

## Cognition, psychosis risk and metabolic measures in two adolescent birth cohorts†

## Original Article

**Cite this article:** Ramsay H, Barnett JH, Murray GK, Miettunen J, Mäki P, Järvelin M-R, Smith GD, Ala-Korpela M, Veijola J (2018). Cognition, psychosis risk and metabolic measures in two adolescent birth cohorts. *Psychological Medicine* **48**, 2609–2623. <https://doi.org/10.1017/S0033291718001794>

Received: 16 June 2017

Revised: 22 March 2018

Accepted: 19 June 2018

First published online: 24 July 2018

**Key words:**

ALSPAC; cognition; fatty acids; lipoprotein lipids; metabolomics; NFBC 1986; psychosis risk

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**Abstract**

**Background.** Psychoses, especially schizophrenia, are often preceded by cognitive deficits and psychosis risk states. Altered metabolic profiles have been found in schizophrenia. However, the associations between metabolic profiles and poorer cognitive performance and psychosis risk in the population remain to be determined.

**Methods.** Detailed molecular profiles were measured for up to 8976 individuals from two general population-based prospective birth cohorts: the Northern Finland Birth Cohort 1986 (NFBC 1986) and the Avon Longitudinal Study of Parents and Children (ALSPAC). A high-throughput nuclear magnetic resonance spectroscopy platform was used to quantify 70 metabolic measures at age 15–16 years in the NFBC 1986 and at ages 15 and 17 years in ALSPAC. Psychosis risk was assessed using the PROD-screen questionnaire at age 15–16 years in the NFBC 1986 or the psychotic-like symptoms assessment at age 17 years in ALSPAC. Cognitive measures included academic performance at age 16 years in both cohorts and general intelligence and executive function in ALSPAC. Logistic regression measured cross-sectional and longitudinal associations between metabolic measures and psychosis risk and cognitive performance, controlling for important covariates.

**Results.** Seven metabolic measures, primarily fatty acid (FA) measures, showed cross-sectional associations with general cognitive performance, four across both cohorts (low density lipoprotein diameter, monounsaturated FA ratio, omega-3 ratio and docosahexaenoic acid ratio), even after controlling for important mental and physical health covariates. Psychosis risk showed minimal metabolic associations.

**Conclusions.** FA ratios may be important in marking risk for cognitive deficits in adolescence. Further research is needed to clarify whether these biomarkers could be causal and thereby possible targets for intervention.

**Introduction**

Brain structure and function develop rapidly during adolescence. Problems with this development may be evident in cognitive performance problems or in psychiatric symptoms in

response to increasing challenges in the adolescent environment. Psychoses, especially schizophrenia and psychotic disorders are conceptualised as neurodevelopmental disorders (Murray and Lewis, 1988), the result of a series of insults in healthy brain development. In this neurodevelopmental process, the adolescent period plays an important role (Rapoport *et al.*, 2005; Paus *et al.*, 2008). Risk for psychosis is increasingly being measured at this age, both in clinical samples (Fusar-Poli *et al.*, 2013) and at a general population level (Kelleher *et al.*, 2012). The static and dynamic cognitive deficits that are known to precede schizophrenia, such as deficits in general intelligence and specific cognitive domains, have also increasingly been considered (Reichenberg *et al.*, 2010), both as markers of risk for later illness and as independent predictors of functioning in young adults with mental disorders (Fett *et al.*, 2011; McIntyre *et al.*, 2013; Holshausen *et al.*, 2014) and at risk states for mental disorders (Carrión *et al.*, 2013). Better understanding of the biological signature of brain development and of relative problems in brain development has the potential to improve public mental health and individual functional outcomes.

