

## Research report



## Associations of adolescents' diet and meal patterns with school performance in the Northern Finland Birth Cohort 1986: A Mendelian randomisation study

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## ABSTRACT

**Background:** Several observational studies indicate that dietary habits in children and adolescents are associated with school performance. These associations are heavily confounded by socio-economic characteristics, such as household income and parents' educational attainment, amongst other factors. The objective of this study was to explore the association between diet and school performance in adolescents from the Northern Finland Birth Cohort 1986 (NFBC1986).

**Methods:** Dietary and school performance data were collected using self-reported questionnaires from adolescents in the NFBC1986 cross-sectional, 16-year follow-up study. In this work we derived exploratory factors for the dietary variables, frequency of skipping main meals and school performance variables, performed genome-wide association studies (GWAS) against these factors to obtain genetic association data and conducted one-sample and two-sample Mendelian randomisation (MR) analyses using individual level data for up to 9220 adolescents in NFBC1986 and GWAS results from external cohorts. We report observational and MR effects of diet on school performance and cognition-related phenotypes.

**Results:** The observational study and the one-sample Mendelian randomisation analysis showed that high fat, salt and sugar (HFSS) consumption was associated with poor school performance in general/science subjects (−0.080, −0.128 to −0.033) and staple food consumption with better school performance in general/science subjects (0.071, 0.024 to 0.119) and physical education (0.065, 0.021 to 0.110). Findings from our two-sample MR analysis identified dietary principal components described best as whole brain bread, wheat, cheese, oat cereal and red wine to be associated with higher educational attainment and other cognition-related phenotypes.

**Conclusion:** Using genetics, we highlighted the potential role of HFSS food consumption and consumption of the components of a staple food diet for school performance. However, further research is required to find conclusive evidence that could support a causal role of diet on school performance.

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## 1. Introduction

Diets that contain a high proportion of fruit, vegetables, cereals and olive oil, moderate amounts of fish, dairy and low amounts of saturated fat and meat have been associated with a wide variety of positive health benefits, including improved cognitive function in adults (Loughrey et al., 2017) and adolescents (Tapia-Serrano et al., 2021). The most recent theories suggest that these well-balanced diets reduce inflammation and/or oxidative stress and protect levels of brain-derived neurotrophic factor (Frisardi et al., 2010). In contrast, diets defined by high intake of fat, salt and sugar increase the likelihood of insulin resistance and have been identified as a leading cause of cognitive dysfunction (Allen et al., 2004; Fu et al., 2017; Pilato et al., 2020). These studies raise the possibility that particular diets can protect against cognitive decline and may also be important for optimal cognitive development. Such advantageous diets may lead to improved scholastic attainment in early life, particularly reading comprehension (Naveed et al., 2020).

Individual dietary markers that enhance optimal cognitive performance or protect against cognitive decline remain elusive, and it may be more useful to consider diet in general. The most promising individual nutritional markers related to improving cognitive function/efficiency and mental health have been supplementation with either vitamin D (Azzam et al., 2015; Focker et al., 2017; Hajiluan et al., 2017; Przybelski & Binkley, 2007) or omega-3 polyunsaturated fatty acids (PUFA) (Patrick & Ames, 2015; Richardson et al., 2012; Sinn et al., 2010). Recent large scale replication studies have indicated that nutritional supplementation with omega-3 (PUFA) does not alter executive functions (Montgomery et al., 2018), although the correlation between eating fish (a primary source of omega 3 PUFA) and educational attainment remains (Pilato et al., 2020; Teisen et al., 2020). While single markers such as specific nutrients or food groups may also have some impact on these outcomes, whole diet or food quality assessments are likely to be more comprehensive and capture the synergistic effects of different nutrients and foods in a child's diet. A recent comprehensive review of the literature suggests that modulation of single nutrients within a whole diet is unlikely to result in improvements in educational attainment or performance (Kadosh et al., 2021).

Identifying a nutrient or food that will improve educational attainment and cognitive performance is laudable, but data indicate that a poor diet, defined by high intakes of fat, salt and sugar made up from a combination of foods, is associated with poor cognitive performance (Naveed et al., 2020) and neurobiological deficits (Stadterman et al., 2020). Observational studies have concluded that diets defined by processed foods (Wiles et al., 2009) or skipping meals (Lien, 2007) were associated with behavioural problems (Overby & Hoigaard, 2012) and poor cognitive performance (Pilato et al., 2020). However, "correlation is not causation" and it is important to determine whether a poor diet directly cause the associations observed or are simply acting as markers of other factors (such as socio-economic status, for example). Indeed, determining whether a well-balanced diet improves/maintains (or a poor diet decreases) educational performance is the frontier of this field of research and one of the principal aims of the current study.

Previous attempts to assess diet have investigated specific nutrients rather than employing whole diet and have often relied on associations between food frequency questionnaires and single time-point psychometric assessments. This approach restricts conclusions and causes difficulty in assessing the impact of confounding variables (Kadosh et al., 2021). Food preferences are, at least partially, genetically determined, with heritability believed to be ranging between 36% and 58% (Pallister et al., 2015), and specific polymorphisms have been associated with self-reported diet (Guenard et al., 2017). In addition, food preferences are a primary determinant of dietary intake and behaviours, and they persist from early childhood into later life (Beckerman et al., 2017). These facts suggest that the application of Mendelian randomisation (MR) to disentangle the complex relationships between diet and educational performance is possible. For this approach, genetic markers

are used as proxies for characteristics that are difficult to reliably control in population studies (Evans & Davey Smith, 2015). Since genetic variation in offspring is allocated randomly at conception, based on the genetic variation of parents, and is independent of other characteristics, as postulated in the 2nd law of Mendel, genetic variants can be used as though they were interventions in a randomised controlled trial (Burgess et al., 2017). This allows us to use MR approaches to examine causative relationships between associated variables.

