Title: Omega 3 polygenic score protect against altered eating behavior in intrauterine growth restricted children

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Impact statements.

- A genetic background related to a higher polygenic score for omega 3 PUFA protected infants born IUGR against eating behavior alterations, while a higher polygenic score for omega 6/omega 3 PUFA ratio increased the risk of having eating behavior alterations only in infants born IUGR, irrespective of their adiposity in childhood.
- Genetic individual differences modify the effect of being born IUGR on eating outcomes, increasing the vulnerability/resilience to eating disorders in IUGR group and likely contributing to their risk for developing metabolic diseases later in life.

Running title: Omega 3 against eating alterations

ABSTRACT

Background: Alterations in eating behavior are common in infants with intrauterine growth restriction (IUGR); omega-3 polyunsaturated fatty acids (PUFA) could provide protection. We hypothesized that those born IUGR with a genetic background associated with increased production of omega-3-PUFA will have more adaptive eating behaviours during childhood.

Methods: IUGR/non-IUGR classified infants from MAVAN and GUSTO cohorts were included at the age of 4y or 5y, respectively. Their parents reported child's eating behaviors using the child eating behavior questionnaire-CEBQ. Based on the GWAS on serum PUFA (Coltell 2020), three polygenic scores were calculated.

Results: Significant interactions between IUGR and polygenic score for omega-3-PUFA on emotional overeating (β=-0.15, P=0.049 GUSTO) and between IUGR and polygenic score for omega-6/omega-3-PUFA on desire to drink (β=0.35, P=0.044 MAVAN), pro-intake/anti-intake ratio (β=0.10, P=0.042 MAVAN), and emotional overeating (β=0.16, P=0.043 GUSTO) were found. Only in IUGR, a higher polygenic score for omega-3-PUFA associated with lower emotional overeating, while higher polygenic score for omega-6/omega-3-PUFA ratio was associated with higher desire to drink, emotional overeating, and pro-intake/anti-intake.

Conclusion: Only in IUGR, the genetic background for higher omega-3-PUFA is associated with protection against altered eating behavior, while the genetic score for higher omega-6/omega-3-PUFA ratio is associated with altered eating behavior.

INTRODUCTION

Obesity has increased in the last forty years around the world. In 2016, WHO estimates that 39% and 13% of adults have overweight and obesity diagnoses, respectively. At the same time, about 6.7% of children and adolescents around the world have obesity, with a higher prevalence in boys than in girls, and in middle and low-income regions [1]. Obesity is a multifactorial condition that increases the severity of the symptoms and the risk of dying from infectious diseases [2,3], as well as the risk of non-communicable diseases such as diabetes, coronary heart disease, specific cancers, and psychopathology. Genome-wide association studies (GWAS) have shown that the association between genetic, environmental, and lifestyle factors (i.e. physical activity and diet) might be amplifying or mitigating the genetic risk for obesity [4].

The evidence has shown that obesity and eating behavior are associated throughout life. Children with obesity have higher food approach and lower avoidant responses to foods [5,6]. We and others have shown in humans that early exposure to early adverse environments is associated with alterations in eating behavior and physical activity [7-11], increasing the risk for altered body composition and metabolic disease later in life. Subjects exposed prenatally to an insufficient supply of calories during the Dutch famine had higher total calorie intake, fat-density diet, lower physical activity [12,13], greater weight, BMI and fat deposits in the second and fifth decade of life [14,15]. The thrifty eating hypothesis proposes that the eating behavior could be programmed early in life as a way to survive in response to low food availability, however this programming could promote obesity in a food environment of excess calories [16-20]. Thereby, intrauterine growth restriction (IUGR), a condition caused by

maternal, fetal, or placental features and inadequate fetal growth has been considered as a model to study the thrifty eating hypothesis. Infants born IUGR are predisposed to attention deficit hyperactivity syndrome in childhood and diseases in adulthood (e.g., obesity, type 2 diabetes mellitus, coronary artery disease, stroke, and depression) [21,22]. Altered hedonic response to sweet food in IUGR subjects has been described already at birth [23]. IUGR girls are more impulsive towards palatable foods [11] and this continues until adult ages [7]. IUGR boys are also affected, with increased intake of fat and altered physical activity [24,25].

Although folic acid supplementation has been widely used around the world to prevent neural tube defects with the mechanisms of this action still poorly understood[26] and the effect of folic acid supplementation on increasing central nervous system components regeneration after injury has been shown in adults[27], omega 3 (eicosapentaenoic fatty acid, EPA, and docosahexaenoic fatty acid, DHA) and omega 6 (arachidonic fatty acid, AA) long chain polyunsaturated fatty acids (LC-PUFA) have long been considered to be the most limiting nutrients for neural growth and complexity during fetal and early childhood development [28]. Specifically, omega 3 fatty acids mediate a variety of key neurotransmitter functions, including monoaminergic response, signal translation, and phospholipid turnover [29,30]. These fatty acids should be obtained from the diet or they can be biosynthesized by human tissues. However, the current western diets are deficient in omega 3 fatty acids having a ratio of omega 6/omega3 fatty acids of 10:1 to 20-25:1 compared with the ratio 1:1 during the Paleolithic period when the human genetic profile was established [31], the endogenous biosynthesis is associated with several single nucleotide polymorphisms (SNP) in the *FADS1-2* gene

complex [32]. *FADS1-2* genes code for Δ5-desaturase and Δ6-desaturase enzymes that together with elongases (*ELOVL2* and *ELOVL5*) participate in position-specific desaturation and carbon chain-elongation of linoleic fatty acid (LA) and α-linolenic fatty acid (ALA) precursors to obtain omega 6 and omega 3 PUFA and LC-PUFA, respectively [31]. Based on our previous evidence in individuals born IUGR, omega 3 PUFA protect against altered eating behavior associated with poor inhibitory control by decreasing food fussiness in MAVAN (Maternal Adversity, Vulnerability and Neurodevelopment) cohort participants [33] and food intake in response to external food cues in individuals of the PROTAIA cohort (The multidimensional evaluation and treatment of anxiety in children and adolescents) [8].

Understanding the interaction effect between individual variations in biological functions associated with the production of omega 3 fatty acids and the exposure to fetal adversity could be informative for developing interventions to reduce the non-communicable chronic diseases prevalence and alleviating current and future personal and economic costs. This study aims at analyzing the interaction effect between being born IUGR and polygenic scores associated with plasma polyunsaturated fatty acids on eating behavior outcomes in childhood. We hypothesized that children born IUGR and having a genetic background associated with increased production of these fatty acids will have more adaptive eating behaviours during childhood.

METHODS

Study participants

This study included cross-sectional analyses of two subset of participants from two prospective birth cohorts, one based in Canada (MAVAN) and the other in Singapore (Growing Up in Singapore Toward Healthy Outcomes - GUSTO).

