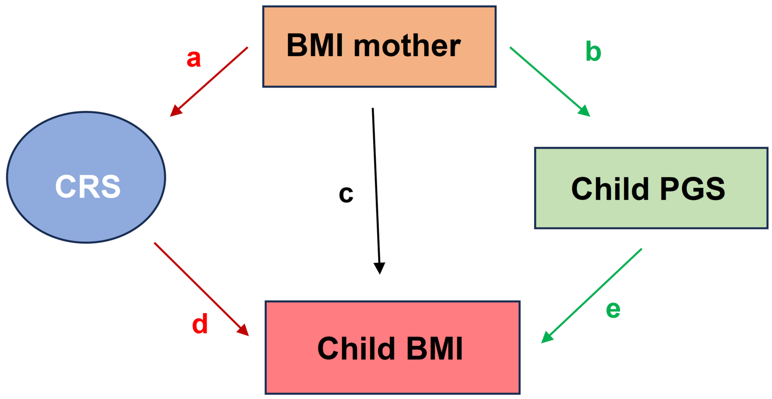

Figure 1: Structural Equation Model

1.3 Preliminary results

Below we summarize preliminary results from both data sets.

First, regarding the construction of the latent variable of CRS, both databases point to the same relevant domains. Stress and sleep quality consistently under perform whether they are included jointly or separately. They both yield posterior factor loadings smaller than 0.2, reflecting a weak correlation between the observed and the latent factor. This magnitude is one half of the cutoff proposed by Stevens (2001) or the 0.32 for "poor" correlations suggested by Comrey & Lee (1992). Additionally, the CFA reveals that models with sleep and stress yield higher Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) than models without those variables. This suggest that these models fit the data poorly and have worse explanatory power compared to other nested models. These preliminary results indicate either that the indicators of stress and sleep quality in these survey are poorly identified or, as suggested by recent findings (Antczak et al. 2020), that they are indeed the least relevant factors shaping a household obesogenic landscape.

Second, the best performing latent constructs in both datasets are those that include dietary, physical activity, and parental education variables as all factor loadings exceed 0.4. Parental education shows the highest value, ranging from 0.8 to 0.9, depending on the configuration of the construct. These results suggest that the home environment is mainly comprised by these components.

Third, the estimated effects of a child's PGS for BMI in the baseline model is of 0.924 in Add Health but only 0.657 in Fragile Families. The difference is likely accounted for by the age differences

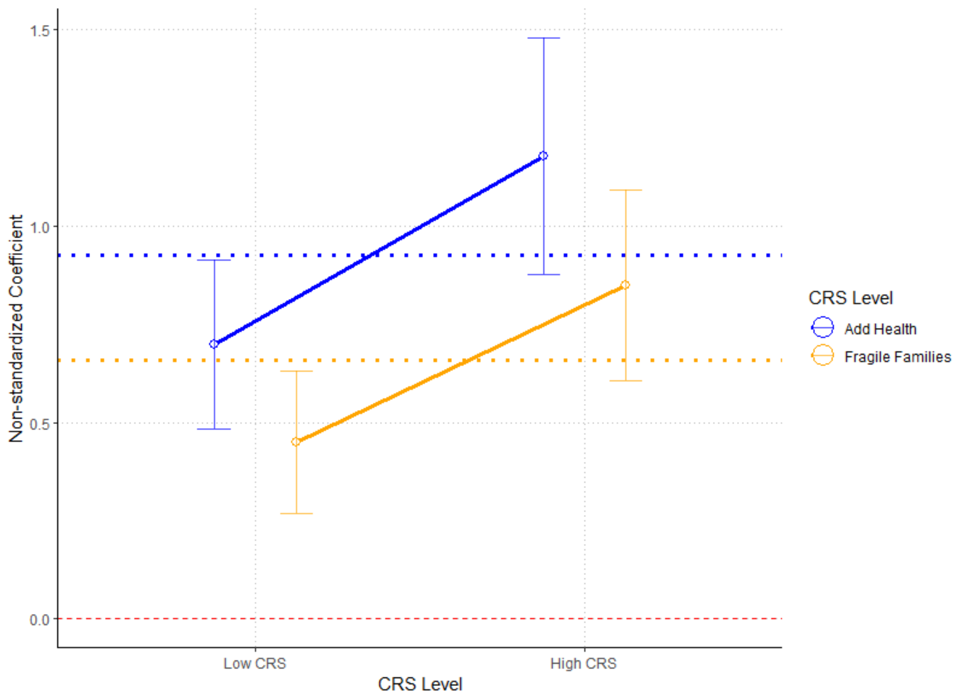

Figure 2: Coefficients of Child's PGS on Child's BMI by levels of CRS

in the samples' population as it is well known that the correlation between PRS for BMI and BMI is age-dependent. In contrast, the variation of PGS coefficients in the two CRS groups is remarkably similar in both datasets, 0.399 (0.848-0.449) for Fragile Families and 0.479 (1.177-0.698) for Add Health. These quantities reflect deviations of about 60.7% and 51.8% from the baseline coefficient respectively and suggest significant variation of genetic penetrance across CRS groups. The most important inference from this finding is that there are non-trivial GxE interaction effects involving genes and the CRS that guide the trajectory of the phenotype across ages (Martinson et al. 2011). These results are displayed in Figure 2.

1.4 Next steps

We are currently working on the following extensions of the model and its estimation: We will define a more fine-tuned categorization of CRS groups by using tertiles and quartiles of the CRS distribution. It may well be the case that significant differences are likely to be concentrated at the extremes of this distribution, both of which are poorly represented by the current two-group classification. To complete the model, we will include parental PRS for BMI and corresponding interactions. This addition will enable us to detect, albeit, partially indirect genetic effects. We will identify different data sets with indicators for the obesity-related domains that are similar to those in FF and AH. We will then predict values of individuals' CRS and assess their out of sample predictive power.

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