The aim of the current study was to explore the association between diet and school performance using population data from the Northern Finland Birth Cohort 1986 (NFBC1986) and genetic association data from independent cohorts. Previous research has suggested that individuals with a balanced diet would achieve better outcomes than individuals who habitually consume comparatively higher quantities of fat, salt and sugar food items. It will also assess whether diet affects all scholastic subjects equally, supporting a general improvement in educational attainment, rather than specific effects. Here, we conducted Mendelian randomisation analyses to investigate potentially causal relationships of HFSS, staple food diet and traditional Finnish diet with school performance, but also explore the role of having breakfast and snacks in school performance.

## 2. Methods

### 2.1. Study sample

Northern Finland Birth Cohort 1986 (NFBC1986) is a prospective cohort, which included mothers in the two northernmost provinces on Finland (Oulu and Lapland) with an expected date of delivery between 1.7.1985 and 30.6.1986; the study design and population of the NFBC1986 have been described in (Jarvelin et al., 1993). Altogether 9479 children were born into the cohort, 9432 of them live-born. In addition to the data on delivery, follow-ups have been conducted at four different time points i.e., at 1, 7–8, 15–16 and 33–35 years of age. Collected data include prenatal and early life measurements, information on motor, social, psychological and mental development in childhood. In adulthood data has been collected on social background, lifestyle, medication, diagnosed diseases, organ-specific and psychiatric symptoms, workload and occupational health, economy, personal traits, functioning, quality of life, and family history of diseases (University of Oulu, 1986). In the 16-year follow-up study, questionnaire data were received from 7182 (77.9%) adolescents. More detailed description can be found at <https://www.oulu.fi/nfbc/>.

### 2.2. Dietary data

The adolescents' 16-year follow-up questionnaire contained a set of questions on the frequency of consumption of a wide variety of foods. We used data on 45 dietary traits, variable IDs for all traits can be found in [Supplementary Table S1](#). In this questionnaire, adolescents were asked how many slices of bread they had in a day, and how often they had eaten uncooked vegetables the previous week. Moreover, they were asked about the frequency of having consumed specific foods during the previous six months. All dietary data were numerically transformed into 'times consumed per week', in order to apply quantitative meaning to the diet variables. In the same questionnaire, the adolescents were asked whether they usually had breakfast/lunch/dinner on weekdays and on weekends, in a Yes/No question. To assess their meal patterns, variables were transformed into 'times had breakfast/lunch/dinner per week'. In total, 35 dietary variables and 6 meal patterns were investigated. Collecting data in this manner and from this age group has been found to be valid and reliable with a long history of effective assessment of diet (Rockett et al., 1997; Vilela et al., 2019; Willett et al., 1987).

### 2.3. School performance

In the 16-year follow-up study, adolescents were asked to report how well they were doing in various school subjects: Finnish language, general subjects, such as history and religious studies, mathematics, biology, physics, chemistry, art and physical education, compared to other pupils of their age. The question had four levels of possible answers: Better than average, average, worse than average and really badly.

### 2.4. Genetic data

Genetic information was available for 3834 individuals. In our genetic quality control, we excluded 26 samples from the analysis, determined to be outliers for ‘missingness’ and ‘heterozygosity’ and four samples due to sex mismatch. In addition, another 24 samples were removed due to relatedness and 37 samples as duplicates (checked by the ID numbers). After filtering, a total of 3743 individuals remained for analysis. In total, 928 272 autosomal single nucleotide polymorphisms (SNPs) were available prior to imputation. SNPs with a Hardy-Weinberg equilibrium p-value threshold smaller than  $10^{-4}$  were removed from the analysis. The total number of genotyped SNPs that passed the quality control was 889 119. Imputation was performed using the 1000 Genomes phase three reference panel. From 81 571 831 imputed and directly genotyped SNPs, the variants with an imputation info score lower than 0.9 were excluded. Only variants with minor allele frequency greater than 0.01 were included. After filtering, 11 009 294 variants remained.

### 2.5. Imputation of missing phenotypic values

Individuals with six or more missing dietary values (out of 38) and more than one missing school performance value (out of six) were excluded from the analysis. To address missing phenotypic data and gain statistical power on the observational calculations, a multivariate imputation by chained equations (MICE) was created. The MICE algorithm creates multiple imputations – replacement values – for multivariate missing data. Creating multiple imputations, as opposed to single imputations, accounts for the statistical uncertainty in the imputations and maintains an unbiased sample variance. For both datasets, we used the predictive mean matching imputation method with five multiple imputations and 50 iterations on each step, for high accuracy.

### 2.6. Statistical analysis

#### 2.6.1. Exploratory factor analysis

Exploratory factor analysis (EFA) with varimax rotation was performed separately for dietary variables (Kent et al., 1979), meal patterns (Pilato et al., 2020) and school performance variables (Pilato et al., 2020). Varimax rotation was preferred to maximise the shared variance among items, so that findings could represent more discretely how variables correlate with each exploratory factor. The purpose was to describe the variability among variables by searching for joint variations, but also to reduce the dimensions of the dietary dataset and increase the interpretability of results. Here we used the Bartlett factor score method, which is based on maximum likelihood estimates and provides unbiased estimates of the true factor scores (Hershberger, 2005). Factor loadings were calculated for each variable, indicating the amount of variable information described by each factor. The number of factors that best represents the data was determined by performing a scree test (Kent et al., 1979). Foods and meal patterns with loadings above 0.3 on a factor were considered to have a strong association with that factor and were the most informative in describing the dietary factors (Northstone & Emmett, 2008). School performance variables with factor loadings greater than 0.3 were considered most representative of these factors.

#### 2.6.2. Multivariable regression of observational data

The 16-year follow-up NFBC1986 data were used to undertake a cross-sectional study. Multivariable linear regression was conducted to estimate the association of diet with school performance. In the analysis we adjusted for potential confounders: sex, household income, family financial status, mother and father education. Regressions were completed for each school performance factor against every dietary factor and meal pattern factor. Associations were considered statistically significant if the p-value was lower than the Bonferroni corrected threshold of  $P = 0.05/15 = 3.33 \times 10^{-3}$ , to account for multiple tests. Findings that reached nominal significance ( $P < 0.05$ ) were taken forward for MR analysis.