Metabolomics approaches utilising nuclear magnetic resonance (NMR) spectroscopy have shown increasing promise in characterising the molecular signature of body fluids for disease risk (Ala-Korpela, 2007a, 2007b). NMR spectroscopy is particularly suited to study the molecular signature of disease and event risk in larger epidemiological samples. The approach has uncovered metabolic associations with: disease risk states, such as obesity (Würtz *et al.*, 2014) and insulin resistance (Würtz *et al.*, 2012); illnesses and illness events, such as diabetes (Wang *et al.*, 2015), cardiovascular events (Würtz *et al.*, 2015), and all-cause mortality (Fischer *et al.*, 2014); and health-related behaviours, such as alcohol consumption (Würtz *et al.*, 2016) and physical activity (Kujala *et al.*, 2013).

In the study of brain development and disorders, NMR spectroscopy approaches have identified patterns regarding schizophrenia (Holmes *et al.*, 2006) and mild cognitive impairment in older people (Tukiaainen *et al.*, 2008), and have suggested possible molecular associations with cognitive reaction times in young people with schizophrenia (Scoriels *et al.*, 2015). Mass spectrometry metabolomics approaches have also shown promise in mapping molecular features of schizophrenia (Orešić *et al.*, 2011; He *et al.*, 2012; Yang *et al.*, 2013) and of cognitive impairment in older people (Trushina *et al.*, 2013; Mapstone *et al.*, 2014).

Difficulties in adolescent cognitive performance and psychosis risk are associated with negative outcomes in adulthood. To our knowledge, metabolomics approaches have not been utilised to examine these adolescent characteristics at a general population level. Characterisation of the metabolic measures associated with relatively poorer cognition and psychosis risk in adolescence has the potential to improve understanding of their development. This study examines if there are cross-sectional and longitudinal associations between a panel of metabolic measures and broad cognitive ability and psychosis risk in late adolescence.

## Methods

### Study populations

Serum metabolic profiles were quantified from two independent general population-based birth cohorts: the Northern Finland Birth Cohort 1986 (NFBC 1986) and the Avon Longitudinal Study of Parents and Children (ALSPAC) from the United Kingdom (UK).

The NFBC 1986 is a longitudinal birth cohort, covering 99% of births in the two northernmost provinces of Finland, Oulu and Lapland, who had an expected delivery date between 1 July 1985 and 30 June 1986, details of which have been described elsewhere (Järvelin *et al.*, 1993; <http://kelo.oulu.fi/NFBC/>). In brief, the cohort consisted of 9432 live-born children, of whom 6985 (76%) completed questionnaires (Miettunen *et al.*, 2008; Taanila *et al.*, 2009; Koivukangas *et al.*, 2010; Mäki *et al.*, 2014; Metcalf *et al.*, 2017) and 5606 (59%) provided serum samples for NMR metabolomics analysis at age 15–16 years. The study received ethics approval from the ethics committees of the Northern Ostrobothnia Hospital District and the University of Oulu and all participants and their parents provided written informed consent.

ALSPAC is a longitudinal birth cohort, consisting of 72% of eligible expectant mothers in Bristol, UK, and surrounding areas, who had an expected delivery date between 1 April 1991 and 31 December 1992, details of which have been described elsewhere (Golding *et al.*, 2001; Boyd *et al.*, 2013; <http://www.bristol.ac.uk/alspac/>). In brief, this consisted of 14 062 live-born children. Of these, 9985 were invited to follow-up at age 15 years and 5253 attended (and 3366 provided plasma samples for NMR-based metabolomics). A further 10 101 were invited to follow-up at age 17 years (including 782 not in the original sample), of whom 5217 attended (and 3176 provided plasma samples for NMR-based metabolomics). Please note that the study website contains details of all the data that is available through a fully searchable data dictionary (<http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/>). Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees, and all participants and their parents provided written informed consent.