MAVAN is a longitudinal, multidisciplinary, and collaborative study cohort, established in 2003 and designed to assess the consequences of fetal adversity as a function of the quality of the postnatal environment, focusing on mother-child dyad interactions. The study recruited pregnant women in the second trimester, older than 18 years from the Montreal and Hamilton areas (Canada), in obstetric clinics and hospitals. Exclusion criteria included serious obstetric complications during the pregnancy or delivery of the child, extremely low birth weight, (<2000g) prematurity (<37 weeks' gestation), or any congenital diseases [34]. Pregnant women were interviewed between 24 and 36 weeks of gestation and their infants were evaluated at 3, 6, 12 and 18 months after birth, and annually from 2 to 6 years of age. Characteristics and procedures of the cohort have been previously published [34].

GUSTO is a prospective, longitudinal study, designed to examine the potential roles of fetal, developmental, and epigenetic factors in early pathways to metabolic and neurodevelopmental outcomes. The study recruited 1,200 women aged 18 years and above at 10-14 weeks of gestation at either the National University Hospital or the KK Women's and Children's Hospital between June 2009 and September 2010. Mothers receiving chemotherapy, psychotropic drugs or who had type I diabetes mellitus were excluded. The mothers had ultrasound scans, maternal evaluations including oral

glucose tolerance testing and nutritional assessment during pregnancy, and at delivery a cord and placental tissues were collected, and cord blood drawn for their babies (1,176). Physical growth, health and nutritional assessment were done at 3 weeks and at 3, 6, 9, 12, 15, 18, 24 months, and every six months or annually up to 12 years of age of the participants, and buccal DNA and stool samples were collected. Characteristics and procedures of the GUSTO have been previously published [35].

Inclusion criteria. For these analyzes, all infants with genotyping data, IUGR status classification at birth and CEBQ (Child Eating Behavior Questionnaire) at 4y of age in MAVAN and 5y of age in GUSTO were included.

Anthropometry. Birth weight information was obtained from the birth records at the birthing units. Newborns were classified as IUGR when they had a birth weight ratio lower than 0.85 [36] calculated as the ratio between the newborn birth weight and the sex-specific mean birth weight for each gestational age for the local population [37].

When the participants were 4y (MAVAN) or 5y (GUSTO) of age, they attended a follow up visit with their mothers. For each child, weight (kg) was measured in light clothing using a digital floor scale (TANITA BF625, Arlington Heights, Illinois) (to the nearest 0.1 kg), and height (cm) without shoes with the use of a stadiometer (Perspective Enterprises, PE-AIM-101, Portage, Michigan) (to the nearest 0.1 cm). BMI was calculated as weight (kg)/height (m^2). BMI-for-age z-score was calculated using Word Health Organization values for childhood measures as references [38].

Eating behavior evaluation

During the 4y (MAVAN) and 5y (GUSTO) of age follow-up visit, the child eating behaviour was evaluated using the CEBQ. CEBQ is a parent-report questionnaire that was filled out by children's parents or caregivers. This instrument has 35 items and uses a Likert scale (1: never, 2: seldom, 3: sometimes, 4: often and 5: always) to assess dimensions of the child´s eating style on eight subscales: satiety responsiveness (SR), slowness in eating (SE), food fussiness (FF), emotional undereating (EU), food responsiveness (FR), enjoyment of food (EF), desire to drink (DD) and emotional overeating (EO) [39]. Four subscales refer to food-approach called pro-intake (FR, EF, DD, EO), while the other four are related to food-avoidance called anti-intake (SE, SR, FF, and EU). Higher scores on pro-intake subscales indicate tendency for food intake whereas higher scores on anti-intake subscales relate to food avoidance. Scores for pro-intake and anti-intake were calculated based on four food-approach or four food-avoidance subscales, respectively [5]. Finally, for each child a pro-intake/anti-intake ratio was calculated by dividing the pro-intake score by the anti-intake score [5]; values higher than 1 mean higher food-approach than food-avoidance and values less than 1 mean higher food-avoidance than food-approach.

Genotyping

Saliva samples collected from MAVAN participants were processed to obtain buccal epithelial cells of which 200 ng of genomic DNA were extracted. Using the genomic DNA and following the manufacturer´s guidelines and under our quality control procedures 242,211 autosomal SNPs were genotyped utilizing genome-wide platforms (PsychArray/ PsychChip, Illumina). SNPs with a low call rate (<95%), low p values on

Hardy-Weinberg Equilibrium exact test (p<1e-40), and minor allele frequency (<5%) were removed. Afterwards, imputation was performed using the Sanger Imputation Service [40] resulting in 20,790,893 SNPs with an info score >0.80 and posterior genotype probabilities >0.90.

In GUSTO, genotyping was performed using Infinium OmniExpressExome array and split by ethnicity for quality checks. Non-autosomal SNPs, SNPs with call rates <95%, minor allele frequencies <5%, and failed Hardy-Weinberg equilibrium p value of 10–6 were removed. Variants discordant with their respective subpopulation in the 1,000 G reference panel were removed (Chinese: EAS with a threshold of 0.20; Malays: EAS with a threshold of 0.30; Indian: SAS with a threshold of 0.20). Samples with call rate <99%, cryptic relatedness and sex/ ethnic discrepancies were excluded. The resulting data were pre-phased using SHAPEIT v2.837 with family trio information. We then used Sanger Imputation Service for imputation, choosing 1,000 G Phase 3 as reference panel and imputed “with PBWT, no pre-phasing” as the pipeline. Imputed data that were non-monomorphic, had biallelic SNPs and an INFO score >0.80 were retained. Imputed genotyping data that were common in all three ethnicities (5,771,259 SNPs) were used for further analyses.

The population structure of the MAVAN and GUSTO cohorts were evaluated using principal component analysis of all autosomal genotyped SNPs that passed the quality control, without low allele frequency (MAF<5%) and not in high linkage disequilibrium (r2 >0.2) across 500 kb regions [41,42]. To account for population stratification, the first three principal components (PC) were included in the analysis.

