Eat2beNICE

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Executive summary

Within Deliverable 1.06 ("Candidate gene pathways x diet/lifestyle interactions on impulsivity and compulsivity"), two manuscripts haves been prepared, one focused on hildren and one focused on adults. Here we report on these. Part 1 of this report details the results from the examination of the effects of breastfeeding and genetics (both parental and offspring) has on the development of attention-deficit/hyperactivity disorder (ADHD) symptoms in children in a longitudinal design, including the exploration of the effects of interaction of ADHD genetics and breastfeeding on the child's development of ADHD symptoms. Part 2 of this report details the effects of diet-gene and diet-lifestyle interactions on impulsivity in the general population of adults.

Part 1

ADHD is characterized by maladaptive hyperactivity and impulsivity, inattention, or a combination of these symptoms. Further, ADHD is a childhood onset condition with an increased risk of development of other psychiatric disorders, among others; some with compulsive traits like obsessive compulsive disorders and substance use disorders.

We aimed to examine the effect of each month of breastfeeding in the first six months, as a continuous variable, on the overall development and the longitudinal change of ADHD symptoms at three, five and eight years of age accounting for the child's and parental genetic propensity to ADHD, in addition to effect of the ADHD genetics-breastfeeding interaction on these associations, in the Norwegian Mother, Father, and Child Cohort Study (MoBa), a prospective population-based pregnancy cohort study.

ADHD is of polygenic and environmental origins, a common neurodevelopmental disorder characterized by hyperactivity and impulsivity, inattention, or a combination of these symptoms. The child's first diet, breastmilk, is one of the environmental factors that are potentially modifiable to target modification of neurodevelopmental disorders. Breastfeeding has been reported to be associated with a reduced risk of childhood ADHD. Our study sample consisted of 20,474 mother-father-child units, with available mother-reported information on full and partial breastfeeding in the first six months of life from the MoBa questionnaire, and with completed questionnaires on ADHD symptoms when the offspring were three, five and eight years of age. All analyses controlled for the genetic liability of ADHD in child, mother, and father using ADHD polygenic scores, calculated using MoBa genetic data and a large genome-wide association study of clinically diagnosed ADHD (20,183 cases and 35,191 controls) published, and socioeconomic factors like maternal education. We examined the effect on overall levels of ADHD symptoms in offspring using multivariate regression models, and on change in offspring's ADHD symptoms using latent growth curve models. Our exposures were full (i.e., predominately) breastfeeding and partial breastfeeding, both as continuous variables. Our outcome was a constructed „ADHD score" for offspring at either three, five or eight years of age, utilizing information from several instruments collected through MoBa questionnaires. We found that full breastfeeding was positively associated with less reported ADHD-related behaviour at all ages, suggesting that each month of full breastfeeding up to six months was associated with lower ADHD symptoms in childhood. Partial breastfeeding was only weakly associated with ADHD symptoms in childhood. We found no effect of the interaction of ADHD PGS and full breastfeeding on the ADHD symptoms. Further, full or partial breastfeeding were not associated with the longitudinal change in ADHD symptoms between three to eight years. Further studies are needed to understand the underlying mechanisms of the effects of breastfeeding on ADHD.

Part 2

Twin studies have shown that genetic factors play a more prominent role in ADHD development in the presence of high consumption of sugar and unhealthy foods, which suggests the existence of diet-gene interactions in ADHD symptoms. However, few researchers have addressed this based on molecular genetics, and research exploring interactions between genetic factors and a wide range of lifestyle

factors in impulsivity is also lacking. Therefore, our aim was to investigate if an unhealthy diet and other lifestyle behaviors modify the genetic risk of impulsivity using the polygenic risk score (PRS) in the general population.

In a Dutch population-based study, we found that the ADHD PRS was significantly associated with impulsivity. Poorer diet, higher intake of energy, and higher intake of fat were all associated with higher impulsivity, and high intake of energy amplified the effect of ADHD PRS on impulsivity. The other lifestyle factors, namely short and long sleep duration, current and past smoking, higher alcohol intake, and more time spent on moderate-to-vigorous physical activity were associated with higher impulsivity, but no interaction effect was observed.

We concluded that in line with twin-based research, high intake of energy exacerbated the genetic susceptibility to impulsivity. Potential explanations include diet's influence on gene expression. Our study helps to improve our understanding of the role of diet and genetic factors in impulsivity.

1. DELIVERABLE REPORT

1.1 DELIVERABLE REPORT PART 1

Note: publishers' policies prevent sharing of detailed results prior to publication in a peer-reviewed journal. Detailed results, tables and uncompromised figures will be made available upon acceptance and/or as soon as the publisher's embargo has been lifted.

Breastfeeding and the development of ADHD symptoms considering the child's ADHD genetics: A longitudinal study in The Norwegian Mother, Father, and Child Cohort.

Attention-deficit/hyperactivity disorder (ADHD) is a common childhood onset neurodevelopmental disorder characterized by maladaptive hyperactivity and impulsivity, inattention or a combination (American Psychiatric Association, 2013), of polygenic and environmental origins, and with an estimated heritability of 70-80% found in twin- and family studies (Chen et al., 2016; Faraone & Larsson, 2019; Pettersson et al., 2019). ADHD symptoms persist into adulthood in about two-third of cases (Franke et al., 2018), and increase the risk of somatic and psychiatric comorbid disorders, among others; some with compulsive traits like obsessive compulsive disorders, and substance use disorders (Brem, Grünblatt, Drechsler, Riederer, & Walitza, 2014; Instanes, Klungsoyr, Halmoy, Fasmer, & Haavik, 2018; Kessler et al., 2005; Solberg et al., 2018; Yang et al., 2021).