### Molecular profiling

NMR spectroscopy allows for the application of metabolomics approaches in large-scale epidemiological samples (Soininen *et al.*, 2015) and has been extensively used in multiple large-scale epidemiological studies (Mahendran *et al.*, 2013; Auro *et al.*, 2014; Fischer *et al.*, 2014; Würtz *et al.*, 2015; Würtz *et al.*, 2016). The precise methodology is described elsewhere (Soininen *et al.*, 2009, 2015). In brief, the NFBC 1986 participants provided serum samples at age 16 years, while ALSPAC participants provided EDTA plasma samples at ages 15 and 17 years and these were stored at  $-80^{\circ}\text{C}$  for subsequent biomarker profiling. A high-throughput NMR spectroscopy metabolomics platform was used for the quantification of 70 metabolic measures (Soininen *et al.*, 2015), representing a broad molecular signature of systemic metabolism, including lipoprotein lipids and subclasses, lipoprotein size, fatty acids (FAs), ratios of FA subclasses to total FAs, amino acids, gluconeogenesis- and glycolysis-related metabolites, ketone bodies and others. All measurements were performed at the NMR Metabolomics Laboratory at the University of Eastern Finland, Kuopio, Finland. Uniform sample preparation protocols and NMR instrumentation and parameter were used. Details have been described elsewhere (Soininen *et al.*, 2009; Inouye *et al.*, 2010). The NFBC 1986 and ALSPAC samples were measured separately using identically calibrated instrumentation, though it is notable that NMR-based metabolic quantifications are stable over long periods (Kettunen *et al.*, 2016). Standardised protocols were used to minimise any issues around sample transport and sample age.

### Academic performance

Our outcomes of interest were cognitive measures and psychosis risk across the two samples. Our main cognitive measure was academic performance, measured in both samples at age 16 years. In the NFBC 1986 information on academic performance was provided by the National Application Register for Upper Secondary Education, Finland, based on nationally comparable grades of the final assessment of basic education. They describe the level of performance in relation to the objectives of basic education at the end of grade 9 (age 16 years). In ALSPAC the data on academic performance were provided by the United Kingdom Department of Education, where performance was measured using the overall points score derived from the General Certificate in Secondary Education (GCSE) or equivalent exam. As we were interested in predictors of poorer performance, in both samples the results were categorised to compare those with performance >1 standard deviation below the mean with the remaining group with better performance.

### Cognition

Participants in the ALSPAC study performed additional cognitive tests at ages 15 and 17 years. The Wechsler Abbreviated Scale of Intelligence (WASI) was performed at age 15 years, at the same time as the measurement of metabolic measures. The N-back and Probability Reversal (PR) tests were performed at age 17 years, 2 years after measurement of metabolic measures. The WASI is a valid brief measure of general intelligence in children as well as adults (Saklofske *et al.*, 2000; Abu-Hilal *et al.*, 2011). The N-back and PR each measure components of executive function. The N-back task is a measure of working memory (Miller *et al.*, 2009). We utilised target identification accuracy on the 2-back task for this test. PR is a test of ability to adapt to specific contingencies. We utilised latency in stage 2 for this test, which was log-transformed for normality.

### Psychosis risk

Psychosis risk in adolescence was measured at age 16 years using the PROD-screen questionnaire (Heinimaa *et al.*, 2003) in the NFBC 1986 (Hurtig *et al.*, 2011; Therman *et al.*, 2011; Mäki *et al.*, 2014). This screening questionnaire includes 21 questions measuring lower level psychosis risk. Full-information item factor analysis has identified a three-dimensional (positive, negative and general) factor structure to the PROD-screen (Therman *et al.*, 2011). Based on these dimensions, we classified individuals as having psychosis risk where they endorsed six or more out of a total of eleven positive items (412/6041, 6%). This cut-off was utilised based on meta-analysis suggesting that the prevalence of psychotic experiences at age 16 is about 7.5% (Kelleher *et al.*, 2012).

Psychosis risk among ALSPAC participants was measured using the clinical interview for psychotic-like experiences ('PLIKS') clinical interview at age 17 years, which was conducted by trained psychology graduates. Three main domains of positive psychotic symptoms were elicited: hallucinations, delusions, and thought interference. Interviewers rated psychosis risk as absent, suspected or definitely psychotic. We classified individuals as having psychosis risk where they showed one or more definite symptoms on interview (Zammit *et al.*, 2009). Based on these criteria, we classified 232/4480 (5%) as having psychosis risk in this sample.