Polygenic scores calculation

Three polygenic scores associated with the serum (percentage of total fatty acids) of omega 3 PUFA, DHA and omega 6/omega 3 PUFA ratio were calculated using PRSoS accelerated pipeline (https://github.com/MeaneyLab/PRSoS) [43] based on a recently published GWAS from Coltell et al. 2020 [44]. Three polygenic scores were calculated for every subject in two cohorts as a sum of the risk alleles account weighted by the effect size of the SNP-outcome associations described in [44] (tables 2, 3 and supplementary table 6 from Coltell study; p-value thresholds $p<1x10^{-5}$ and $p<5x10^{-5}$, respectively). The estimated SNP effects were obtained by Coltell in the models adjusted by sex, age and diabetes status [44]. The polygenic score associated with omega 3 PUFA (%) included 20 SNP from 9 genes (*FADS1, FADS2, MYRF, TMEM258, FEN1, LINC00271*, *WDR70* and *AHI1*). The polygenic score associated with serum DHA (%) included 24 SNP from 11 genes (*FADS1, FADS2, FEN1, MYRF, TMEM258, LINC00271*, *DSPP, DISC1, AHI1, WDR70* and *CTNND2*). Finally, the polygenic score for omega 6/omega 3 PUFA ratio included 21 SNP from 8 genes (*FADS1, FADS2, MYRF, TMEM258, FEN1, NGR3, ASPH and CFAP61*) [44]. For omega 3 PUFA and DHA scores, higher values mean higher serum (%) omega 3 PUFA and higher serum DHA (%), respectively. However, higher values of the omega 6/omega 3 PUFA ratio score mean higher serum (%) omega 6 PUFA than omega 3 PUFA.

Statistical analysis

Descriptive statistics are shown as mean (standard deviation) or number (percentage) for continuous and categorical variables respectively. The normal

distribution of the outcomes (food-approach and food-avoidance subscales, pro-intake score, anti-intake score, and pro-intake/anti-intake ratio), predictors (polygenic scores for polyunsaturated fatty acids omega 3, DHA, and omega 6/omega 3 ratio) and covariables (gestational age, maternal age, breastfeeding duration, birth weight, and BMI z-score at the age at which outcomes were measured) was supported with distribution graphs, finding that all of them were normally distributed. For each cohort, comparisons between study groups on normally distributed continuous variables were done using Student t-test. Chi square test was used to compare categorical variables between study groups, and Fisher´s exact test was used to compare the groups on categorical variables with less than 5 participants classified in one of its categories (income and maternal education classification). Each polygenic score (omega 3 PUFA, DHA, and omega 6/omega 3 PUFA ratio) was standardized (mean=0 and standard deviation=1) and their means were compared between groups (IUGR/non-IUGR) in each cohort using multiple linear regression adjusted by population stratification principal component analysis; the predicted means and 95% confidence interval obtained in multiple linear regressions adjusted by covariates and the p values of the comparisons were reported. In the same way, the mean value of each outcome was compared between groups using multiple linear regression adjusted by city of recruitment, maternal age and BMI z-score at 4y of age in MAVAN, and by BMI z-score at 5y of age in GUSTO, the mean and 95% confidence interval and the p values of the comparisons were reported.

Multiple linear regressions adjusted by three genetic principal components, city of recruitment, maternal age and BMI z-score at 4y of age in MAVAN and by BMI z-score

at 5y of age in GUSTO were applied to analyze the interaction effect between polygenic scores and IUGR/non-IUGR status on eating behavior variables. Influential cases were removed when present. When the interaction effect was significant (P<0.05), simple slope analysis was conducted to describe the effects of polygenic scores on eating behaviours in IUGR and non-IUGR groups. Additionally, simple slope was applied in those interactions whose tendency to be significant (P values between 0.05-0.1). We considered adjustment for multiple testing adjustment using Holm-Bonferroni correction.

We calculated the power of the association using GPower (G*Power Version 3.1) and showed that we could detect an association of small effect size (f2=0.02) in interaction models with a power of 68% in MAVAN and 97% in GUSTO (with the analysis having smallest sample sizes in this study) with a final sample size (after adding covariates) of 294 in MAVAN and 742 in GUSTO.

Data was analyzed using Stata version 15.0 (StataCorp).

Ethical considerations

This study has been performed in accordance with the Declaration of Helsinki and its later amendments. The ethics committees from McGill University, Université de Montréal, Royal Victoria Hospital, Jewish General Hospital, Hospital de l'Université De Montréal, Hôpital Maisonneuve-Rosemount, St Joseph's Hospital and McMaster University, approved the MAVAN Project. The MAVAN Project was approved by resolution number 03/45 to the Research Ethical Board of Douglas Mental Health Research Institute. The ethics committees from Domain-Specific Review Board of the NUH and the Centralized Institutional Review Board of the KKH approved the GUSTO

study. An informed consent was obtained from each participant or from their parents or caregivers.

RESULTS

Descriptive statistics

These analyses included 299 children, 43 were classified as IUGR and 256 as non-IUGR in MAVAN and 746 children, 59 were classified as IUGR and 687 as non-IUGR in GUSTO (**Figure 1**). **Table 1** shows the sociodemographic and anthropometric variables at birth and at follow-up by study group in MAVAN and GUSTO cohorts. In MAVAN, forty-seven percent of the participants were females; six percent of the participants´ mothers reported low socioeconomic status; and the duration of the breastfeeding was 7.5 (±4.6) months of infant age. There were differences between cities of recruitment; three-quarters of the IUGR children were from Montreal, while 50% of the non-IUGR children were recruited from the same city (P = 0.003). Maternal age (1.4 years mean difference) and BMI z-score at 4y of age (0.29 units mean difference) were lower in the IUGR compared with non-IUGR group (all P < 0.05). In GUSTO, forty-seven percent of the participants were females; maternal age at delivery was 31.3 (±5.1) years; 16% of the families reported a monthly household income lower than 2,000 SGD and 30% of the mothers had secondary or lower level of education, without differences between groups (all P > 0.05). IUGR had 0.55 lower BMI z-score at 5y of age than non-IUGR (P = 0.001). Variables that were different between groups at birth and at follow-up (P < 0.05) were included as adjustment variables in the subsequent analyses.

There were no differences in the mean values of standardized polygenic scores for omega 3 PUFA, DHA or omega 6/omega 3 PUFA ratio between groups after adjustment by three genetic principal components in the two cohorts (**Table 2**).

Eating behavior was evaluated in infants at mean age of 4.10 (SD = 0.11) in MAVAN and at 5.11 (SD = 0.04) years in GUSTO. Only SE score was 0.27 units lower in IUGR compared to non-IUGR infants in MAVAN (P = 0.041), no other differences in CEBQ variable were observed between the groups. There were no differences in eating behavior variables between groups in GUSTO (all Ps > 0.05) (**Table 3**).

Effect of the interaction between IUGR status and polygenic scores on eating behavior in childhood

We applied multiple linear regression analysis adjusted for city of recruitment, maternal age, BMI z-score at 4y of age, and the first three genetic principal components in MAVAN, and BMI z-score at 5y of age and the first three genetic principal components in GUSTO to evaluate the effect of the interaction between IUGR status and polygenic scores on eating behavior.

Polygenic score for omega 3 PUFA. A significant interaction effect was found between IUGR status and the polygenic score for omega 3 PUFA on EO subscale (β = -0.15, P = 0.049) in GUSTO (**Table 4**). Simple slope analyses showed that a higher polygenic score for omega 3 PUFA was associated with a lower EO only in IUGR group (IUGR: β = -0.17, P = 0.032; non-IUGR: β = -0.002, P = 0.928) at 5y of age in GUSTO (**Figure 2**).

