Eat2beNICE

Effects of Nutrition and Lifestyle on Impulsive, Compulsive, and Externalizing Behaviours

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D1.4 Manuscript 4: how genetic contributions to impulsivity and compulsivity depend on dietary intake and lifestyle using twin modelling

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Executive Summary

Within Deliverable 1.4 ("How genetic contributions to impulsivity and compulsivity depend on dietary intake and lifestyle using twin modelling"), one manuscripts have been prepared with the title of "Does the heritability of ADHD vary as a function of dietary intake? Evidence from a Swedish twin sample".

The manuscript reports on associations between dietary habits and attention deficit/ hyperactivity disorder (ADHD) in the general population of adults. ADHD is a multifactorial disorder influenced by the complex interplay between many genetic and environmental factors. To date, no single factor or biomarker has been identified for screening the risk of the disorder or facilitating the diagnostic procedure. Gene–environment (GxE) interactions are becoming increasingly recognised as important in the pathogenesis of ADHD, but this area is currently under-investigated. In a Swedish population-based twin study, we found in middle-aged adulthood, the genetic variance of ADHD increased with higher intake of high-sugar food and unhealthy food, indicating a diets–gene interaction effect on ADHD. The results suggest that further insight into the effects of gene–environment interactions would improve understanding of the etiology of ADHD

Abbreviations

ADHD	Attention deficit / hyperactivity disorder
HI	Hyperactivity-impulsivity
IA	Inattention
STR	Swedish Twin Regist

1. Deliverable report

Does the heritability of ADHD vary as a function of dietary intake? Evidence from a Swedish twin sample?

Motivations

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopment disorder characterized by inattention or hyperactivity–impulsivity, or both (1). Although with onset in early childhood, ADHD commonly persists into adulthood (2, 3). ADHD is associated with many adverse outcomes across development, exerting an enormous burden on the patients, families and society (4). However, the pathophysiological mechanisms underlying ADHD are unclear and its diagnostics and treatment remain challenging.

It is a well-known finding that ADHD is heritable: depending on the age of the sample, the estimation method used, ratings from different informants, genetic differences between individuals account for between approximately 30% and 80% of the variance in ADHD (5-7). Although a substantial fraction of the etiology of ADHD is due to genes, previous studies show that many environmental factors also increase the risk for the disorder, including but not limited to exposure to toxicants, dietary habits and nutrient deficiencies, events during pregnancy and birth (8, 9). In our previous work related to the Eat2BeNice Project (7), we examined the relationships between inattention and hyperactivity/impulsivity subtypes and dietary habits among almost 18,000 middle-aged twins from the Swedish Twin Register (STR). We found adults with ADHD were more likely to be eating high-sugar food and neglecting fruits and vegetables while eating more meat and fats. We further found both genetic and environmental factors contribute to the observed associations.

In addition to the importance of environmental and genetic factors to ADHD across development, gene–environment (GxE) interactions are becoming increasingly recognised as important in the pathogenesis of ADHD, but this area is currently under-investigated (10). G × E describes any phenotypic events that are due to interactions between the environment and genes. That is, the importance of genetic factors may be dependent on key environmental factors at any given point genes (11).

Previous studies have reported several genotype–environment interaction effects on ADHD. For example, the ADHD-risk gene ADGRL3 expression can be decreased by starvation but increased by nicotine (12). Further, a study showed child hyperactivity and impulsivity were associated with the 480-bp DAT1 risk allele only when a child also had exposure to maternal prenatal smoking (13). Another study revealed significant interactions of LPHN3 rs1868790 collaborating with blood lead levels and maternal stress during pregnancy to modify ADHD risk in offspring (14). However, few studies have addressed the overall effects of dietary factors in modifying the role of genetic effects on ADHD, particularly in adults. Therefore, in this paper, we aim to explore whether dietary habits in adulthood moderates genetic risk for ADHD.

Methods

We identified 1,581 individuals aged 20–47 years from Swedish Twin Register with completed information on two important dietary habits (high-sugar dietary habits and unhealthy dietary patterns), which were found to be associated with ADHD both genetically and phenotypically in our previous work (7).The definitions of ADHD symptoms, dietary habits could also found in the paper (7). For our primary analyses, we evaluated whether dietary habits moderated the etiology of ADHD using the 'extended univariate G × E' model, which estimates how variance in traits change across levels of a measured environmental moderator by including its effect on the paths for each component (15). We performed a global test of moderation by constraining the moderation effects on all of the components to be zero. All analyses used the OpenMx package in R. Age and sex was included as covariates on the mean of the phenotype.

Findings

All genetic correlations, except for hyperactivity/impulsivity with unhealthy food, were statistically significant, ranging from 0.09 (95% CI: 0.002, 0.19) for hyperactivity/impulsivity and high-sugar food to 0.16 (95% CI: 0.07, 0.25) for inattention and high-sugar food. All non-shared environmental correlations were statistically significant. The bivariate heritability estimates (the fraction of phenotypic covariance explained by genetic influences) were 44% (95% CI: 18%, 70%), 40% (95% CI: 10%, 69%), and 37% (95% CI: 1%, 71%) for inattention and high-sugar food, inattention and unhealthy dietary pattern, and hyperactivity/impulsivity and high-sugar food, respectively. These results were reported elsewhere (7).