### Confounding variables

We considered three main potential confounders to any association between the metabolic measures and cognitive performance/psychosis risk: sex, socioeconomic status and body mass index (BMI). Sex is associated with academic performance and also with levels of various metabolic measures (Serbin *et al.*, 1990; Ishikawa *et al.*, 2014). Socioeconomic status is associated with academic performance and with lifestyle factors (e.g. diet) likely to influence metabolic measures (Coe *et al.*, 2013). The socioeconomic status of adolescents in the NFBC 1986 was controlled for using the variable 'maternal education'. At birth, mothers were asked about their own level of education attainment and this was classified into four groups: (1) up to 8 years of primary education; (2) 9–10 years of primary education; (3) vocational school or college for at least 6 months and; (4) commenced university education. Socioeconomic status was controlled for using the social class of the mother based on occupation in the ALSPAC sample. This included six groups: professional, managerial and technical, skilled non-manual, skilled manual, partly skilled, and unskilled. Both socioeconomic variables were treated as linear for the purposes of analyses. BMI was calculated from height and weight, which were measured during clinical examination in adolescence for both samples. The standard formula for BMI was used (weight (kg)/height (m)<sup>2</sup>).

In addition to controlling for these factors across both cohorts, it was possible to control for additional mental health factors (anxiety and depression, psychosis risk) and physical health factors (visits to a doctor in the past six months, physical exercise, healthy diet) in the NFBC sample. Anxiety and depression were measured at age 16 years using 16 questions from the Youth Self Report (Song *et al.*, 1994). Psychosis risk was assessed as outlined above, using the PROD-screen (Heinimaa *et al.*, 2003). Adolescents were asked at age 16 years about their physical health, physical exercise and diet. Number of visits to the doctor in the previous 6 months was used as a proxy for physical health, comparing those with 2 or more visits with those with 0 to 1 visits. Those who described lower levels of physical activity were compared with those with higher levels of physical activity, comparing 0–1 hour/week of brisk physical activity with >1 hour/week, excluding physical activity during school hours (Koponen *et al.*, 2008). Diet was considered healthy or unhealthy, depending on the amount of fruits, vegetables and berries used (with healthy considered as any of these on three or more days per week) (Koponen *et al.*, 2008).

### Statistics

Cognitive measures were transformed into binary outcomes for ease of interpretation, comparing individuals more than 1 standard deviation (s.d.) below the mean scores to the remainder of the sample. Psychosis risk status was a binary outcome, as described above. Metabolic measures with skewed distribution were normalised by log-transformation prior to analyses and all metabolic measures were *z*-transformed to examine the effect of each 1 standard deviation increase on the odds for the cognitive outcome. The metabolic measures were therefore transformed into ordinal measures for interpretation, but they were treated as continuous for the purpose of analysis. Due to the correlated nature of the data, principal component analysis was used to evaluate the appropriate number of independent tests to correct for multiple testing. In this case, 90% of the variance in the 70 measures was explained by at most 12 principal components in each cohort.