Both genetic and environmental factors contribute to the development of ADHD symptoms, their trajectories, and comorbidities. Understanding what environmental factors drive the development of ADHD is important and if potentially modifiable, prevention is possible. Diet is one of the environmental factors that are potentially modifiable to target intervention of neurodevelopmental disorders (Adan et al., 2019), and breastmilk is the infants first diet. The Norwegian health authorities recommend exclusive breastfeeding for the first six months of life, echoing the WHO recommendation (World Health Organization, 2002). Almost all mothers in Norway initiate breastfeeding (98 %). Some 80% still breastfeed at six months, but only 9% do so exclusively. The largest decrease in exclusive breastfeeding, occurs between three and four months (from 63% to 46%) (Haggkvist et al., 2010). Breastfeeding has been reported to be associated with a reduced risk of childhood ADHD (Tseng, Yen, et al., 2019). Further, in a mouse model, sialyllactose (6'SL) in breastmilk has been found to adjust cognitive development like working memory and attention, cognitive factors that could be related to ADHD. The 6'SL seems to act through a short-term upregulation of genes modulating neuronal patterning in the prefrontal cortex in mice, and with modulation of the microbiome that impacts the metabolism of key molecules for neurodevelopment (Hauser et al., 2021). The previous observed associations between breastfeeding and offspring ADHD symptoms or ADHD trajectories observed in epidemiological studies may be subject to unmeasured familial confounding (Larsson et al., 2013; Skoglund, Chen, D'Onofrio, Lichtenstein, & Larsson, 2014). Breastfeeding in wealthy countries is associated with healthy behavior (Haggkvist et al., 2010) suggesting that maternal behavior favoring breastfeeding may be due to other genetic/environmental/behavioral factors in the mother. Higher ADHD polygenic score (PGS) is associated with ADHD symptoms and ADHD diagnoses in childhood and ADHD PGS can be used to test to which degree ADHD genetics can explain the associations found in observational studies. Thus, there is need for studies that can address the contributions from both environmental (breastfeeding) and genetic factors, and the interaction from these factors, on the risk for ADHD.

In this study, we aimed to explore the effects of per month full and partial breastfeeding on the overall ADHD symptoms and the change in ADHD symptoms over time, also taking into account the genetic liability and the gene/breastfeeding interaction to ADHD in the participants in a sample of a unique prospective population-based pregnancy cohort, The Norwegian Mother, Father and Child Cohort Study (MoBa).

The study is based on data from The Norwegian Mother, Father and Child Cohort Study (MoBa) and the Medical Birth Registry of Norway (MBRN). MoBa is a prospective population-based pregnancy

cohort study conducted by the Norwegian Institute of Public Health. Pregnant women were recruited from across Norway from 1999 to 2008 (Magnus et al., 2016). The women consented to initial participation in 40.6% of the pregnancies. The total cohort includes 114 500 children, 95 200 mothers and 75 200 fathers. Data from MoBa participants are routinely linked to the MBRN, a national health registry based on mandatory reporting of information on pregnancies and birth outcomes for all births in Norway since 1967 (Irgens, 2000). The current study was approved by The Regional Committee for Medical Research Ethics (2015/2055). The phenotypes used in this study are based on version 12 of the quality-assured phenotypic data files released for research in 2019, while the genotypic

data were obtained through MoBaGENETICS version 1.0 (https://github.com/folkehelseinstituttet/mobagen/wiki/MoBaGenetics1.0).

Our study sample consisted of 20,474 children with available information on full and partial breastfeeding in the child's first six months of life, and genetic information of either child, mother and/or father, and with completed questionnaires on behavioural phenotypes of ADHD symptoms when the offspring was either three, five or eight years of age. In this study, we excluded participants who were twins/triplets, not attending when child was either three, five or eight years of age, not born to term (born before week 37 or after week 43), no information of breastfeeding when child was six months, unlikely daily energy intake (< 0.25 percentile/900 kcal or > 99.75 percentile/6000 kcal), and an unlikely daily total fiber intake during pregnancy (< 0.25 percentile/8 grams or > 99.75 percentile/85 grams), or no genetic data available **(Flowchart, Figure 1).** All participants were of European ancestry (based on their genetics).

Full breastfeeding is defined by World Health Organization as both exclusive breastfeeding (cannot receive solid or semi-solid foods, formula or other non-human milk or waterbased drinks or fruit juices, daily or weekly), or predominant breastfeeding (may receive water-based drinks/fruit juices, cannot receive solid or semi-solid foods, formula or other non-human milk or waterbased drinks or fruit-juices daily or weekly), (https://www.emro.who.int/nutrition/breastfeeding/index.html). Ongoing breastfeeding or formula feeding was assessed through a mother-reported questionnaire when the child was about six months old. Information about infant feeding from the first week in monthly intervals and age at introduction of solids was specified up until completion. Full breastfeeding was defined as breastfeeding from birth and onwards without any formula or solids. This allows for water and vitamins, which is not allowed in the definition of exclusive breastfeeding. With information about any breastfeeding, age at introduction of milk other than breastmilk and age at introduction of weaning food, we could compute a variable denoting full breastfeeding. Exclusive breastfeeding was not possible to define due to the variables available in MoBa data. Partial breastfeeding was defined as the number of months infant is being partially breastfed, allowing for introduction of complementary foods (formula or solid foods) in infants from birth and onwards up to six months. For most of the mothers this is duration of breastfeeding after cessation of full breastfeeding. Both full and partial breastfeeding was continuous variables.

To examine ADHD symptoms in our sample, we constructed a score of „ADHD symptoms" as our outcome variable for offspring at three (ADHD3), five (ADHD5), and eight years (ADHD8) of age, utilizing information from several instruments collected through MoBa questionnaires (Table 1). Each questionnaire was filled out by mothers and contained information on frequency of offspring behaviours on Likert scales. The scores were constructed by summing up the Likert ratings, the larger score reflected a more frequent ADHD behaviour.

We utilized the following instruments to construct the ADHD score, including both inattention and hyperactivity/impulsivity items: (1) Child Behavior Checklist (CBCL) at three and five years of age (Achenbach, 2019), (2) Child Behaviour and Manner questionnaire (CBM) at three years of age (American Psychiatric Association, 2000), (3) Conner's Parent Rating Scale-Revised, Short Form (CPRS-R (S)) at five years of age (Conners, Sitarenios, Parker, & Epstein, 1998) and (4) the Parent/Teacher Rating Scale for Disruptive Behaviour Disorders (RS-DBD) at eight years of age (Silva et al., 2005). The

CBCL and CBM items were rated on a three-point Likert response scale (1 = never/rarely, 2 = sometimes, 3 = often/very often), while the CPRS-R (S) and the RS-DBD on a four-point Likert scale (1 = never/rarely, 2 = sometimes, 3 = often, 4 = very often). For the CPRS-R (S) and RS-DBD, the response options (3) and (4) were collapsed to correspond to those of CBCL and CBM. Only one missing item per instrument was allowed in calculation of the score. The selection of these items to derive the ADHD symptom score was confirmed by confirmatory factor analyses (Figure 2).

The genetic data were obtained from blood samples collected from parents during pregnancy and from children (umbilical cord) at birth (Paltiel et al., 2014). The genotypes undergone a standard quality control and were then imputed using IMPUTE software, while taking into account relatedness during phasing (https://github.com/folkehelseinstituttet/mobagen). MoBa genotypes and ADHD GWA study summary statistics were subjected to a quality control prior to PGS calculations, where single nucleotide polymorphisms (SNPs) were removed if their: (1) imputation quality measure (INFO) was below 0.9, (2) minor allele frequency was below 1%, (3) alleles or minor alleles were different to those in one thousand genomes CEU (European population) reference, and (4) minor allele frequencies differed from those in one thousand genome CEU reference population by more than 0.2. The PGSes for the child, mother, and father were calculated in MoBa genetic data using PRSice2 software and the largest genome-wide association study of clinically diagnosed ADHD published (20,183 cases and 35,191 controls) (Demontis et al., 2019).