Table 1 presents the path estimates from the extended univariate GxE models for ADHD symptoms dimensions and dietary intake for the best fitting models (AE models). In the associations between inattention and high-sugar food intake, we found that at higher levels of high-sugar food intake, genetic components had a stronger influence. As seen in table 1, A accounted for 45% of the variance in ADHD at the highest level of high-sugar food intake, but only 36% at the lowest level of high-sugar food intake. Environmental variance explained the larger proportion (55%-64%) of the variance regardless of the different levels of dietary habits. Similar patterns were also found in the associations between inattention and unhealthy dietary intake, hyperactivity/impulsivity and high-sugar/unhealthy dietary intake. Overall, heritability of ADHD changed because of the shift in both genetic and non-shared environmental variances across levels of high-sugar and unhealthy dietary intake. Genetic influences contributed relatively less to the standardized variance at the lowest levels of high-sugar/unhealthy food intake (range: 30%-36%) compared to the highest levels of high-sugar/unhealthy food intake (range: 45%-51%). These results indicate the presence of a diet–gene interaction effects on ADHD.

In summary, we found in middle-aged adulthood, the genetic variance of ADHD increased with higher intake of high-sugar food and unhealthy food, indicating a diet–gene interaction effects on ADHD. Our results suggest that further molecular genetic insight into the effects of gene–environment interactions would improve understanding of the aetiology of ADHD.

2. Tables and other supporting documents where applicable and necessary

Table 1. Extended univariate GxE models for ADHD symptoms dimensions and dietary intake.

AE model		Mean	Total variance	Variance (A)	Variance (E)	Proportion of total variance (A) /Heritability	Proportion of total variance (E)
IA							
High-sugar food intake	Low	2.03 (1.95, 2.12)	3.90(3.59, 4.23)	1.40(0.95, 1.91)	2.49(2.07, 2.95)	0.36(0.25, 0.47)	0.64(0.53, 0.75)
	Medium	4.07 (3.90, 4.24)	4.45(4.22, 4.69)	1.81(1.31, 2.12)	2.63(2.40, 2.89)	0.41(0.30, 0.46)	0.59(0.54, 0.65)
	High	6.10 (5.84, 6.36)	5.05(4.66, 5.50)	2.28(1.25, 2.88)	2.78(2.33, 3.31)	0.45(0.25, 0.54)	0.55(0.46, 0.65)
IA							
Unhealthy dietary intake	Low	2.03 (1.95, 2.12)	3.95(3.65, 4.28)	1.20(0.78, 1.68)	2.75(2.32, 3.2)	0.30(0.2, 0.41)	0.70(0.59, 0.80)
	Medium	4.07 (3.90, 4.24)	4.43(4.19, 4.68)	1.81(1.34, 2.11)	2.61(2.38, 2.87)	0.41(0.31, 0.46)	0.59(0.54, 0.65)
	High	6.10 (5.84, 6.36)	5.03(4.63, 5.49)	2.55(1.55, 3.17)	2.48(2.05, 3.00)	0.51(0.31, 0.60)	0.49(0.40, 0.60)
HI							
High-sugar food intake	Low	2.07 (1.99, 2.16)	4.28 (3.95, 4.65)	1.36 (0.91, 1.83)	2.92 (2.51, 3.37)	0.32 (0.22, 0.41)	0.68 (0.59, 0.78)
	Medium	4.14 (3.97, 4.32)	4.58 (4.35, 4.83)	1.79 (1.43, 2.10)	2.79 (2.55, 3.07)	0.39 (0.32, 0.45)	0.61 (0.55, 0.67)
	High	6.22 (5.96, 6.48)	4.94 (4.55, 5.38)	2.27 (1.68, 2.85)	2.67 (2.24, 3.17)	0.46 (0.35, 0.55)	0.54 (0.45, 0.64)
HI							
Unhealthy dietary intake	Low	2.07 (1.99, 2.16)	4.36 (4.02, 4.74)	1.29 (0.69, 1.79)	3.02 (2.57, 3.52)	0.31 (0.16, 0.40)	0.69 (0.59, 0.79)
	Medium	4.15 (3.97, 4.32)	4.55 (4.26, 4.83)	1.79 (1.40, 2.11)	2.76 (2.48, 3.05)	0.39 (0.31, 0.45)	0.61 (0.55, 0.67)
	High	6.22 (5.96, 6.48)	4.90 (4.50, 5.36)	2.38 (1.66, 3.02)	2.50 (2.06, 3.04)	0.49 (0.35, 0.58)	0.51 (0.41, 0.62)

IA: Inattention, HI: Hyperactivity-impulsivity

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