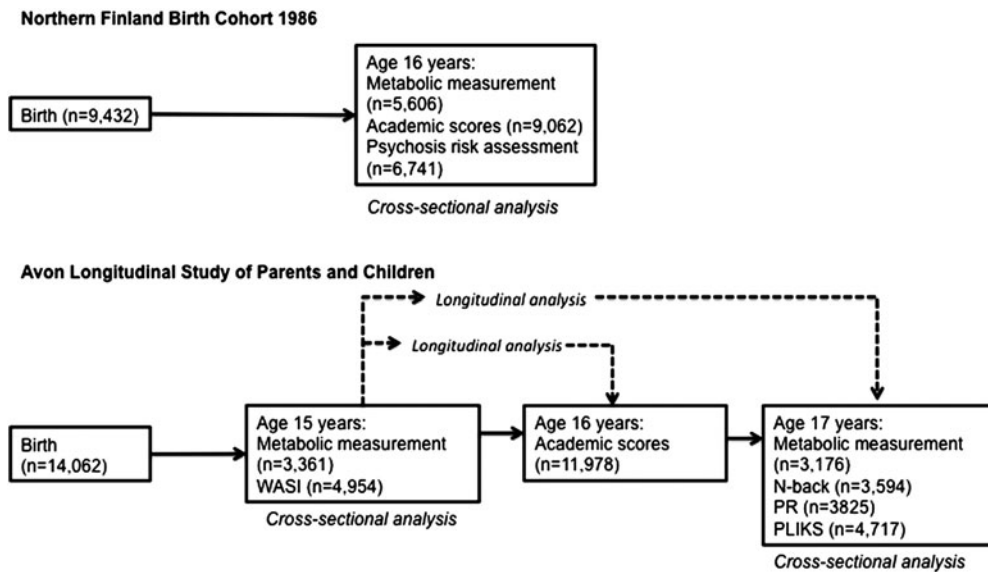


Fig. 1. Overview of cross-sectional and longitudinal measurements.

Multiple testing correction, therefore, accounted for 12 independent tests using the Bonferroni method, resulting in a corrected  $p$  value of  $<0.004$ .

Our primary hypotheses were that cognitive difficulties and psychosis risk status (the outcomes of interest) were associated with differences in metabolic measures (the main exposure of interest), both cross-sectionally and longitudinally. The temporal relationship between exposures and outcomes and the cross-sectional and longitudinal associations under review are presented in Fig. 1. For the cross-sectional analyses, a logistic regression model was fitted for each outcome measure (academic performance at age 16 years in the NFBC 1986, psychosis risk at age 16 years in the NFBC 1986, WASI performance at age 15 years for ALSPAC, executive skills performance at age 17 years for ALSPAC, and psychosis risk at age 17 years for ALSPAC), using metabolic measures as the explanatory variable. Individuals with higher cognitive performance or lower psychosis risk were used as the reference group, so the odds ratios calculated reflect the association between increasing standard deviations of metabolic measures and poorer cognitive performance/higher psychosis risk. The two cohorts were analysed separately. In all analyses, we initially adjusted for sex (model 1). Where an association was observed at the required  $p$  value, we sequentially adjusted for socioeconomic status (model 2) and BMI (model 3).

Additional longitudinal analyses were performed with ALSPAC (see Fig. 1). In this case, cognitive performance and psychosis risk were also the outcomes of interest and metabolic measures were the explanatory variables of interest. Logistic regression models were fitted for each outcome (academic performance at age 16 years, executive function at age 17 years, psychosis risk at age 17 years) with metabolic measures taken at age 15 years as the explanatory variables of interest. In these analyses, we initially adjusted for sex (model 1) and, where an association was observed at the required  $p$  value, we then adjusted sequentially for socioeconomic status (model 2) and BMI (model 3).

Secondary hypotheses were tested in the cohorts separately. Our first secondary hypothesis was that metabolic associations with cognitive performance were not explained by anxiety and

depression but were influenced by psychosis risk status. In order to test this, we compared model 3 above to a model controlling for depression and anxiety (model 4) in the NFBC 1986. We then compared this model 4 (or model 3 in the case of the ALSPAC) with a further model, controlling for psychosis risk (model 5). These models controlling for psychosis risk were then compared with a model considering the interaction between psychosis risk and the metabolic measures. Our second secondary hypothesis was that metabolic associations with cognitive performance were not explained by physical health factors. This could only be tested in the NFBC 1986 sample, by comparing model 3 to a model controlling for doctors visits in the previous 6 months, physical exercise and healthy diet (model 6).