We analysed two main models, 1) multi-variate regression models to examine the association of each month of full and partial breastfeeding on ADHD symptom levels at each age, three, five and eight years of age, where we added covariates stepwise (crude model, model I adding genetic information and model II (full model) adding socioeconomic variables), and 2) longitudinally examining the association of each month of full and partial breastfeeding on the change in ADHD score symptoms from three to five and from five to eight years of age using Latent Growth Curve Models (LGCM), both taking into account the ADHD genetic liability. All full models included the variables: sex of child (boy/girl) obtained from MBRN, ADHD PGS from child and parents (as proxies for ADHD genetic liability), maternal education (obtained from MoBa), parental age when becoming parents, as covariates. Maternal education (used as a proxy for socio-economic status) was specified as a categorical variable with three categories: low (less than high school), middle (high school) or high (4 years or more of college/university). Parental ages were treated as continuous variables.

To test for the interaction effect of ADHD PGS and full breastfeeding on ADHD symptoms at three examined timepoints, an interaction term (ADHD PGS X Full breastfeeding) was added into the full model. Further, to control for healthy behavior in mothers, we examined the results adjusted for maternal total daily intake of fiber during pregnancy as a proxy for diet quality.

We used maximum likelihood with robust standard errors (MLR) in all analyses, which is robust to non-normality in data.(Kline, 2016) Due to FIML estimation, models were performed using the data from all included individuals.

Analysis took place between October 2022 and January 2023, and were carried out in STATA (Muthén & Muthén, 1998-2019) version 16.1 (StataCorp. 2015. StataCorp LP), and Mplus version 8 (Muthén & Muthén, 1998-2019).

After quality control, a final sample of 20,474 child – mother-father trios were identified, where the child had information on ADHD symptoms at either three, five or eight years of age (17,980 (85.7%); 13,137 (62.6%); and 13,459 (64.2%), respectively). Of these offspring, 10,350 (49.3%) were girls (Table 2). Further, about 70% of mothers had high level of education (four years or more of college/university). The mean ADHD symptoms on the full sample at three, five and eight years of age were 3.6 (SD 2.1), 2.5 (SD2.2), and 3.3 (SD2.5), respectively.

In the overall model, model 1), in the crude unadjusted analysis, full breastfeeding was significantly associated with lower ADHD symptoms at all three ages (adjusted b_{age3}= -0.09(95% confidence intervals

(CI) -0.11, -0.07), b_{age5}= -0.08(95%CI -0.10, -0.06), b_{age8}=-0.10(95%CI -0.13, -0.07)), suggesting that each month of full breastfeeding was associated with lower ADHD symptoms in early childhood. The effect of full breastfeeding on ADHD symptoms remained at all ages after adjusting for offspring and parental ADHD polygenic scores (model I) and socioeconomic factors (model II), (Table 4/Figure 3 (full models)). Partial breastfeeding, meaning addition of solid or semi-solid foods from birth in addition to breastmilk, was only associated with ADHD symptoms at eight years of age, however, weaker than for full breastfeeding ($b_{age8=}$ -0.03(95%CI -0.06, -0.01). In model II, the contribution of exposures and covariates explained 2.2-5.0% (R-squared) of total variance in ADHD symptoms, with the highest R-squared observed at eight years of age (Table 4).

In model 2, the change model, we found that the estimated baseline ADHD symptoms level at three years of age was associated with full breastfeeding ($b_{baseline3}$ = -0.08 (95%CI -0.1, -0.06), suggesting that longer full breastfeeding was associated with a lower baseline level of ADHD symptoms in the offspring (Table 5). However, only partial breastfeeding was found to be associated with the change in ADHD symptoms between five to eight years of age ($b_{change5\text{-}8}$ -0.04 (95%CI -0.6, -0.01).

It is noteworthy that offspring ADHD-PGS revealed suggestive associations with both the estimated baseline level of ADHD symptoms and change in ADHD symptoms from three to five ($b_{baseline}$ 0.12 (95%CI 0.08, 0.17); $b_{change3\text{-}5}$ = 0.08 (95% CI 0.01,0.13), (Table 5).

Adding maternal fiber intake during pregnancy into model II did not change any of the results (not shown). Further, the effect of the interaction between ADHD genetic and breastfeeding was not significantly affecting the ADHD symptom levels at age three, five and eight, and therefore the interaction term was not used in the change model.

Discussion and future directions

The key finding of the present study is that full breastfeeding was associated with lower ADHD symptoms at all studied ages in a large prospective populations study. The results remained after adjusting for offspring and parental ADHD polygenic scores and socioeconomic factors, and interestingly, were stronger by eight years of age. Partial breastfeeding showed weaker associations. Only partial breastfeeding was associated with the change in ADHD symptoms between three to eight years.

Our results indicate that breastfeeding, especially full breastfeeding, defined by no introduction to other non-solid or solid food (from birth), may influence in reduced ADHD symptoms in early childhood. This observation is in line with previous findings linking breastfeeding to ADHD (Tseng, Chen, et al., 2019).

When we added information about ADHD genetic liability in parents and offspring, the estimates only slightly changed. Therefore, our finding of the association between full breastfeeding and ADHD symptoms may be explained by other factors, either genetic factors other than related to ADHD, environmental factors, or the biological effects of breastmilk. The behaviours in mothers influencing full breastfeeding may be due to other genetic factors facilitating other developmentally supportive strategies for the child. Breastfeeding in wealthy countries has been reported to be associated with healthy behavior (Haggkvist et al., 2010) suggesting that maternal behavior favoring breastfeeding may be due to other genetic/environmental/behavioral factors in the mother. However, our subanalyses adding fiber as a proxy of healthy behavior to the model did not change the results. Most mothers in the MoBa study predominantly breastfed and then continued to do partial breastfeeding (Haggkvist et al., 2010). We also know the MoBa cohort participants have higher education level than the general population, and we know that high level of education is associated with duration of full breastfeeding (Neves et al., 2021).

The main strengths of the study include the large sample size of a prospective study; however, an important limitation is selection bias in MoBa, with underrepresentation of young parents and parents with less education. That said, we had adequate variability in the data to find the link between breastfeeding and ADHD symptoms.