Although an interaction between polygenic score for omega 3 PUFA and IUGR in SR (β = 0.21, P = 0.090), anti-intake score (β = 0.82, P = 0.057), and pro-intake/anti-intake ratio (β = -0.10, P = 0.062) were a trend in MAVAN, when simple slope analyses were applied the effect of PRS was significant only in IUGR participants for pro-

intake/anti-intake ratio (IUGR: β = -0.11, P = 0.029; non-IUGR: β = 0.01, P = 0.644). These associations were not significant in GUSTO.

Polygenic score for DHA. There was no statistically significant interaction effect between IUGR status and the polygenic score for DHA on any eating behavior at 4y (MAVAN) or 5y (GUSTO) of age (all P > 0.05) (**Table 5**). Interaction effects with P values between 0.05 – 0.1 were observed on DD (β = -0.33, P = 0.086) in MAVANA and on EU (β = -0.20, P = 0.066) in GUSTO, however, polygenic score for DHA was not significantly associated with either of the outcomes for groups of participants IUGR or non-IUGR when simple slope analysis was applied.

Polygenic score for omega 6/omega 3 PUFA ratio. There was a significant interaction effect between the polygenic score for omega 6/omega 3 PUFA ratio and IUGR status on DD score (β = 0.35, P = 0.044) and on pro-intake/anti-intake ratio (β = 0.10, P = 0.042) measured at 4y in MAVAN, and on EO score (β = 0.16, P = 0.043) at 5y in GUSTO (**Table 6**). A higher polygenic score for omega 6/omega 3 PUFA ratio was associated with a higher DD only in IUGR group (IUGR: β = 0.29, P = 0.089; non-IUGR: β = -0.05, P = 0.406) (**Figure 3A**), a greater tendency to pro-intake than anti-intake only in IUGR group (IUGR: β = 0.08, P = 0.030; non-IUGR: β = -0.01, P = 0.680) (**Figure 3B**) and a higher tendency to increase the intake in response to negative emotions in IUGR group (IUGR: β = 0.16, P = 0.069; non-IUGR: β = -0.03, P = 0.273) (**Figure 3C**).

Although an interaction between polygenic score for omega 6/omega 3 PUFA ratio and IUGR status on pro-intake score (β = 0.64, P = 0.067) in MAVAN and FR (β = 0.17, P = 0.074) in GUSTO was a trend (P values < 0.1), there was no significant

association seen between the polygenic score and the outcomes in the IUGR or non-IUGR group when simple slope analyses was conducted.

After considering adjustment for multiple testing, no interaction effect remained significant.

DISCUSSION

Main findings

This study analyzed the interaction effect between the IUGR and three polygenic scores associated with omega 3 PUFA, DHA and omega 6/omega 3 PUFA ratio in the eating behavior in childhood in two different cohorts. We observed that a higher polygenic score related to a higher serum omega 3 PUFA is associated with lower emotional overeating behavior, while a higher polygenic score related to a higher omega 6/omega 3 PUFA ratio is associated with higher desire to drink, higher emotional overeating and greater pro-intake than anti-intake inclination to eat only in children born IUGR.

Behavior, metabolism and brain function changes associated with early exposure to adversity

Alterations in the food choice, eating behavior, insulin sensitivity and brain connectivity in areas related to reward, decision-making and implicit memory have been described in individual exposed early to adversity. Adolescents (from PROTAIA study) who were born small for gestational age selected snacks with higher caloric density, exhibited alterations in food memory, and their level of HOMA-IR was associated with their external eating behavior [10]. In the same cohort, adolescents born small for gestational age were shown to use less money to buy snacks compared to controls, and they showed negative resting-state functional connectivity between the orbitofrontal cortex and dorsal striatum, and amygdala, while lower connectivity between the orbitofrontal cortex and dorsolateral prefrontal cortex. Furthermore, higher levels of connectivity between orbitofrontal cortex and dorsolateral prefrontal cortex compared to controls

were described in children who were born small for gestational age (MAVAN cohort) [9]. All of these areas are related to reward, self-control and value determination.

Omega 3 polyunsaturated fatty acids and altered eating behavior

We have described the protective role of the omega 3 PUFA against altered eating behavior associated with poor inhibitory control in vulnerable children. Specifically, a genetic profile associated with higher serum omega 3 PUFA was associated with a lower tendency to increase the intake as a result of negative emotions in IUGR participants. In a subset of participants from the MAVAN cohort, the consumption of omega 3 PUFA decreased food fussiness (an eating behavior related to being highly selective about a range of foods), an eating behavior associated with poor inhibitory control early in infancy, only in those born IUGR [33]. In adolescents from the PROTAIA study, higher serum DHA concentration was associated with decreased food intake in response to external food cues in IUGR individuals, who had increased activation of the right superior frontal *gyrus* (an area related to inhibitory control) in response to palatable food images during fMRI [8].

Our study shows that the genetic background associated with omega 3 PUFA levels is responsible for individual differences in the effect of IUGR altering eating behavior in childhood. The polygenic scores are innovative tools for research, they combine multiple genetic variants obtained through the GWAS into a single score [45]. Our polygenic score was built based on a previously published GWASs [44], where top SNPs were located in the genes: FADS1/FADS2 cluster, *MYRF* (myelin regulatory factor), *TMEM258* (transmembrane protein 258), *FEN1* (flap structure-specific

endonuclease 1), *LINC00271* (long intergenic non-protein coding RNA 271), *DSPP* (dentin sialophosphoprotein), *WDR70* (WD Repeat Domain 70) and AHI1 (Abelson Helper Integration Site 1) some of them had already been identified by other GWAS as related to omega 3 fatty acids [46-49].

Regarding the mechanism that could explain our results, one possible candidate is the modulation of dopaminergic neurotransmission by omega 3 PUFA. Animals deficient in omega 3 PUFA have increased activity in the mesolimbic dopamine reward pathway than in the mesocortical dopamine pathway [50]. The mesolimbic dopamine pathway is related to promotion palatable food intake and regulation of meal duration [51], which has been shown to be altered in IUGR individuals [45]. Another possible mechanism involved could be the increased effect of omega 3 PUFA on *BDNF* gene transcription and BDNF signaling in neurons. BDNF (brain-derived neurotrophic factor) is a growth factor involved in synaptic efficacy, neuronal connectivity, dendritic arborization and neuroplasticity [52].