#### 2.6.3. Genome wide association analysis

Under the additive genetic model, we tested for associations between 11 009 294 genetic variants that passed quality control and five dietary and three school performance exploratory factors for up to 3743 individuals in the NFBC1986. The association of each genetic variant was tested using a regression model adjusting for sex and the first four genetic principal components to control for population structure. We adjusted for the first 4 genetic principal components, since they accounted for 90% of the genetic variation. Including more components would adjust for more subtle differences between the quite homogeneous Finnish samples and would induce overfitting. We used the FUMA web application (Watanabe et al., 2017) to generate Manhattan and Quintile-Quintile plots and to annotate genetic associations. Moreover, the Genotype-Tissue Expression (GTEx) project database was used to assess the expression of the identified genes in various human tissues (Lonsdale et al., 2013). Gene expression analysis from GTEx is integrated in FUMA.

#### 2.6.4. One-sample mendelian randomisation

Two-stage least squares (2SLS) regression analysis was performed in the NFBC1986 to investigate the causal relationship between diet and school performance. For each dietary exposure, independent variants ( $r^2 < 0.01$ ) were used as genetic instruments for the analysis at a P-value threshold of  $10^{-4}$ . In the first step of the analysis, each dietary factor was regressed against the genetic instruments and the measured confounders: sex, household income, family financial status, mother’s, and father’s education level. In the second step of the analysis, each school performance factor was regressed against the fitted values from the first step of the analysis. To assess the validity of the MR assumptions, one-sample Mendelian randomisation sensitivity analysis was performed. To test whether the genetic variants used in the analysis were associated with the potential confounders, we regressed the confounding variables against the genetic variants associated with the exposure. SNPs with evidence of association with the confounders were then removed and the two-stage least squares regression analysis was repeated to investigate whether this significantly altered the regression results. The robustness of the results to violations was tested by applying two sample MR methods on the data, including MR-Egger (Bowden et al., 2015), MR weighted median (Bowden et al., 2016) and MR weighted mode (Hartwig et al., 2017) analyses. To correct for type I errors due to multiple testing, we used a Bonferroni correction threshold  $P = 0.05/9 = 5.55 \times 10^{-3}$ .

#### 2.6.5. Two-sample mendelian randomisation

To address the limitations of one-sample MR analysis, we conducted two-sample MR, using external summary statistics from independent cohorts for dietary traits and cognition related phenotypes to further explore the association between diet and school performance. For diet traits, we used publicly available genome-wide association study (GWAS) results from Cole et al. (Cole et al., 2020) on 60 dietary principal components (PCs) in UK Biobank and leveraged GWAS results from Pirastu et al. (Pirastu et al., 2022) against 14 diet phenotypes in UK Biobank, where the authors removed recall bias that is prevalent in

self-reported dietary data. In the first stage of this analysis, we used school performance genetic association data from our GWAS on the NFBC1986 as the outcome. To consider statistical significance of findings, we used Bonferroni correction, dividing the nominal P-value threshold by the total number of independent tests, i.e.,  $0.05/(14 \times 3) = 1.19 \times 10^{-3}$  when using Pirastu et al. dietary phenotypes and  $0.05/(60 \times 3) = 2.78 \times 10^{-4}$  for Cole et al. dietary principal components.

In the second stage, we obtained data on 9 cognition-related traits, including educational attainment in 766 345 European ancestry individuals from Lee et al. (Lee et al., 2018), general cognition traits (reaction time and verbal-numeric reasoning) in up to 168 033 individuals of European ancestry from a GWAS meta-analysis (Davies et al., 2018), reading skills and language skills traits (word reading, nonword reading, spelling, phoneme awareness and nonword repetition) in up to 27 180 European ancestry participants from a meta-analysis of GWAS (Eising et al., 2022) and ‘extremely high intelligence’ in 9410 samples of European ancestry (Zabaneh et al., 2018), to use them as outcomes in the MR analysis. Again, we used Bonferroni corrected p-value thresholds to account for multiple tests, i.e.,  $0.05/(14 \times 9) = 3.97 \times 10^{-4}$  when using Pirastu et al. dietary phenotypes and  $0.05/(60 \times 9) = 9.26 \times 10^{-5}$  for Cole et al. dietary principal components.

### 2.6.6. Statistical software

Analysis was conducted in R version 4.0.2 (Team, 2013), two-sample MR was performed using the “TwoSampleMR” package v0.5.6 (Hemani et al., 2018), and figures were produced using the R package “forestplot” (Gordon et al., 2016) v.3.1.1.

## 3. Results

The demographic characteristics of the sample can be seen in Table 1. A flowchart with information on the study sample size after inclusion/exclusion criteria is provided in Fig. 1.

### 3.1. Exploratory factor analysis

To identify food clusters that share common variation and can be explained by the same exploratory factor, dietary data and school performance data on 5337 adolescents were included in the analysis. For the diet analysis, the first three exploratory factors were determined sufficient to describe the data, explaining 21% of total variance in the dietary dataset. Little variance was explained by the rest of the factors. The first factor was characterised by foods high in fat, salt and sugar and thus named “HFSS” food. In the second factor, chicken, fish, rice and pasta loaded highly, so we refer to this as “staple food” diet. The third factor was characterised by foods that constitute traditional Finnish meals, such as different kind of meats, boiled potatoes, baked goods. Therefore, factor three was named “traditional” food. Details of the

**Table 1**  
Characteristics of the sample used in the analysis.

| Sex                            | Family financial status |                                |                 |
|--------------------------------|-------------------------|--------------------------------|-----------------|
| Male                           | 4665<br>(50.6%)         | Many problems                  | 203 (2.2%)      |
| Female                         | 4555<br>(49.4%)         | Some problems                  | 1798<br>(19.5%) |
|                                |                         | Quite good status              | 6168<br>(66.9%) |
|                                |                         | Very good status               | 1051<br>(11.4%) |
| Mother education               |                         | Father education               |                 |
| Less than 9 years              | 406 (4.4%)              | Less than 9 years              | 784 (8.5%)      |
| Comprehensive school education | 5560<br>(60.3%)         | Comprehensive school education | 6601<br>(71.6%) |
| Matriculation examination      | 3254<br>(35.3%)         | Matriculation examination      | 1835<br>(19.9%) |

groups can be seen in Table 2.