To conclude, full breastfeeding associated with less ADHD symptoms in offspring indicating either as an effect of breastmilk itself, or the influence of mothers' behaviour facilitating breastfeeding on the child, or other factors not measured in this study. Although we adjusted for genetic risk and socioeconomic factors, we cannot exclude that these effects also might be subject to remaining genetic/environmental confounding. Further studies are needed to understand the underlying mechanisms of the effects of breastfeeding on ADHD.

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1.1.2 TABLES AND OTHER SUPPORTING DOCUMENTS WHERE APPLICABLE AND NECESSARY

Figure 1. Flowchart

114,731 participants in MoBa recruited 1999-2008

Excluded for one or more of the following reasons:

- Not singleton births (3.96%)
- Not attending either at child age of 3,5 or 8 years of age (36.7%)
- ADHD-score >1 missing item at 3,5 or 8 years of age (0.3%)
- Unlikely energy intake (KCAL <0.25 percentile (900) or >99.75 percentile (6000)) (0.2%)
- Unlikely total fiber intake in grams <0.25 percentile (8) or >99.75 percentile (85) (0.1%)
- Not born to term 36<GA<43 (2.8%)
- No genetic data (36.8%)
- No information about breastfeeding (27.9%)

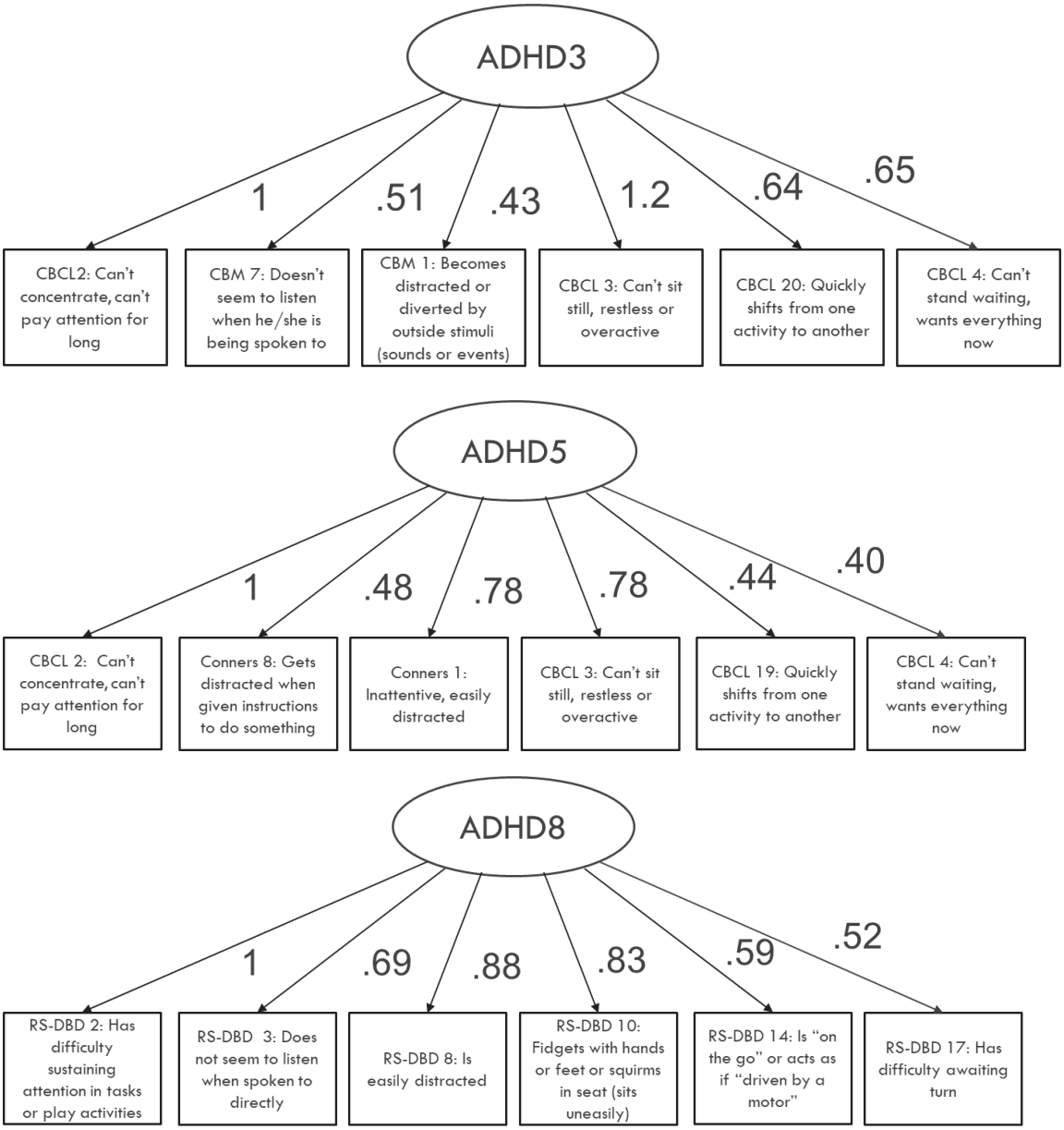
Study sample for analysis: n=20 474

Table 1. ADHD-symptom items from CBCL/CBM/Conners at 3 and 5 years of age compared to Parent/Teacher Rating Scale for Disruptive Behaviour Disorders (RS-DBD) at 8 years of age

3 years CBCL/CBM	**5 years** CBCL/Conners	**8 years** RS-DBD
INATTENTION		
CBCL 2: Can't concentrate, can't pay attention for long	CBCL 2: Can't concentrate, can't pay attention for long	RS-DBD 2: Has difficulty sustaining attention in tasks or play activities
CBM 7: Doesn't seem to listen when he/she is being spoken to	Conners 8: Gets distracted when given instructions to do something	RS-DBD 3: Does not seem to listen when spoken to directly
CBM 1: Becomes distracted or diverted by outside stimuli (sounds or events)	Conners 1: Inattentive, easily distracted	RS-DBD 8: Is easily distracted
HYPERACTIVITY		
CBCL 3: Can't sit still, restless or overactive	CBCL 3: Can't sit still, restless or overactive	RS-DBD 10: Fidgets with hands or feet or squirms in seat (sits uneasily)
CBCL 20: Quickly shifts from one activity to another	CBCL 19: Quickly shifts from one activity to another	RS-DBD 14: Is "on the go" or acts as if "driven by a motor"
CBCL 4: Can't stand waiting, wants everything now	CBCL 4: Can't stand waiting, wants everything now	RS-DBD 17: Has difficulty awaiting turn

CBCL – Child Behavior Checklist; CBM – Child Behaviuor and Manner; Conners - Conners Parent Rating Scale-Revised (CPRS-R (S)); RS-DBD - Parent/Teacher Rating Scale for Disruptive Behaviour Disorders (DSM-IV)