## Results

The characteristics of participants in the two cohorts are given in Table 1. Higher academic performance in both samples was associated with female sex, with having mothers who were more educated or from a higher social class and with lower mean BMI (more markedly in ALSPAC). In the NFBC 1986 sample, higher academic performance was associated with a higher score on anxiety and depression items ( $p < 0.001$ ), higher rates of more physical activity ( $p < 0.001$ ) and higher rates of a healthy diet ( $p < 0.001$ ). In the ALSPAC sample, higher academic performance was associated with lower rates of psychosis risk ( $p < 0.001$ ).

### Cross-sectional associations between metabolic measures and cognitive performance and psychosis risk

A range of apolipoprotein and FA-related metabolic measures showed cross-sectional associations with broad cognitive performance (see Fig. 2). In the NFBC 1986 sample, 18 metabolic measures were associated with academic performance at age 16 years. These included lipids in lipoproteins, lipoprotein diameters, triglyceride measures and, particularly frequently, FA ratios. Among these, low density lipoprotein (LDL) diameter, monounsaturated FA (MUFA) level, ratios of FA subclasses (MUFA, polyunsaturated



**Table 1.** Characteristics of the two cohorts

| Variable                                    | NFBC 1986 higher academic score | Lower academic score | ALSPAC higher academic score | Lower academic score |
|---|---------------------------------|----------------------|------------------------------|----------------------|
| Demographic status                          |                                 |                      |                              |                      |
| Sex   |                                 |                      |                              |                      |
| Male  | 3536 (76%)                      | 1110 (24%)           | 4886 (81%)                   | 1144 (19%)           |
| Female                                      | 3988 (90%)                      | 428 (10%)            | 5233 (88%)                   | 713 (12%)            |
| Maternal education/social class             |                                 |                      |                              |                      |
| Least/classes III-M/IV/V                    | 1537 (75%)                      | 516 (25%)            | 1612 (81%)                   | 388 (19%)            |
| Middle/IV-NM                                | 2886 (82%)                      | 647 (18%)            | 3506 (89%)                   | 448 (11%)            |
| Most/classes I, II                          | 2123 (93%)                      | 151 (7%)             | 2488 (93%)                   | 179 (7%)             |
| Mental health status                        |                                 |                      |                              |                      |
| Psychosis risk                              |                                 |                      |                              |                      |
| Lower risk                                  | 5171 (87%)                      | 785 (13%)            | 3677 (95%)                   | 184 (5%)             |
| Higher risk                                 | 343 (86%)                       | 57 (14%)             | 175 (86%)                    | 28 (14%)             |
| Depression and anxiety scores               | 20.127 (4.347)                  | 19.463 (4.310)       | –                            | –                    |
| Taking medication for anxiety or depression |                                 |                      |                              |                      |
| No  | 6073 (86%)                      | 969 (14%)            | –                            | –                    |
| Yes   | 46 (84%)                        | 9 (16%)              | –                            | –                    |
| Physical health status                      |                                 |                      |                              |                      |
| BMI – mean (s.d.)                           | 21.1 (3.4)                      | 21.4 (4.0)           | 22.8 (4.1)                   | 24.2 (5.7)           |
| Visits to doctor in past 6 months           |                                 |                      |                              |                      |
| 0–1 visits                                  | 4216 (87%)                      | 630 (13%)            |                              |                      |
| 2 + visits                                  | 1649 (86%)                      | 275 (14%)            |                              |                      |
| Taking insulin                              |                                 |                      |                              |                      |
| No  | 5945 (86%)                      | 931 (14%)            |                              |                      |
| Yes   | 24 (92%)                        | 2 (8%)               |                              |                      |
| Physical activity                           |                                 |                      |                              |                      |
| >1 hour/week                                | 3913 (89%)                      | 501 (11%)            |                              |                      |
| ≤1 hour/week                                | 2020 (82%)                      | 433 (18%)            |                              |                      |
| Diet  |                                 |                      |                              |                      |
| Healthy                                     | 3861 (91%)                      | 375 (41%)            |                              |                      |
| Unhealthy                                   | 2068 (79%)                      | 543 (21%)            |                              |                      |