Similarly, exploratory factor analysis on the six meal patterns revealed two principal factors accounting for 15% of total variance in meal pattern variables. The cumulative explained variance did not change when considering a third factor. Breakfast was the only variable that characterised the first factor, whereas evening snacks and snacks between meals had large loadings in the second factor (Table 3). As a result, factor one is referred to as “breakfast” and factor two as “snacks”.

Following the same analysis for school performance, the first three exploratory factors explained 60% of total variance of the variables. The rest did not explain a significant proportion. The first factor, which explains 24% of the total variance, is described by general subjects (history and religious studies), mathematics and physical sciences - biology, physics and chemistry (Table 4). Finnish language had a 0.96 loading on the second factor, which accounts for 20% of the total variance. General subjects also loaded 0.37 on the second factor but was considered on the first factor where it loaded higher (0.47) and thus was described better by the first factor. Physical education has a loading of 0.99 on the third factor, explaining 16% of total variance. Consequently, factors 1, 2 and 3 were named “general/science”, “Finnish” and “Physical Education (PE)”, respectively. Supplementary Table S2-S4 show all factor loadings for diet, meal patterns and school performance variables. Pearson correlation coefficient matrices between dietary factors and school performance factors obtained from EFA are provided in Table 5.

### 3.2. Observational association of diet on school performance

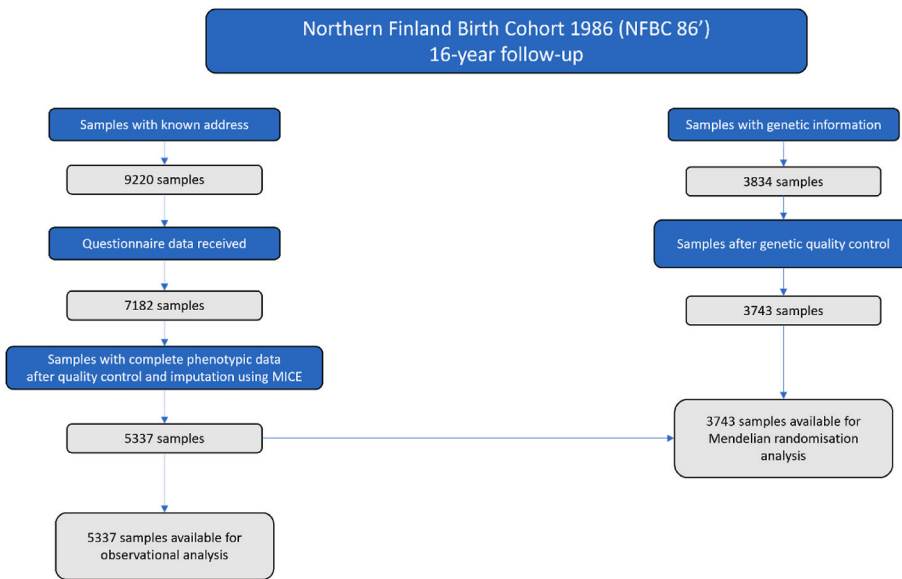
Out of 15 tests, 8 were statistically significant after Bonferroni correction. HFSS foods were negatively associated with school performance in *general/science* and *Finnish* (beta:  $-0.159$ , 95% confidence interval:  $-0.190$  to  $-0.127$ ) and ( $-0.069$ ,  $-0.099$  to  $-0.040$ ), respectively. Staple food eating was positively associated with better school performance in *general/science* (0.057, 0.026 to 0.088) and *PE* (0.051, 0.022 to 0.079), as was *traditional* meal eating with school performance in *general/science* (0.084, 0.055 to 0.113) and *PE* (0.077, 0.050 to 0.104). Eating *breakfast* was positively associated with school performance in *general/science* (0.066, 0.034 to 0.089) and *Finnish* (0.027, 0.006 to 0.049). The association between eating breakfast and school performance in Finnish language attenuated to the null after Bonferroni correction. In addition, there was evidence that eating *snacks* was positively associated with good performance in *PE* (0.035, 0.019 to 0.051). There was no evidence of association between the rest of the dietary and school performance phenotypes. Betas are reported as units of change in school performance per unit increase in the dietary exploratory factor. Results are summarised in Fig. 2 and Supplementary Table S5.

### 3.3. Genome wide association results

Genome wide association with the diet identified 403 SNPs associated with HFSS, 282 with staple food eating, 207 with traditional meal eating, 154 with eating breakfast, and 191 with eating snacks (Supplementary Table S6 and Supplementary Figs. S1-S5). The p-value selected as a cut-off in this work was  $10^{-4}$ , as it was the threshold that provided robust signals for all dietary GWAS and moreover, took into account the relatively small sample size of NFBC1986 compared to existing GWAS of large cohort studies. Integration of association results with GTEx gene expression across 54 tissue types revealed an association of differentially expressed genes in esophagus muscularis with having snacks. FUMA results for all dietary traits are provided in Supplementary Figs. S6-S10.

### 3.4. One-sample mendelian randomisation

A one-sample MR was performed on observational associations between diet and school performance that reached nominal significance.



**Fig. 1.** Study sample size after applying inclusion/exclusion criteria in observational and Mendelian randomisation analysis. Phenotypic data were obtained from the 16-year follow-up study in the Northern Finland Birth Cohort 1986 (NFBC1986). Samples with six or more missing dietary values (out of 38) and more than one missing school performance value (out of six) were excluded from the analysis. A multivariate imputation by chained equations (MICE) was created to impute phenotypic data. After genetic quality control, 26 samples were excluded from the analysis as outliers for ‘missingness’ and ‘heterozygosity’ and 4 samples due to sex mismatch. Another 24 samples were removed due to relatedness and 37 samples as duplicates (checked by the ID numbers).