Figure 2. Results of confirmatory factor analyses of ADHD scores at 3,5 and 8 years of age with loadings from each item used to calculate the score, all p<0.001



ADHD3 – ADHD-score at 3 years of age: ADHD5 – ADHD-score at 5 years; ADHD8 – ADHD-score at 8 years of age; CBCL – Child Behavior Checklist; CBM – Child Behaviuor and Manner; Conners - Conners Parent Rating Scale-Revised (CPRS-R (S)); RS-DBD - Parent/Teacher Rating Scale for Disruptive Behaviour Disorders (DSM-IV)

Table 2. Demographic characteristics of the MoBa study population (N=20,474)

	3 years, N (%)	5 years, N (%)	8 years, N (%)
Number of Trios	17,980	13,137	13,459
Offspring			
Females 10,350 (49.3 %)	8,851 (49.2)	6,495 (49.4)	6,614 (49.1)
Males 10,626 (50.7 %)	9,129 (50.8)	6,642 (50.6)	6,845 (50.9)
Maternal education at pregnancy			
Less than high school	263 (1.5)	160 (1.2)	171 (1.3)
High school	4,931 (27.4)	3,269 (24.9)	3,439 (25.6)
4 years or more of college/university	12,366 (68.8)	9,418 (71.7)	9,548 (70.9)
Missing maternal education (n=58)	420 (2.3)	290 (2.2)	301 (2.2)
Z-score (BW by GA) mean (SD)	0.16 (0.95)	0.14 (0.96)	0.16 (0.96)
Maternal age when giving birth, years (SD)	30.3 (4.3)	30.6 (4.2)	30.6 (4.2)
Paternal age when becoming father, years (SD)	32.7 (5.0)	32.9 (5.0)	32.9 (5.0)
Child PGS (N/%)	11,251 (62.6)	8,376 (63.8)	8,547 (63.5)
Mother PGS (N)	14,331 (79.7)	10,537 (80.2)	10,714 (79.6)
Father PGS (N)	13,003 (72.3)	9,778 74.4)	9,874 (73.4)
Full breastfeeding (mean months/SD)	3.6 (2.0)	3.6 (2.0)	3.6 (2.0)
Partial breastfeeding (mean months/SD)	2.4 (1.9)	2.3 (1.9)	2.4 (1.9)

Table 3. Association between child ADHD PGS and ADHD outcome, mothers' ADHD PGS and full/partial breastfeeding, and mothers' ADHD symptoms

	Child ADHD PGS	Mother ADHD PGS	Father ADHD PGS
ADHD3	**0.13 (0.08,0.18)**	-0.03 (-0.07,0.01)	0.03 (-0.01,0.07)
ADHD5	**0.18 (0.13,0.24)**	-0.01 (-0.06,0.04)	-0.01 (-0.06,0.03)
ADHD8	**0.26 (0.2,0.33)**	-0.04 (-0.09,0.02)	0.05 (-0.01,0.1)
Full breastfeeding		**-0.06 (-0.09, -0.03)**	
Partial breastfeeding		0.02 (-0.01,0.06)	

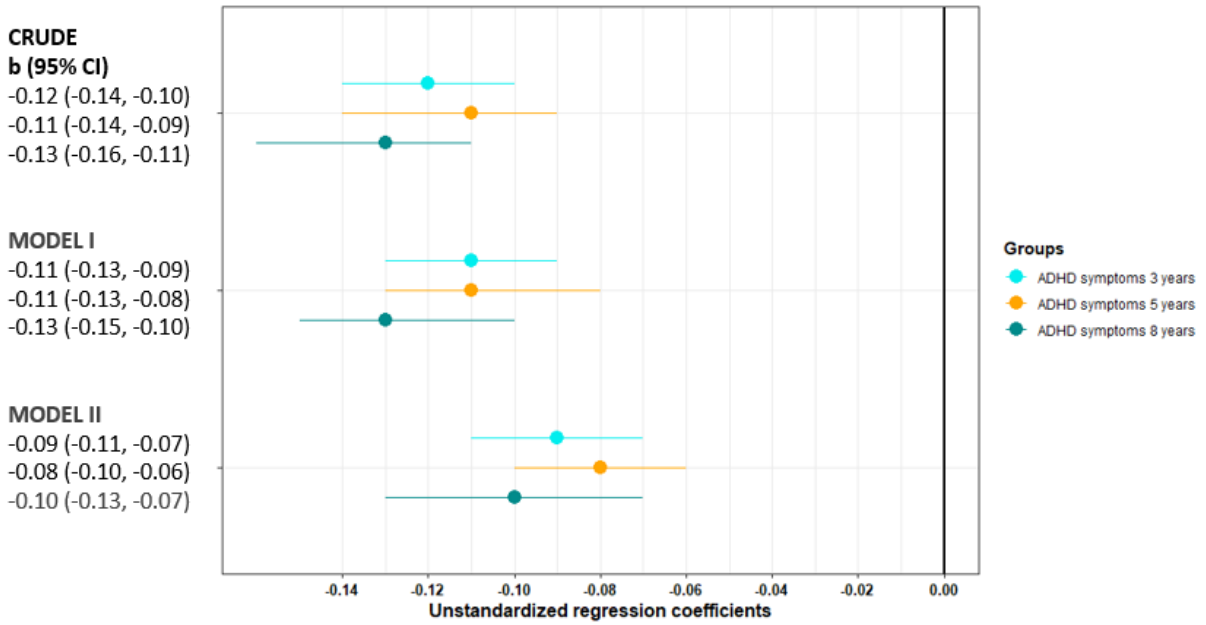
ADHD3 – ADHD-score at 3 years of age: ADHD5 – ADHD-score at 5 years; ADHD8 – ADHD-score at 8 years of age; PGS – polygenic score; unstandardized regression coefficients (95% confidence intervals), bold values are p-values<0.05, all are unadjusted regression analyses.