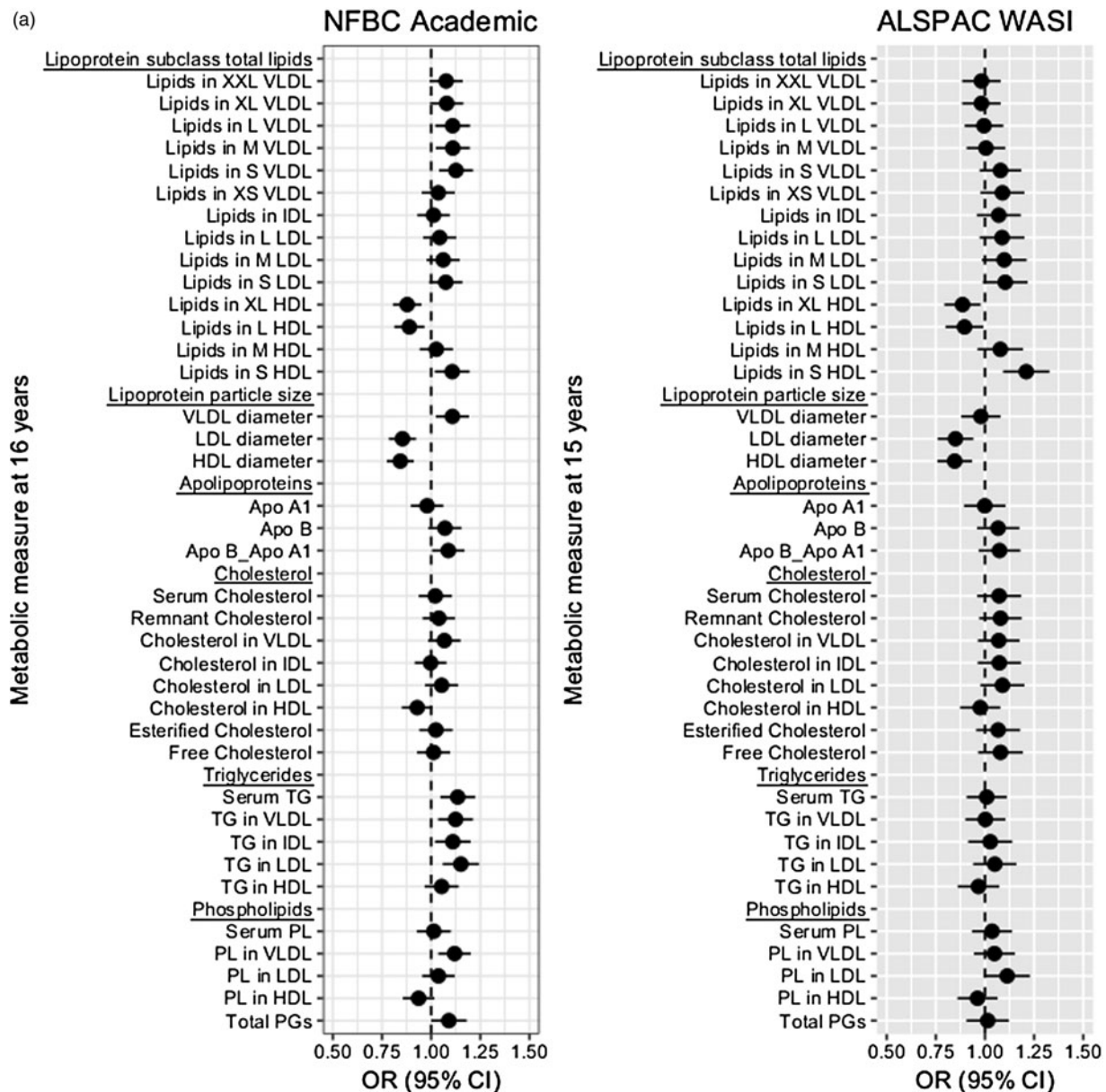
NFBC 1986, Northern Finland Birth Cohort 1986; ALSPAC, Avon Longitudinal Study of Parents and Children.