**Table 2**  
Exploratory factors of dietary variables. HFSS: Foods high in fat, salt and sugar.

| Variables                             | HFSS | Staple food | Traditional |
|---------------------------------------|------|-------------|-------------|
| Cumulative variance explained         | 6.5% | 4.0%        | 3.9%        |
| Glasses of milk                       | -    | -           | -           |
| Glasses of sour milk                  | -    | -           | -           |
| Glasses of other milk products        | -    | -           | -           |
| Slices of dark bread                  | -    | -           | -           |
| Slices of full wheat or oatmeal bread | -    | -           | -           |
| White bread                           | -    | -           | -           |
| Uncooked veg                          | -    | -           | -           |
| Uncooked fruit                        | -    | -           | -           |
| Berries                               | -    | -           | -           |
| Cakes and cookies                     | -    | -           | 0.30        |
| Porridge                              | -    | -           | -           |
| Cold breakfast                        | -    | -           | -           |
| Cheese                                | -    | -           | -           |
| Ice-cream                             | 0.36 | -           | -           |
| Boiled potatoes                       | -    | -           | 0.50        |
| Fried potatoes or French fries        | 0.50 | -           | -           |
| Rice                                  | -    | 0.68        | -           |
| Pasta                                 | 0.30 | 0.55        | -           |
| Fish                                  | -    | 0.60        | -           |
| Chicken                               | -    | 0.69        | -           |
| Sausages                              | 0.33 | -           | 0.36        |
| Cold meats                            | -    | -           | 0.42        |
| Meat dishes                           | -    | -           | 0.59        |
| Ground beef                           | -    | -           | 0.54        |
| Eggs                                  | -    | -           | -           |
| Soft drinks with sugar                | 0.51 | -           | -           |
| Soft drinks without sugar             | -    | -           | -           |
| Chocolate                             | 0.56 | -           | -           |
| Sweets                                | 0.55 | -           | -           |
| Ready-to-eat food                     | 0.45 | -           | -           |
| Salad dressing                        | -    | -           | -           |
| Hamburgers, pizza                     | 0.65 | -           | -           |
| Potato crisps                         | 0.69 | -           | -           |

Independent genetic variants identified in the GWAS as associated with the dietary exposures were used as instruments. Fig. 3 and Supplementary Table S7 summarise the results of the two-stage least squares regression. MR effect estimates are reported as units of change in school performance per unit increase in genetically predicted dietary principal component. HFSS had a negative effect on school performance in general/science, with an effect size of  $-0.080$  ( $-0.128, -0.033$ ). The relationship between HFSS and school performance in Finnish was not

**Table 3**  
Exploratory factors of meal patterns.

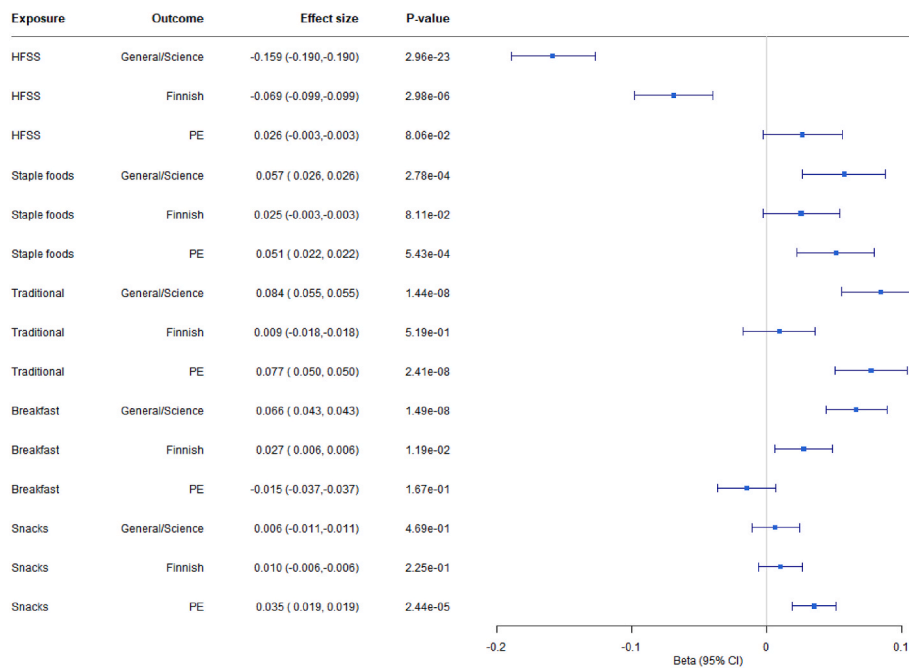
| Variables                     | Breakfast | Snacks |
|-------------------------------|-----------|--------|
| Cumulative variance explained | 8.8%      | 6.0%   |
| Breakfast                     | 0.69      | -      |
| Lunch                         | -         | -      |
| Dinner                        | -         | -      |
| Evening snack                 | -         | 0.31   |
| Snack between meals           | -         | 0.32   |
| Devour food                   | -         | -      |

**Table 4**  
Exploratory factors of school performance variables. PE: Physical education, General subjects: includes history and religious studies.