Table 4. The associations between breastfeeding and the overall level of ADHD symptom scores in children at three, five and eight years of age accounting for child ADHD genetics (PGS) (n=20 474 children) – model II

ADHD symptoms	b	95% CI	*B*	*P*	R^2 %, (*p-value*)
ADHD symptoms at age 3					**2.2 *(<0.001)***
Full breastfeeding	-0.09	-0.11, -0.7	*-0.077*	*<0.001*	
Partial breastfeeding	-0.003	-0.02, -0.003	*-0.002*	*0.784*	
Child PGS	0.16	0.1,0.22	*0.075*	*<0.001*	
Mother PGS	-0.05	-0.09, -0.01	*-0.023*	*0.041*	
Father PGS	0.02	-0.02,0.06	*0.009*	*0.489*	
Maternal education	-0.24	-0.3, -0.18	*-0.057*	*<0.001*	
Maternal age	-0.24	-0.33, -0.16	*-0.048*	*<0.001*	
Paternal age	-0.02	-0.09,0.06	*0.004*	*0.724*	
Sex	-0.16	-0.22, -0.12	*-0.039*	*<0.001*	
Interaction sex x child PGS	-0.06	-0.12,0.005	*-0.020*	*0.128*	
Interaction child ADHD PGSx full breastfeeding	-0.02	-0.04, 0.01	*-0.013*	*0.311*	
ADHD symptoms at age 5					**3.6 (*<0.001*)**
Full breastfeeding	-0.08	-0.10, -0.06	*-0.064*	*<0.001*	
Partial breastfeeding	0.005	-0.02, 0.03	*0.005*	*0.722*	
Child PGS	0.19	0.12, 0.26	*0.085*	*<0.001*	
Mother PGS	-0.03	-0.07, 0.02	*-0.012*	*0.319*	
Father PGS	-0.03	-0.07, 0.02	*-0.011*	*0.336*	
Maternal education	-0.30	-0.37, -0.23	*-0.069*	*<0.001*	
Maternal age	-0.26	-0.36, -0.16	*-0.047*	*<0.001*	
Paternal age	-0.07	-0.15, 0.01	*-0.016*	*0.140*	
Sex	-0.44	-0.50, -0.38	*-0.097*	*<0.001*	
Interaction sex x child PGS	-0.02	-0.09, 0.06	*-0.004*	*0.707*	
Interaction child ADHD PGSx full breastfeeding	-0.01	-0.04, 0.02	*-0.008*	*0.527*	
ADHD symptoms at age 8					**5.0 (*<0.001*)**
Full breastfeeding	-0.10	-0.13, -0.07	*-0.072*	*<0.001*	
Partial breastfeeding	-0.03	-0.06, -0.01	*-0.025*	*0.025*	
Child PGS	0.29	0.21, 0.37	*0.116*	*<0.001*	
Mother PGS	-0.05	-0.10, 0.002	*-0.020*	*0.112*	
Father PGS	0.03	-0.02, 0.08	*0.013*	*0.348*	
Maternal education	-0.28	-0.36, -0.20	*-0.058*	*<0.001*	
Maternal age	-0.20	-0.31, -0.09	*-0.032*	*0.003*	
Paternal age	0.01	-0.08, 0.09	*0.001*	*0.922*	
Sex	-0.79	-0.85, -0.72	*-0.157*	*<0.001*	
Interaction sex x child PGS	-0.05	-0.14, 0.03	*-0.015*	*0.284*	
Interaction child ADHD PGSx full breastfeeding	0.004	-0.03, 0.03	*0.003*	*0.980*	

b - Unstandardized regression coefficient; CI – confidence intervals; *B= standardized regression coefficient; R^2 – R-squared;* PGS – polygenic score

Figure 3. The association between full breastfeeding and the overall level of ADHD symptom scores in children at three, five and eight years of age, crude model, model I, model II (n=20 474 children)



All estimates have p-values<0.001; Crude model – adjusted for sex of child: Model I – Crude +adjusted for child ADHD PGS/ parental ADHD PGS; Model II – Model I + adjusted for SES; PGS – polygenic score; SES (parental age when becoming parents, maternal education), values in unstandardized regression coefficients (95% confidence intervals (CI).

Table 5. The associations between breastfeeding and the change in offspring's ADHD symptom scores over time between three to five and between five to eight years, adjusted for listed covariates (n=20 474)

ADHD symptoms	b	95% CI	*B*	*p*
ADHD symptoms at 3 years of age (estimated baseline)				
Full breastfeeding	-0.079	-0.1, -0.06	*-0.102*	*<0.001*
Partial breastfeeding	-0.001	-0.02, 0.02	*-0.001*	*0.941*
Child PGS	0.123	0.08, 0.17	*0.080*	*<0.001*
Mother PGS	-0.046	-0.08, -0.01	*-0.030*	*0.046*
Father PGS	0.017	-0.02, 0.06	*0.011*	*0.471*
Maternal education	-0.237	-0.30, -0.18	*-0.078*	*<0.001*
Maternal age	-0.248	-0.33, -0.16	*-0.066*	*<0.001*
Paternal age	-0.001	-0.07, 0.07	*0.000*	*0.986*
Sex	-0.175	-0.23, -0.13	*-0.055*	*<0.001*
Intercept (estimated baseline)	3.676	3.64, 3.71		*<0.001*
Change in ADHD symptoms from 3 to 5 years				
Full breastfeeding	0.01	-0.01, 0.03	*0.095*	*0.522*
Partial breastfeeding	0.01	-0.01, 0.03	*0.106*	*0.495*
Child PGS	0.08	0.02, 0.14	*0.476*	*0.027*
Mother PGS	0.007	-0.04, 0.05	*0.046*	*0.795*
Father PGS	-0.05	-0.10, -0.01	*-0.316*	*0.071*
Maternal education	-0.06	-0.13, 0.01	*-0.190*	*0.159*

ADHD symptoms	**b**	**95% CI**	***B***	***p***
Maternal age	-0.01	-0.11, 0.08	*-0.020*	*0.817*
Paternal age	-0.06	-0.14, 0.02	*-0.188*	*0.201*
Sex	-0.26	-0.33, -0.20	*-0.795*	*<0.001*
Intercept change 3-5	-0.957	-1.002, -0.913		*<0.001*
Change in ADHD symptoms from 5 to 8 years				
Full breastfeeding	-0.016	-0.04, 0.01	*-0.141*	*0.311*
Partial breastfeeding	-0.036	-0.06, -0.01	*-0.302*	*0.031*
Child PGS	0.072	0.01 ,0.13	*0.330*	*0.052*
Mother PGS	-0.019	-0.07, 0.03	*-0.085*	*0.537*
Father PGS	0.058	0.01, 0.11	*0.263*	*0.059*
Maternal education	0.008	-0.07, 0.09	*0.018*	*0.888*
Maternal age	0.061	-0.05, 0.18	*0.120*	*0.347*
Paternal age	0.077	-0.01, 0.17	*0.178*	*0.161*
Sex	-0.352	-0.42, -0.28	*-0.801*	*<0.001*
Intercept change 5-8	0.958	0.91, 1.01		*<0.001*

b - Unstandardized regression coefficient; CI – confidence intervals; B= standardized regression coefficient; R^2 – R-squared; PGS – polygenic score

1.1.3 ACKNOWLEDGEMENT AND DISCLAIMER

We are grateful to all the participating families in Norway who take part in this on-going cohort study. The Norwegian Mother, Father and Child Cohort Study is supported by the Norwegian Ministry of Health and Care Services and the Ministry of Education and Research. This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 728018.