Omega 6/omega 3 polyunsaturated fatty acids ratio and eating behavior

Our study found that a genetic background related with a higher omega 6/omega 3 PUFA ratio was associated with a higher DD, a greater tendency to pro-intake than anti-intake and a higher tendency to increase the intake in response to negative emotions, only in IUGR group. No other studies have reported an association between eating behaviour and the omega 6/omega 3 PUFA ratio. However, a study in children and adolescence described an inverse association between the dietary and plasma omega 6/omega 3 ratio and executive functions has been published highlighting the importance

of including omega 6/omega 3 ratio to reflect the balance of fatty acids omega 6 and omega 3 due to their important roles throughout life [53]. Although it is necessary to define the optimal balance between omega 6 and omega 3 fatty acid related to brain functions, inflammation could be involved in the association found between a genetic background associated with a higher omega 6/omega 3 PUFA ratio and altered eating behaviour. In this sense, AA produces molecules with proinflammatory actions such as prostanoids of the family 2 and leukotrienes of the family 4 through the action of COX and LOX enzymes activity, while EPA produces anti-inflammatory molecules as prostanoids of the family 3 and leukotrienes of the family 5 through the action of the same enzymes [54], however, these enzymes have a high affinity for AA, resulting in a more proinflammatory molecules production [55].

The interaction between genetic background and IUGR status on eating behavior was independent of current weight status

In our study, the relationship between the polygenic score related to serum omega 3 PUFA and omega 6/omega 3 PUFA ratio and IUGR status in eating behavior irrespective of whether current BMI of the child was included in the model. It has been shows that BMI has a positive association with subscales related with food-approach behaviours (EF, EO, FR), and is negatively associated with food-avoidance subscales (SR, SE and FF) in infants aged between 7 and 12 years old [5,6]. A longitudinal association has been described between eating behavior, BMI, and body composition during childhood [56]. Our results support the evidence that the genetic background could modulate the effect of adverse exposures early in life.

Limitations and strengths

The small sample size of the IUGR group means that the results of the study should be viewed with caution. However, all the analyses performed on MAVAN cohort, were replicated in a cohort of a larger sample size, GUSTO. The small sample size of the original GWAS could also be considered as a limitation. However, the novelty of our study, the application of advanced genomics in a study identifying GxE interactions in young children, is a strength. Having longitudinal additional information on diet and PUFA serum levels could be useful to dive deeper into the hypothesis.

CONCLUSION

A genetic background linked to a higher level of serum omega 3 PUFA was found to be associated with protection against altered eating behavior while higher serum omega 6/omega 3 PUFA ratio was associated with altered eating behavior only in children born IUGR. Understanding individual differences in the response to fetal adversity may be important for detecting true vulnerability and prompting the development of interventions for those who are in need.

Data Availability Statement

De-identified participant data from the final research dataset used in the published manuscript may only be shared under the terms of a Data Use Agreement. Requests may be directed to: patricia.silveira@mcgill.ca

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Declaration of consent of the patients

This study has been performed in accordance with the Declaration of Helsinki and its later amendments. The ethics committees from McGill University, Université de Montréal, Royal Victoria Hospital, Jewish General Hospital, Hospital de l'Université De Montréal, Hôpital Maisonneuve-Rosemount, St Joseph's Hospital and McMaster University, approved the MAVAN Project. The MAVAN Project was approved by resolution number 03/45 to the Research Ethical Board of Douglas Mental Health Research Institute. The ethics committees from Domain-Specific Review Board of the NUH and the Centralized Institutional Review Board of the KKH approved the GUSTO study. An informed consent was obtained from each participant or from their parents or caregivers.

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Authors Contributions

All authors contributed to this work. Conceptualization PPS, MJM, RDL; data analysis AMJO, IP, SP, VGC; methodology PPS, IP; resources PPS, MJM; writing-original draft AMJO, GTR, DMR; writing-review & editing AMJO, PPS, IP.

Competing interests

The authors declare no competing interests.

Table 1. Sociodemographic and anthropometric variables by group in MAVAN and GUSTO cohorts.

MAVAN	All (n = 299)	IUGR (n = 43)	non-IUGR (n = 256)	*P*
City of recruitment, n (%)				
Montreal	159 (53.2)	32 (74.4)	127 (49.6)	0.003*
Hamilton	140 (46.8)	11 (25.6)	129 (50.4)	
Females, n (%)	141 (47.2)	23 (53.5)	118 (46.1)	0.369
Gestational age, weeks	39.1 (1.2)	39.3 (1.3)	39.1 (1.2)	0.167
Maternal age at infant birth, years	31.1 (4.7)	29.9 (4.4)	31.3 (4.8)	0.041*
Breastfeeding duration, months (n = 289)[1]	7.5 (4.6)	7.7 (4.6)	7.4 (4.6)	0.359
Low income/maternal education, n (%) (n = 228)[2,7]	14 (6.1)	2 (6.5)	12 (6.1)	0.593
Birth weight, kg	3.39 (0.46)	2.74 (0.24)	3.49 (0.39)	<0.001*
BMI z-score at 4y (n = 294)[3]	0.48 (0.97)	0.23 (1.02)	0.52 (0.96)	0.039*
GUSTO	All (n = 746)	IUGR (n = 59)	non-IUGR (n = 687)	*P*
Study centre, n (%)				
KK Women's and Children's Hospital	565 (75.7)	47 (79.7)	518 (75.4)	0.464
National University Hospital	181 (24.3)	12 (20.3)	169 (24.6)	
Females, n (%)	352 (47.2)	30 (50.9)	322 (46.9)	0.557
Gestational age, weeks	38.9 (1.3)	39.0 (1.3)	38.9 (1.3)	0.224
Maternal age at infant birth, years	31.3 (5.1)	31.2 (5.3)	31.3 (5.1)	0.427
Household income <2,000 SGD, n (%) (n = 701)[4]	113 (16.1)	10 (18.2)	103 (15.9)	0.391
Maternal education-secondary or lower (n = 740)[5]	224 (30.3)	21 (35.6)	203 (29.8)	0.216
Birth weight, kg	3.13 (0.42)	2.51 (0.23)	3.18 (0.39)	<0.001*
BMI z-score at 5y (n = 742)[6]	0.07 (1.31)	-0.43 (1.02)	0.12 (1.32)	0.001*

Values are mean (standard deviation) or number (percentage). SDG: Singapore dollar.

Number of participants with information per group: [1]breastfeeding duration IUGR = 41, non-IUGR = 248; [2]income/maternal education IUGR = 31, non-IUGR = 197; [3]BMI z-score at 4y IUGR = 41, non-IUGR = 253; [4]household income IUGR = 55, non-IUGR = 646; [5]maternal education IUGR = 55, non-IUGR = 646; [6]BMI z-score at 5y IUGR = 58, non-IUGR = 684.

Comparison between groups were done using Student t-test for continuous variables and chi square for categorical variables. [7]Fisher´s exact test was used to compare categorical variables with less than 5 participants classified in one of its categories. *P<0.05 was considered significant.