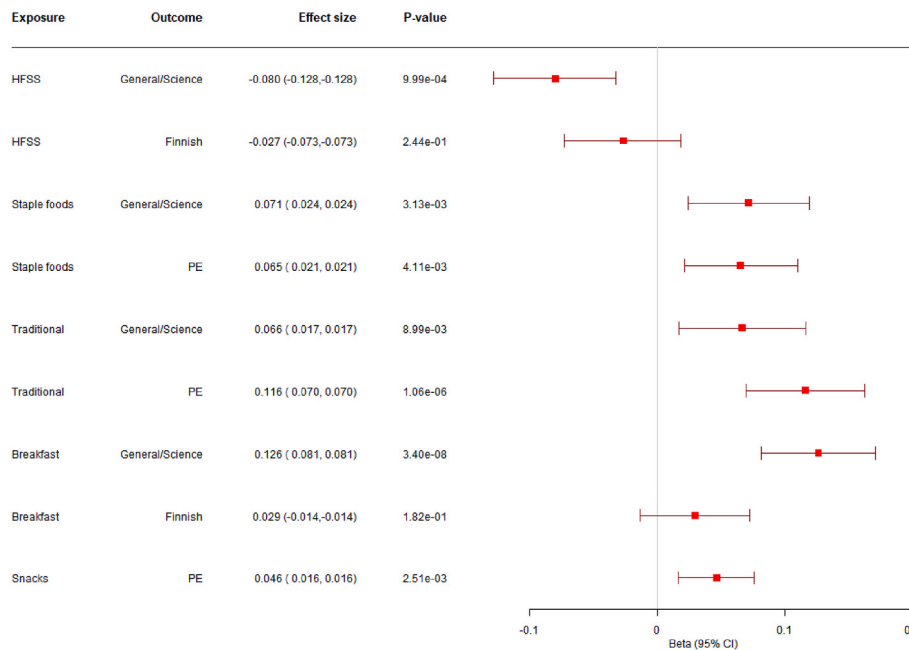
| Variables                     | General/Science | Finnish | PE    |
|-------------------------------|-----------------|---------|-------|
| Cumulative variance explained | 23.9%           | 20.0%   | 16.6% |
| Finnish language              | -               | 0.96    | -     |
| General subjects              | 0.47            | 0.37    | -     |
| Mathematics                   | 0.57            | -       | -     |
| Biology, Physics, Chemistry   | 0.90            | -       | -     |
| Art                           | -               | -       | -     |
| Physical Education            | -               | -       | 0.99  |

**Table 5**  
Pearson correlation coefficient matrix between a) dietary factors and b) school performance factors.

| a)              |                 |             |             |           |        |
|-----------------|-----------------|-------------|-------------|-----------|--------|
|                 | HFSS            | staple food | traditional | breakfast | snacks |
| HFSS            | 1               | -0.07       | -0.06       | -0.14     | 0.08   |
| staple food     | -0.07           | 1           | -0.08       | 0.05      | -0.01  |
| traditional     | -0.06           | -0.08       | 1           | 0.06      | 0.17   |
| breakfast       | -0.14           | 0.05        | 0.06        | 1         | -0.39  |
| snacks          | 0.08            | -0.01       | 0.17        | -0.39     | 1      |
| b)              |                 |             |             |           |        |
|                 | General/Science | Finnish     | PE          |           |        |
| General/Science | 1               | -0.05       | -0.01       |           |        |
| Finnish         | -0.05           | 1           | 0.002       |           |        |
| PE              | -0.01           | 0.002       | 1           |           |        |



**Fig. 2.** Results of the observational study: the effect of an additional weekly meal in dietary exposures on school performance outcomes. We conducted multivariable linear regressions, adjusting for sex, household income, family financial status, mother and father education. All variables were obtained from the Northern Finland Birth Cohort 1986 (NFBC1986).



**Fig. 3.** Results of one-sample Mendelian randomisation: the effect of an additional weekly meal in dietary exposures on school performance outcomes.

distinguishable from the null (−0.027, −0.073 to 0.019). The MR results were in agreement with the observational study, showing a positive effect of staple food diet (primarily chicken, fish, rice and pasta) on school performance in *general/science* (0.071, 0.024 to 0.119) and *PE* (0.065, 0.021 to 0.110). The analysis also confirmed that *traditional* food consumption was associated through MR with better educational outcomes in *PE* (0.116, 0.07 to 0.162), but not with performance in *general/science* (0.066, 0.017 to 0.116), which attenuated to the null after multiple testing correction. Eating *breakfast* was associated with school performance in *general/science* (0.126, 0.081 to 0.171). There was not enough evidence to support the observed positive association of *eating*

*breakfast* with school performance in *Finnish* language (0.029, −0.014 to 0.072). Lastly, eating *snacks* was positively associated with *PE* performance (0.046, 0.016 to 0.075).

### 3.5. Sensitivity analyses

Supplementary Table S8 shows the genetic variants associated with at least one measured confounder below the threshold of  $P = 10^{-4}$ . The forest plot in Supplementary Fig. S11 shows that the excluded variants, which were associated with the measured potential confounders, do not influence the significance of the causal associations between diet and

school performance. The robustness of our results was tested through the use of other MR methods, including MR-Egger, weighted median and weighted mode MR, that are less sensitive to small violations of our assumptions, such as pleiotropy. The results in [Supplementary Table S9](#) show no evidence of pleiotropic effects in the variants involved in the analysis or a substantial change of our results.

### 3.6. Two-sample MR

We conducted two-sample MR to provide further support to our findings with independent datasets. The MR results of the first two-sample MR analysis stage for the effect of diet, using external datasets, on school performance from the NFBC1986 are provided in [Supplementary Tables S10–S11](#). Only three MR associations reached nominal significance using UK Biobank dietary traits from Pirastu et al. (Pirastu et al., 2022), but all attenuated to the null after Bonferroni correction. MR effect estimates are reported as units of change in school performance per unit increase in genetically predicted dietary phenotypes. An increase in genetically predicted fish consumption showed a positive effect on *PE* (0.54, 0.14 to 0.93), increasing fruit consumption was positively associated with performance in *Finnish* (0.41, 0.07 to 0.74) and increasing cooked vegetables consumption was also associated with *Finnish* (1.71, 0.08 to 3.33). Similarly, seven nominally significant MR associations were identified out of 180 tests using UK Biobank dietary PCs derived from Cole et al. (Cole et al., 2020), which did not survive the Bonferroni correction. Among others, PC42 – a staple food diet component – was positively associated with *general/science* (1.73, 0.46 to 2.99) and PC16 – an HFSS component – was negatively associated with *general/science* (−0.68, −1.24 to −0.13). Principal component loadings derived from Cole et al. can be found in [Supplementary Table S12](#).