1.2 DELIVERABLE REPORT PART 2

Abbreviations

ADHD	Attention-Deficit/Hyperactivity Disorder
PRS	Polygenic risk score
FFQ	Food frequency questionnaire
Lifelines	The Lifelines cohort study

1.2.1 Deliverable report

Note: publishers' policies prevent sharing of detailed results prior to publication in a peer-reviewed journal. Detailed results, tables and uncompromised figures will be made available upon acceptance and/or as soon as the publisher's embargo has been lifted.

Impulsivity is a complex, multidimensional trait that may be defined as 'a predisposition toward rapid, unplanned reactions to internal or external stimuli, with diminished regard to the negative consequences that such reactions may have for the impulsive individual or others' (Moeller et al., 2001; Potenza, 2007). Impulsivity is also one of core symptoms of attention-deficit/hyperactivity disorder (ADHD) (Faraone et al., 2015). Individuals with excessive or maladaptive impulsivity are at increased risk of developing psychiatric disorders such as bipolar spectrum disorders, and substance use disorders (Moeller et al., 2001). These problems justify research on impulsivity to better understand its complicated etiology, particularly modifiable factors which may be potential targets in preventive interventions.

Both genetic and environmental factors influence impulsivity. A meta-analysis of twin, family and adoption studies demonstrated that approximately 50% of the variance in impulsivity was explained by genetic influences (Bezdjian et al., 2011). Previous research has also revealed associations between impulsivity and environmental factors such as lifestyle choices. Furthermore, etiological theories highlight interactions between genes and environment underlying impulsivity (Assary et al., 2018). Twin studies have shown that genetic factors play a more prominent role in ADHD development in the presence of high consumption of sugar and unhealthy foods, which suggests the existence of diet-gene interactions in ADHD symptoms (Li et al., 2021). Several studies also used a candidate gene approach to explore gene-environment interaction in ADHD or impulsivity (Brookes et al., 2006; Kahn et al., 2003). However, few studies have addressed diet-gene interaction in impulsivity using the polygenic score approach, and research exploring interactions between genetic factors and a wide range of lifestyle factors in impulsivity is also lacking. Therefore, our aim was to investigate if an unhealthy diet and other lifestyle behaviors modify the genetic risk of impulsivity using the polygenic risk score (PRS) in the general population.

We conducted the current study in The Lifelines cohort study (Lifelines) which is a multi-disciplinary prospective population-based cohort study examining the health and health-related behaviors of 167,729 persons living in the North of the Netherlands (Sijtsma et al., 2021). Impulsivity was calculated based on 32 selected items of NEO personality index (NEO-PI-R (Costa & McCrae, 1992)) at baseline using principal component analyses. 32 selected items included all items constituting the impulsivity facet of the neuroticism scale, the excitement-seeking facet of the extraversion scale, and the deliberateness and self-discipline facets of the conscientiousness scale. ADHD polygenic risk score (PRS) was built using the most recent meta-GWAS of ADHD conducted in 38,691 ADHD cases and 186,843 controls of European ancestry (Demontis et al., 2022) and PRS-PCA approach. Four indices of poor diet were computed: low overall diet quality, excess intake of energy, excess intake of fat, and excess intake of free sugars using a 110-item semi-quantitative food frequency questionnaire (FFQ)

(Vinke et al., 2018). Other lifestyle behaviors (i.e., physical activity, sleep, smoking, drinking) were calculated based on self-reported questionnaires. Each diet index and other lifestyle behavior was tested for its interaction on the effect of ADHD PRS on impulsivity using a linear regression model with adjustment for covariates.

A total of 33,047 participants (mean age=42.1 years, 59.8% females) from the Dutch Lifelines cohort were included. The ADHD PRS was significantly associated with impulsivity (B = 0.03 (95% CI: 0.02, 0.04); P=2.61×10^{-9}). Poorer diet, higher intake of energy, and higher intake of fat were all associated with higher impulsivity, and high intake of energy amplified the effect of ADHD PRS on impulsivity (e.g. for the interaction term of ADHD PRS and highest tertile of intake of energy, B=0.038 (95% CI: 0.014, 0.062); P=0.002) (Table 1, Figure 1). The other lifestyle factors, namely short and long sleep duration, current and past smoking, higher alcohol intake, and more time spent on moderate-to-vigorous physical activity were associated with higher impulsivity, but no interaction effect was observed (Table 2). In conclusion, we found that high intake of energy exacerbated the genetic susceptibility to impulsivity. Our study helps to improve our understanding of the role of diet and genetic factors in impulsivity.

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1.2.2. TABLES AND OTHER SUPPORTING DOCUMENTS WHERE APPLICABLE AND NECESSARY

Table 1. Results[a] of diet indicators and their interactions with the ADHD PRS on impulsivity.

	B (95% CI)	*P* Value	Beta
Overall diet quality (LLDS_I) (ref=Q1)[b]			
LLDS_I_Q2	0.058 (0.033, 0.083)	5.36×10^{-6}	0.027
LLDS_I_Q3	0.14 (0.115, 0.166)	6.91×10^{-27}	0.068
ADHD PRS	0.025 (0.008, 0.043)	0.004	0.025
ADHD PRS×LLDS_I_Q2	0.009 (-0.016, 0.034)	0.467	0.005
ADHD PRS×LLDS_I_Q3	0.005 (-0.019, 0.029)	0.674	0.003
Intake of energy (KCAL) (ref=Q1)[b]			
KCAL_Q2	0.058 (0.034, 0.082)	3.08×10^{-6}	0.028
KCAL_Q3	0.128 (0.103, 0.153)	2.81×10^{-23}	0.061
ADHD PRS	0.008 (-0.009, 0.025)	0.371	0.008
ADHD PRS×KCAL_Q2	0.032 (0.008, 0.057)	0.009	0.019
ADHD PRS×KCAL_Q3	0.038 (0.014, 0.062)	0.002	0.022
Intake of fat (FAT) (ref=Q1)[b]			
FAT_Q2	0.065 (0.041, 0.089)	1.32×10^{-7}	0.031
FAT_Q3	0.145 (0.12, 0.169)	9.50×10^{-32}	0.069
ADHD PRS	0.019 (0.002, 0.036)	0.03	0.019
ADHD PRS×FAT_Q2	0.017 (-0.007, 0.041)	0.161	0.01
ADHD PRS×FAT_Q3	0.016 (-0.008, 0.04)	0.192	0.009
Intake of sugar (SUGAR) (ref=Q1)[c]			
SUGAR_Q2	0.001 (-0.02, 0.021)	0.94	0.0004
ADHD PRS	0.031 (0.018, 0.045)	4.42×10^{-6}	0.032
ADHD PRS×SUGAR_Q2	-0.002 (-0.022, 0.018)	0.833	-0.001

a results from the models adjusted for all covariates.

b Q1 indicates tertile 1; Q2, tertile 2; Q3, tertile 3.

c Q1: Free sugar intake ratio (SUGAR) ≤1; Q2: SUGAR>1.