Table 2. Standardized polygenic scores for polyunsaturated fatty acids by group in MAVAN and GUSTO cohorts.

MAVAN	IUGR (n = 43)	non-IIUGR (n = 256)	P
Polygenic score for omega 3 PUFA	-0.15 (-0.40, 0.13)	0.03 (-0.08, 0.13)	0.220
Polygenic score for DHA (C22:6 n-3)	-0.01 (-0.31, 0.13)	-0.001 (-0.12, 0.13)	0.954
Polygenic score for omega 6/omega 3 PUFA ratio	-0.16 (-0.46, -0.14)	0.03 (-0.09, -0.15)	0.246
GUSTO	IUGR (n = 59)	non-IIUGR (n = 687)	P
Polygenic score for omega 3 PUFA	-0.08 (-0.32, 0.17)	0.01 (-0.06, 0.08)	0.523
Polygenic score for DHA (C22:6 n-3)	-0.01 (-0.24, 0.23)	0.001 (-0.07, 0.07)	0.962
Polygenic score for omega 6/omega 3 PUFA ratio	-0.06 (-0.29, 0.17)	0.01 (-0.06, -0.07)	0.589

Reported are predicted means (95% CI) of each standardized polygenic score and p-value for association between IUGR status and polygenic score, which were obtained in multiple linear regression analysis adjusted by population stratification.

Table 3. Eating behaviour variables in childhood by group in MAVAN and GUSTO cohorts.

	MAVAN[1]	IUGR (n = 41)	non-IIUGR (n = 253)	P
	Child age, years	4.08 (4.05, 4.11)	4.11 (4.09, 4.12)	0.148
Anti-intake	Satiety responsiveness (SR) score	3.19 (2.98, 3.40)	3.19 (3.11, 3.27)	0.964
	Slowness in eating (SE) score	2.89 (2.64, 3.13)	3.16 (3.06, 3.26)	0.041*
	Food fussiness (FF) score	2.96 (2.70, 3.22)	3.04 (2.94, 3.15)	0.574
	Emotional under eating (EUE) score	2.78 (2.51, 3.05)	3.02 (2.91, 3.13)	0.114
	Anti-intake score	11.81 (11.10, 12.53)	12.41 (12.13, 12.69)	0.128
Pro-intake	Food responsiveness (FR) score	2.10 (1.86, 2.35)	2.28 (2.18, 2.37)	0.193
	Enjoyment of food (EF) score	3.56 (3.32, 3.79)	3.58 (3.49, 3.67)	0.849
	Desire to drink (DD) score	2.87 (2.55, 3.18)	3.09 (2.96, 3.21)	0.211
	Emotional overeating (EO) score	1.49 (1.31, 1.68)	1.63 (1.55, 1.70)	0.188
	Pro-intake score	10.02 (9.39, 10.65)	10.57 (10.32, 10.82)	0.112
Pro-intake/anti-intake ratio		0.89 (0.80, 0.98)	0.89 (0.86, 0.93)	0.921
	GUSTO[2]	IUGR (n = 58)	non-IIUGR (n = 684)	P
	Child age, years	5.11 (5.09, 5.12)	5.11 (5.10, 5.11)	0.987
Anti-intake	Satiety responsiveness (SR) score	2.91 (2.76, 3.05)	2.90 (2.86, 2.94)	0.919
	Slowness in eating (SE) score	2.86 (2.66, 3.06)	2.97 (2.91, 3.03)	0.306
	Food fussiness (FF) score	2.93 (2.74, 3.12)	3.01 (2.96, 3.06)	0.410
	Emotional under eating (EUE) score	2.76 (2.56, 2.97)	2.81 (2.75, 2.87)	0.677
	Anti-intake score	11.46 (10.93, 11.98)	11.68 (11.53, 11.84)	0.409
Pro-intake	Food responsiveness (FR) score	2.40 (2.22, 2.58)	2.40 (2.35, 2.45)	0.996
	Enjoyment of food (EF) score	3.49 (3.29, 3.69)	3.49 (3.44, 3.55)	0.988
	Desire to drink (DD) score	2.66 (2.43, 2.89)	2.74 (2.67, 2.81)	0.533
	Emotional overeating (EO) score	1.78 (1.63, 1.93)	1.81 (1.77, 1.86)	0.651
	Pro-intake score	10.33 (9.81, 10.86)	10.45 (10.30, 10.60)	0.683
Pro-intake/anti-intake ratio		0.95 (0.88, 1.02)	0.93 (0.91, 0.95)	0.624

Reported are predicted means (95% CI) of eating behavior variables and p-value for association between IUGR status and eating behavior variables, which were obtained in multiple linear regressions [1]adjusted by city of recruitment, maternal age, and BMI z-score at 4y of age; [2]BMI z-score at 5y of age. *P<0.05 was considered significant.

Table 4. Estimated effect of the interaction between IUGR status and standardized polygenic score for omega 3 polyunsaturated fatty acids on eating behavior outcomes in childhood in MAVAN and GUSTO.

	Outcome	MAVAN[1] (n = 294)			GUSTO[2] (n = 742)		
		β	95% CI	P	β	95% CI	P
Anti-intake	Satiety responsiveness (SR) score	0.21	-0.03, 0.46	0.090	-0.08	-0.16, 0.15	0.309
	Slowness in eating (SE) score	0.15	-0.15, 0.44	0.322	-0.09	-0.30, 0.11	0.378
	Food fussiness (FF) score	0.02	-0.30, 0.34	0.894	0.07	-.13, 0.26	0.490
	Emotional under eating (EU) score	0.26	-0.09, 0.61	0.143	-0.07	-0.27, 0.14	0.535
	Anti-intake score	0.82	-0.03, 1.67	0.057	-0.17	-.70, 0.37	0.538
Pro-intake	Food responsiveness (FR) score	-0.08	-0.37, 0.21	0.592	-0.09	-0.27, 0.10	0.346
	Enjoyment of food (EF) score	-0.01	-0.29, 0.27	0.927	0.07	-0.14, 0.27	0.527
	Desire to drink (DD) score	-0.17	-0.55, 0.21	0.387	0.01	-0.23, 0.24	0.938
	Emotional overeating (EO) score	-0.01	-0.24, 0.21	0.909	-0.15	-0.31, -0.001	0.049*
	Pro-intake score	-0.27	-1.03, 0.48	0.477	-0.17	-0.70, 0.37	0.542
Pro-intake/anti-intake ratio		-0.10	-0.21, 0.01	0.062	0.01	-0.06, 0.08	0.708

Reference group was non-IUGR. Multiple linear regressions adjusted by [1]city of recruitment, maternal age, BMI z-score at 4y of age, population stratification; [2]BMI z-score at 5y of age and population stratification. *P<0.05 was considered significant.