In the second stage of the two-sample MR analysis using external datasets on cognition-related phenotypes as outcomes, we identified 6 nominally significant associations out of 126 tests, when using the Pirastu et al. dietary traits as exposures, which could be attributed to chance findings, since they did not retain their significance after the Bonferroni correction ([Supplementary Table S13](#)). Interestingly, we identified 13 significant associations that retained their significance after correcting for multiple tests ([Supplementary Table S14](#)). More specifically, we found that whole grain bread consumption (PC1) was

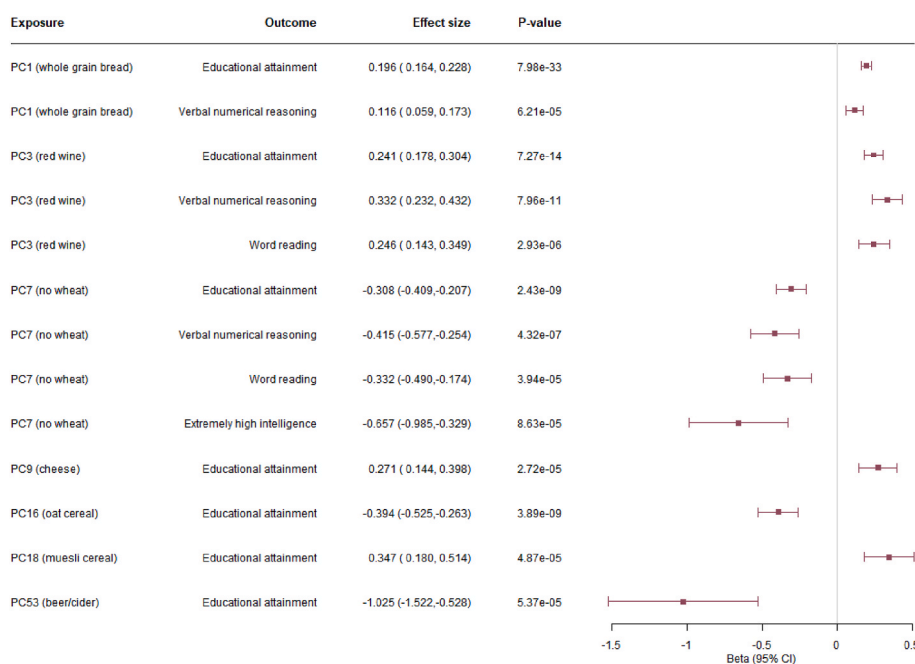
associated with higher educational attainment and verbal-numerical reasoning (0.196, 0.164 to 0.228) and (0.116, 0.059 to 0.173), respectively. Surprisingly, red wine consumption (PC3) was associated with higher educational attainment (0.241, 0.178 to 0.304), verbal-numerical reasoning (0.332, 0.232 to 0.432) and word reading (0.246, 0.143 to 0.349). No wheat eating (PC7) was associated with lower educational attainment (−0.308, −0.409 to −0.207), verbal-numerical reasoning (−0.415, −0.577 to −0.254), word reading (−0.332, −0.490 to −0.174) and extremely high intelligence (−0.657, −0.985 to −0.329), cheese consumption was associated with higher educational attainment (0.271, 0.144 to 0.398), as was muesli cereal consumption (PC18) (0.347, 0.180 to 0.514). Last, beer/cider (PC53) and oat cereal consumption (PC16) were associated with lower educational attainment (−1.025, −1.522 to −0.528) and (−0.394, −0.525 to −0.263), respectively. Significant associations are shown in [Fig. 4](#).

## 4. Discussion

The purpose of this work was to explore the effect of diet on school performance in adolescents in the NFBC1986 and validate findings in independent cohorts. Our genetic findings provide suggestive evidence of a potentially causal association of diet with school performance. More specifically, in the observational part of this study, negative associations between HFSS food and school performance, and positive associations between staple food diet, traditional meal eating, eating breakfast and having snacks were found with school performance in various subjects. Most findings were confirmed by the one-sample MR analysis findings, whereas two-sample MR findings provided inconclusive evidence of associations between various dietary traits and school performance or cognition-related traits.

Dietary principal components which could be described as whole grain bread, wheat, cheese, muesli oat and red wine consumption were associated with higher educational attainment and cognition-related phenotypes whereas beer was associated with lower educational attainment.

The traditional Finnish diet, up until the 1960's, was typified by a diet high in fat and saturated fat (Prättälä, 2003). With increased globalisation and socioeconomic changes, the Finnish diet has progressively altered in line with European health-related drives and lifestyles. Increases in vegetables and low-fat alternative products have been



**Fig. 4.** Two-sample Mendelian randomisation (MR) findings. Only significant MR associations are shown. Cognition-related trait beta estimates are shown per one unit increase in dietary exposures. For the exposures we used summary statistics from UK Biobank participants coming from Cole et al. (Cole et al., 2020) on dietary phenotypes. For the genetic associations with cognition-related phenotypes, we used genome-wide association study results from external datasets. In the exposure column, after the number of the dietary principal component (PC) from Cole et al. we denoted in parenthesis the food trait with the highest loading in that PC.

observed (Pietinen et al., 2001). In Finland, as in all developed countries, there has been an increased demand for plant-based products and a move away from traditional meat and dairy food choices (Huan-Niemi et al., 2020). Primary motivators for this change in behaviour relate to climate change (Roos et al., 2020) and perceived health benefits (Willett et al., 2019).