ADHD PRS×variable represents the interaction term between ADHD PRS and the variable.

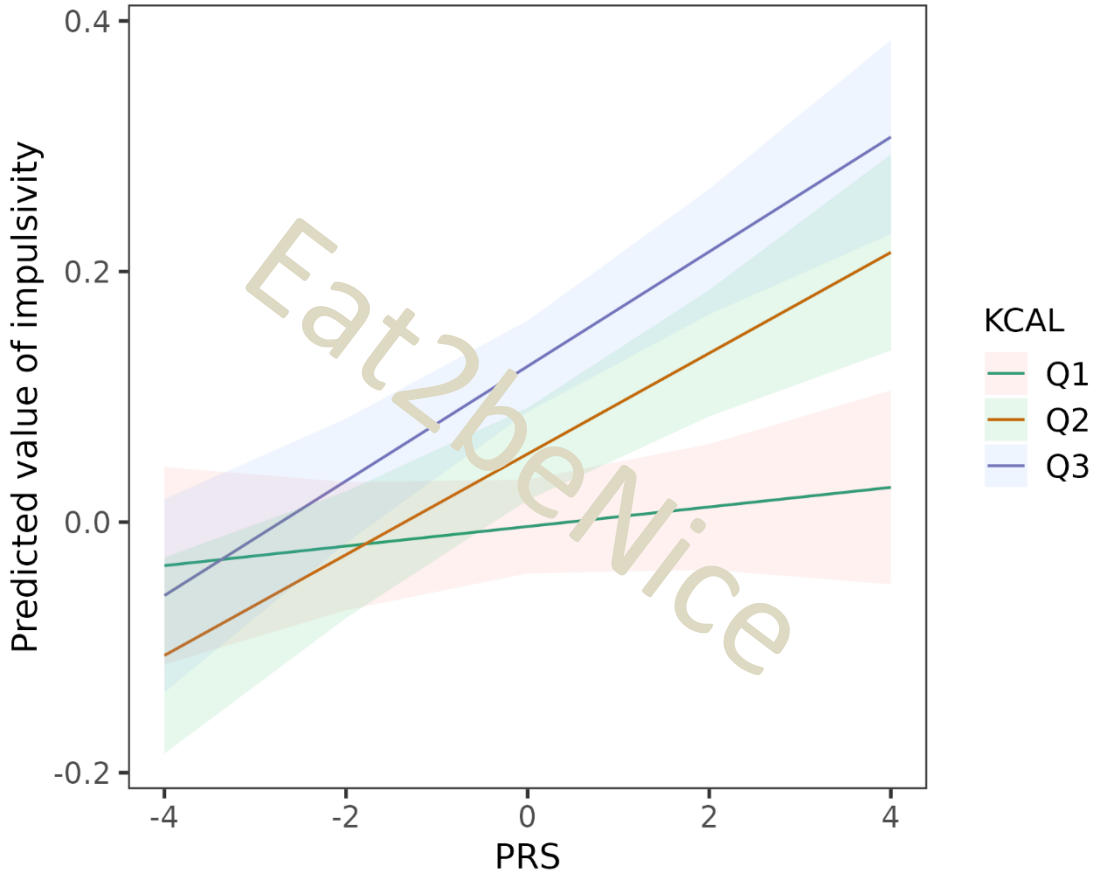
Table 2. Results[a] of other lifestyles and their interactions with the ADHD PRS on impulsivity.

	B (95% CI)	*P* Value	Beta
Sleep duration (ref=middle)			
Short sleep duration	0.078 (0.045, 0.112)	4.19×10^{-6}	0.024
Long sleep duration	0.049 (0.016, 0.082)	0.004	0.015
ADHD PRS	0.027 (0.015, 0.038)	3.10×10^{-6}	0.027
ADHD PRS×short sleep duration	0.022 (-0.011, 0.055)	0.187	0.007
ADHD PRS×long sleep duration	0.011 (-0.022, 0.044)	0.508	0.004
Smoking (ref=never)			
Current smoking	0.302 (0.275, 0.328)	6.70×10^{-107}	0.12
Past smoking	0.208 (0.185, 0.232)	7.50×10^{-67}	0.098
ADHD PRS	0.03 (0.016, 0.044)	3.55×10^{-5}	0.03
ADHD PRS×current smoking	-0.012 (-0.038, 0.015)	0.382	-0.005
ADHD PRS×past smoking	-0.013 (-0.036, 0.009)	0.227	-0.008
Alcohol intake (ref=no)			
Occasional alcohol intake	0.091 (0.058, 0.124)	5.37×10^{-8}	0.037
Light alcohol intake	0.267 (0.238, 0.296)	1.06×10^{-71}	0.135
Moderate alcohol intake	0.435 (0.397, 0.472)	4.44×10^{-113}	0.15
Heavy alscohol intake	0.498 (0.433, 0.563)	6.13×10^{-51}	0.083
ADHD PRS	0.025 (0.001, 0.049)	0.045	0.025
ADHD PRS×occasional alcohol intake	0.018 (-0.015, 0.05)	0.287	0.008
ADHD PRS×light alcohol intake	-0.001 (-0.029, 0.028)	0.965	0
ADHD PRS×moderate alcohol intake	0.001 (-0.035, 0.037)	0.944	0
ADHD PRS×heavy alcohol intake	0.042 (-0.022, 0.105)	0.196	0.007
Physical activity			
MVPAQ	0.019 (0.012, 0.026)	3.87×10^{-7}	0.027
ADHD PRS	0.03 (0.006, 0.054)	0.016	0.03
ADHD PRS×MVPAQ	-0.001 (-0.008, 0.007)	0.88	-0.002

[a] results from the models adjusted for all covariates.

MVPAQ indicates semi-continuous quintile scores of minutes per week spent in moderate-to-vigorous physical activity.

Figure 1. Mean predicted value of impulsivity with the ADHD PRS for individuals at each tertile of energy intake. KCAL represents intake of energy. Q1 indicates tertile 1; Q2, tertile 2; Q3, tertile 3.



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END OF REPORT