Table 5. Estimated effect of the interaction effect between IUGR status and standardized polygenic score for docosahexaenoic fatty acid on eating behavior outcomes in childhood in MAVAN and GUSTO.

Outcome		MAVAN[1] (n = 294)			GUSTO[2] (n = 742)		
		β	95% CI	P	β	95% CI	P
Anti-intake	Satiety responsiveness (SR) score	0.20	-0.05, 0.44	0.111	-0.10	-0.26, 0.06	0.207
	Slowness in eating (SE) score	0.01	-0.29, 0.30	0.974	-0.15	-0.36, 0.06	0.151
	Food fussiness (FF) score	0.01	-0.30, 0.33	0.941	0.01	-0.19, 0.21	0.905
	Emotional undereating (EU) score	0.09	-0.23, 0.41	0.587	-0.20	-0.41, 0.01	0.066
	Anti-intake score	0.30	-0.54, 1.15	0.479	-0.44	-0.99, 0.11	0.114
Pro-intake	Food responsiveness (FR) score	-0.04	-0.33, 0.25	0.806	-0.06	-0.25, 0.13	0.539
	Enjoyment of food (EF) score	0.004	-0.27, 0.28	0.978	0.09	-0.12, 0.30	0.381
	Desire for drink (DD) score	-0.33	-0.70, 0.05	0.086	0.06	-0.18, 0.30	0.637
	Emotional overeating (EO) score	-0.004	-0.23, 0.22	0.973	-0.09	-0.25, 0.07	0.259
	Pro-intake score	-0.37	-1.11, 0.38	0.337	0.002	-0.54, 0.55	0.993
Pro-intake/anti-intake ratio		-0.06	-0.17, 0.05	0.271	0.05	-0.03, 0.12	0.227

Reference group was non-IUGR. Multiple linear regressions adjusted by [1]city of recruitment, maternal age, BMI z-score at 4y of age, population stratification principal components; [2]BMI z-score at 5y of age and population stratification principal components.

Table 6. Estimated effect of the interaction effect between IUGR status and standardized polygenic score for omega 6/omega 3 polyunsaturated fatty acids (PUFA) ratio on the eating behavior outcomes in childhood in MAVAN and GUSTO.

Outcomes		MAVAN[1] (n = 294)			GUSTO[2] (n = 742)		
		β	95% CI	P	β	95% CI	P
Anti-intake	Satiety responsiveness (SR) score	-0.12	-0.35, 0.10	0.282	-0.05	-0.20, 0.11	0.546
	Slowness in eating (SE) score	-0.16	-0.42, 0.11	0.245	-0.08	-0.28, 0.13	0.484
	Food fussiness (FF) score	-0.13	-0.42, 0.16	0.371	-0.11	-0.30, 0.09	0.298
	Emotional under eating (EU) score	-0.22	-0.51, 0.07	0.134	0.09	-0.12, 0.30	0.407
	Anti-intake score	-0.63	-1.40, 0.13	0.105	-0.14	-0.68, 0.40	0.617
Pro-intake	Food responsiveness (FR) score	0.15	-0.11, 0.41	0.262	0.17	-0.02, 0.35	0.074
	Enjoyment of food (EF) score	0.11	-0.14, 0.36	0.395	0.07	-0.14, 0.27	0.532
	Desire to drink (DD) score	0.35	0.01, 0.70	0.044*	-0.07	-0.30, 0.17	0.585
	Emotional overeating (EO) score	0.02	-0.18, 0.23	0.824	0.16	0.01, 0.32	0.043*
	Pro-intake score	0.64	-0.04, 1.32	0.067	0.33	-0.21, 0.87	0.234
Pro-intake/anti-intake ratio		0.10	0.004, 0.20	0.042*	0.03	-0.04, 0.10	0.438

Reference group was non-IUGR. Multiple linear regressions adjusted by [1]city of recruitment, maternal age, BMI z-score at 4y of age, population stratification principal components; [2]BMI z-score at 5y of age and population stratification principal components. *P<0.05 was considered significant.

Fig. 1 Flow diagram

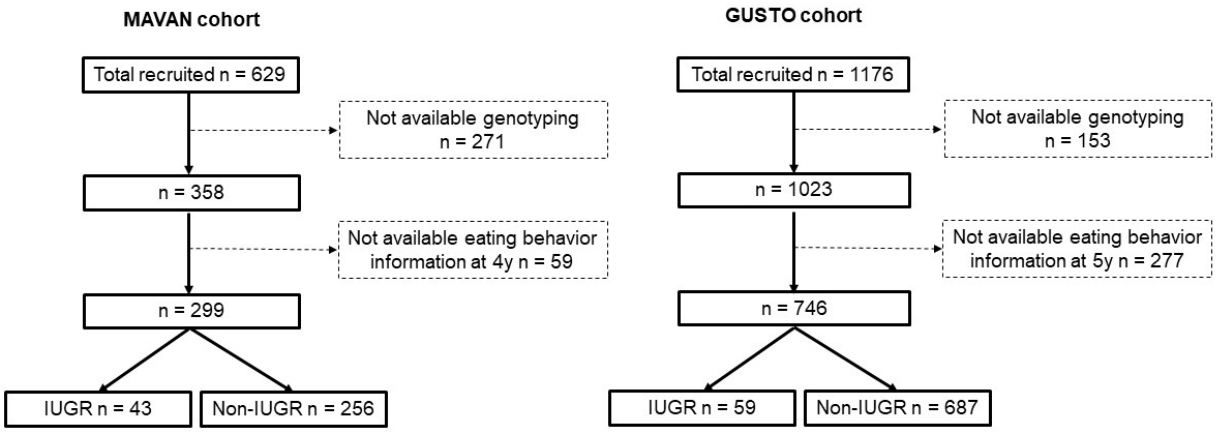


Fig. 2 Moderator effect of IUGR status in the association between standardized polygenic score for omega 3 PUFA and emotional overeating score in childhood in GUSTO cohort.