The current study supports and extends previous findings. Diets rich in fish and low saturated fat meats enhance educational attainment (Loughrey et al., 2017; Tapia-Serrano et al., 2021) while consuming HFSS foods, such as fried potatoes, sausages, soft drinks with sugar, chocolate, sweets, ready-to-eat meals, hamburgers, pizza, potato crisps and ice-cream, appears to be detrimental to educational attainment (Naveed et al., 2020). Evidence suggests that eating breakfast and having consistent mealtimes may be important factors in promoting academic success in children (Lien, 2007) but more research is needed to fully understand the relationship between timing of eating and school performance. Among these diets, it should be noted that fruit and vegetable intakes did not represent a significant component of any of the main patterns found. This outcome is aligned with a novel hypothesis that the impact of diet on educational attainment is associated with protein and carbohydrate macronutrient intakes rather than with micronutrient intakes (Jansen et al., 2020; Teisen et al., 2020). This suggestion needs to be investigated further, leveraging findings from Taba et al. (Taba et al., 2021) on the associations of blood metabolites with markers of diet and explore their impact on cognitive performance. Interestingly, the positive association of alcohol consumption with higher educational attainment has been already captured in previous MR studies (Rosoff et al., 2021; Zhou et al., 2021), which may be attributed to the relation of drinking culture with socio-economic status (Huerta & Borgonovi, 2010).

SNPs associated with HFSS had previously been reported as associated with heel bone density (Lim, 2018), blood cell measures (Astle et al., 2016), autoinflammatory problems and cardiometabolic relevant traits such as pulse pressure and high-density lipoprotein (HDL-c) cholesterol levels (Evangelou et al., 2018). SNPs for *staple food* eating had previously been reported as associated with physical activity (Doherty et al., 2018), being a morning person (Jones et al., 2019), and loneliness (Lim et al., 2018). SNPs associated with a *traditional* diet, eating *breakfast* and eating *snacks* have not been previously reported as associated with traits relevant to diet.

Information exploring the quality of the food eaten is still in its infancy, but the interpretation of our data could support the premise that dietary quality may play an influential role (Kadosh et al., 2021). Focus on assessing the dose dependent effects of healthier food intake in children and its impact on education poses few ethical concerns than exploring the detriment incurred by consuming HFSS foods. However, these data assert that it is within the adolescents with HFSS diets and skipping breakfast that the most educational attainment gains could be achieved. Researchers should also be aware that the relative impact of diet on educational attainment explains, at best, 13% of the overall variation in educational attainment. Most variables within this study explained 5% of the variation. Therefore, focus on diet should be tempered by realistic expectations of the potential impact their modulation could have.

While our study provides valuable insights, it is important to consider some limitations. Firstly, dietary and school performance data were obtained from self-reported questionnaires, and therefore may be subject to social desirability and recall bias. In addition, one-sample MR effect estimates using a relatively small sample size may be subject to weak instrument bias (biased towards the confounded estimation of association) or winner's curse bias (overestimation of effects) and therefore these findings need to be interpreted with caution. Furthermore, dietary and school performance factors identified by the exploratory factor analysis explained 15%–24% of the total variable variance. This was sufficient to obtain meaningful dietary cluster (Emmett et al., 2015) but could be potentially improved by increasing the sample size of

the study. A further limitation of our study is the possibility of residual confounding due to socio-economic factors that may bias the estimation of causal effect of behavioural traits, despite the relative robustness of Mendelian randomisation in comparison to traditional epidemiological studies.

Another issue was that dietary exploratory factors in NFBC1986 and dietary principal components in UK Biobank were not similarly represented by food loadings. This was due to the different nature of the datasets and availability of variables between the two studies. It is unclear therefore, if the significant associations found in the one-sample MR analysis that were not validated using external datasets were subject to type I error or indeed true associations that are not translatable to a middle-aged sample. To maximise statistical power, we have performed a multivariate imputation by chained equations in the exposure and outcome datasets, which is a useful technique to handle missing data. However, imputation cannot address non-response bias, which could occur when participants who do not respond to a study are systematically different from the ones who do respond. Therefore, imputation could affect the precision of estimates and can increase the uncertainty in the analysis.

Diet is a cultural characteristic and the associations observed here may not necessarily apply to other cultural backgrounds; although with increased globalisation and equity in development, diet does appear to be homogenising. Furthermore, our approach of linking diet to genetics and, by extension, to biological changes, makes it more likely that these findings will be more widely valid. The genetics of diet, especially at the adolescent stage of life, are still underexplored, which has prevented validation of the identified MR associations. Related to this point, the sample size used was satisfactorily large for meaningful statistical calculations but still modest in terms of statistical power, so that, instances where an MR association was not observed could be attributed to lack of statistical power.

To summarise, our work provides suggestive evidence through the Mendelian randomisation paradigm that would support a potentially causal association between diet and school performance. However, given the limitations, evidence was inconclusive and additional analyses are required to further explore the potential causal mechanisms underlying the observed associations. With successful triangulation of evidence that would support a connection of diet with school performance, this study could contribute to the statement that dietary interventions might be able to increase pupils' educational attainment. However, this should be considered as only one part of the environment relevant to education. The identified associations are part of a wider and more complex potentially causal network where additional interventions could reduce, or amplify, what was observed in this population. Considering the same questions in different educational and cultural settings would aid in understanding these relationships. Mapping the biological processes underpinning these findings will be integral to uncovering unbiased outcomes. Finally, providing healthy and nutritionally balanced school meals to all children may improve not only their physical health, but also extend the benefits to education outcomes; however, it seems that eliminating HFSS could have a larger effect on educational outcomes than providing healthier alternatives.

#### Consent for publication

Not applicable.

#### Availability of data and materials

Please contact author for data requests.

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### Author's contributions

Conceptualization: F.D. and T.D.; Funding acquisition: F.D. and T.D.; Formal Analysis: L.Z.; Data curation: L.Z.; Supervision: F.D., A.B. and T.D.; Methodology: L.Z., F.D., P.E. and T.D.; Resources: T.N., T.H. and M-R.J.; Writing – original draft: L.Z., F.D. and T.D.; Writing – review & editing: L.Z., F.D., P.E., A.B., T.N., T.H., M-R.J. and T.D.

### Ethical approval and consent to participate

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving research study participants were approved by the NFBC. Written informed consent was obtained from all subjects/patients.

### Declaration of competing interest

None declared.

### Data availability

Data will be made available on request.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.appet.2023.107036>.

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