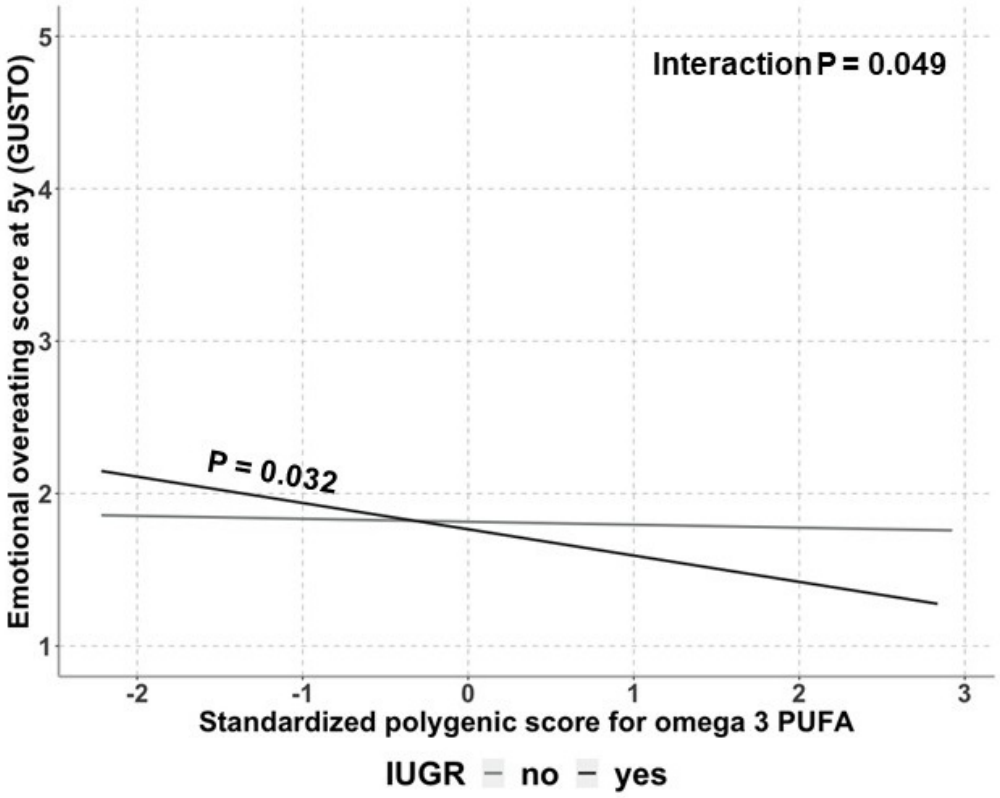
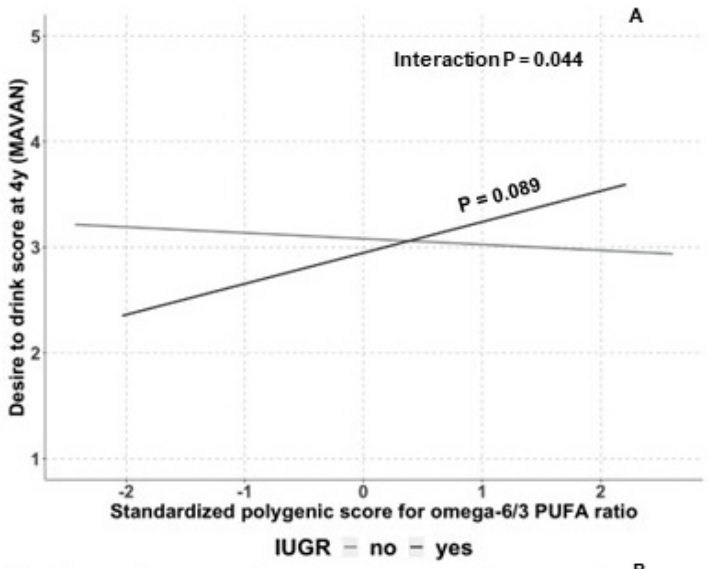
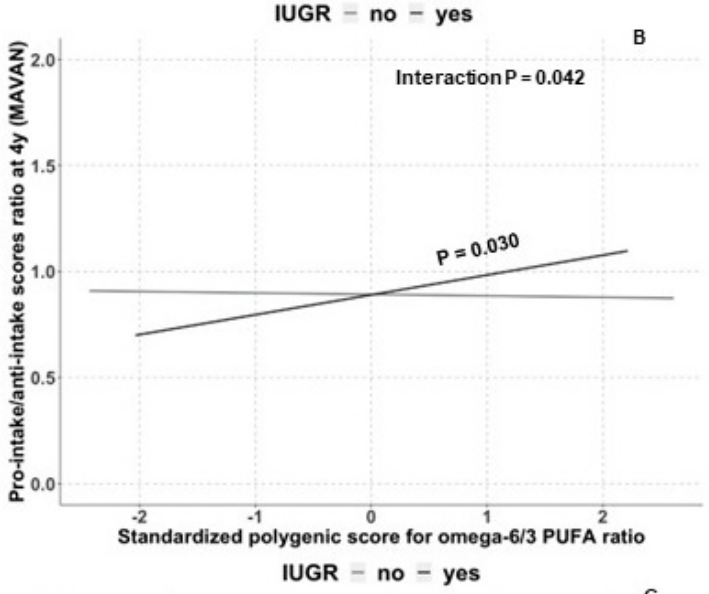
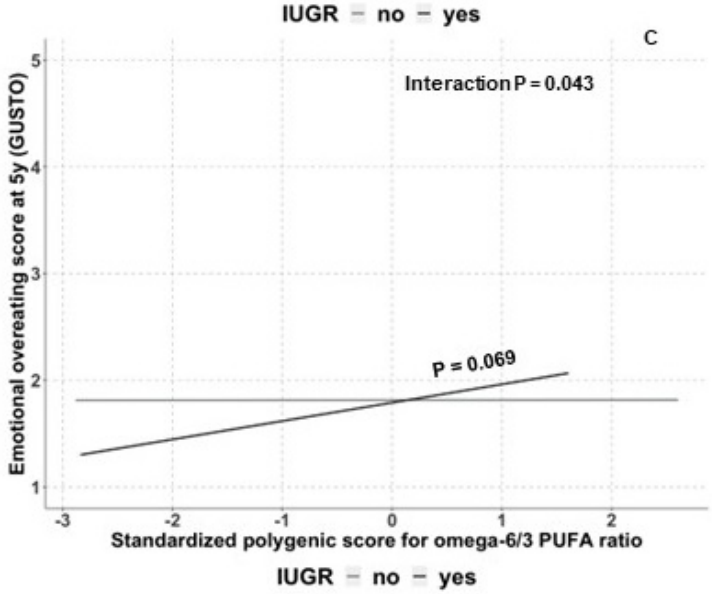


Fig. 3 Moderation effect of IUGR status in the association between standardized polygenic score for omega 6/omega 3 PUFA ratio and emotional undereating (A. Desire to drink score; B. Pro-intake/anti-intake scores ratio; C. Emotional overeating score) in childhood in MAVAN and GUSTO cohorts.


A
Interaction P = 0.044
P = 0.089
Desire to drink score at 4y (MAVAN)
Standardized polygenic score for omega-6/3 PUFA ratio
IUGR no yes


B
Interaction P = 0.042
P = 0.030
Pro-intake/anti-intake scores ratio at 4y (MAVAN)
Standardized polygenic score for omega-6/3 PUFA ratio
IUGR no yes


C
Interaction P = 0.043
P = 0.069
Emotional overeating score at 5y (GUSTO)
Standardized polygenic score for omega-6/3 PUFA ratio
IUGR no yes