FA (PUFA), omega-6, omega-3, docosahexaenoic acid (DHA), % unsaturation) to total FAs, citrate and creatinine remained associated with academic performance even after controlling for maternal education and BMI (see Table 2). In ALSPAC, nine metabolic measures were associated with general intelligence scores at age 15 years. Among these, lipids in small HDL, LDL diameter, FA levels (omega-3, DHA), and ratios of FA subclasses (MUFA, omega-3, DHA) to total FAs were associated at  $p < 0.004$  after controlling for maternal social class and BMI.

There were no cross-sectional associations at  $p < 0.004$  between any of the metabolic measures at age 17 years and PR at age 17 years (see online Supplementary Fig. S1). In the case of N-back accuracy, increasing standard deviations of the two DHA measures were associated with better performance. DHA level at age 17 years

was associated in model 1 (OR 0.81, 95% CI 0.70–0.93,  $p = 0.004$ ), borderline associated in model 2 (OR 0.79, 95% CI 0.66–0.93,  $p = 0.006$ ) and associated in model 3 (OR 0.77, 95% CI 0.65–0.92,  $p = 0.003$ ). Ratio of DHA to total FAs at age 17 years was associated with N-back accuracy in model 1 (OR 0.78, 95% CI 0.68–0.90,  $p = 0.001$ ), model 2 (OR 0.76, 95% CI 0.64–0.90,  $p = 0.001$ ) and model 3 (OR 0.76, 95% CI 0.64–0.90,  $p = 0.001$ ).

There was minimal evidence against the null hypothesis for cross-sectional associations between FA levels and psychosis risk in the NFBC 1986 sample, with none showing associations at  $p < 0.004$  (see online Supplementary Fig. S2). In the ALSPAC sample, there were weak cross-sectional associations between DHA levels and psychosis risk, though these did not reach our  $p$  value threshold (see online Supplementary Fig. S2). One



**Fig. 2.** Cross-sectional associations between metabolic measures and cognitive performance in adolescence, controlling for sex.

metabolic measure, acetate, was associated with lower risk for psychosis (OR 0.37, 95% CI 0.16–0.57,  $p < 0.001$ ). The evidence for this association against the null hypothesis was weaker after controlling for maternal social class (OR 0.38,  $p = 0.003$ ) and BMI (OR 0.42,  $p = 0.008$ ).

#### *Longitudinal associations between metabolic measures and cognitive performance and psychosis risk*

The longitudinal associations between metabolic measures and cognitive performance are presented in Fig. 3. In brief, there were various associations between metabolic measures associated with apolipoproteins and FAs and cognitive function longitudinally. Specifically, nine measures at age 15 years were associated with academic performance at age 16 years (lipids in large HDL, LDL diameter, HDL diameter, MUFA, DHA, ratios of FA subgroups to total FAs) (see Table 3). Among these, four remained associated after

controlling for maternal social class and BMI: higher LDL diameter, MUFA level, ratios of MUFA and DHA to total FAs. Five FA measures at age 15 years were associated with PR latency at age 17 years (PUFA, omega-6, linoleic acid, omega-3 and DHA) at  $p < 0.004$  and these associations were broadly similar after controlling for maternal social class and BMI.

No metabolic measures at age 15 years were associated with N-back accuracy at 17 years or psychosis risk at 17 years (see online Supplementary Fig. S3).

The observed cross-sectional and longitudinal associations are presented together in Table 4.

#### *Metabolic measures and cognitive performance in the context of mental and physical health factors*

Cross-sectional associations between metabolic measures and cognitive performance, which were significant in both samples,

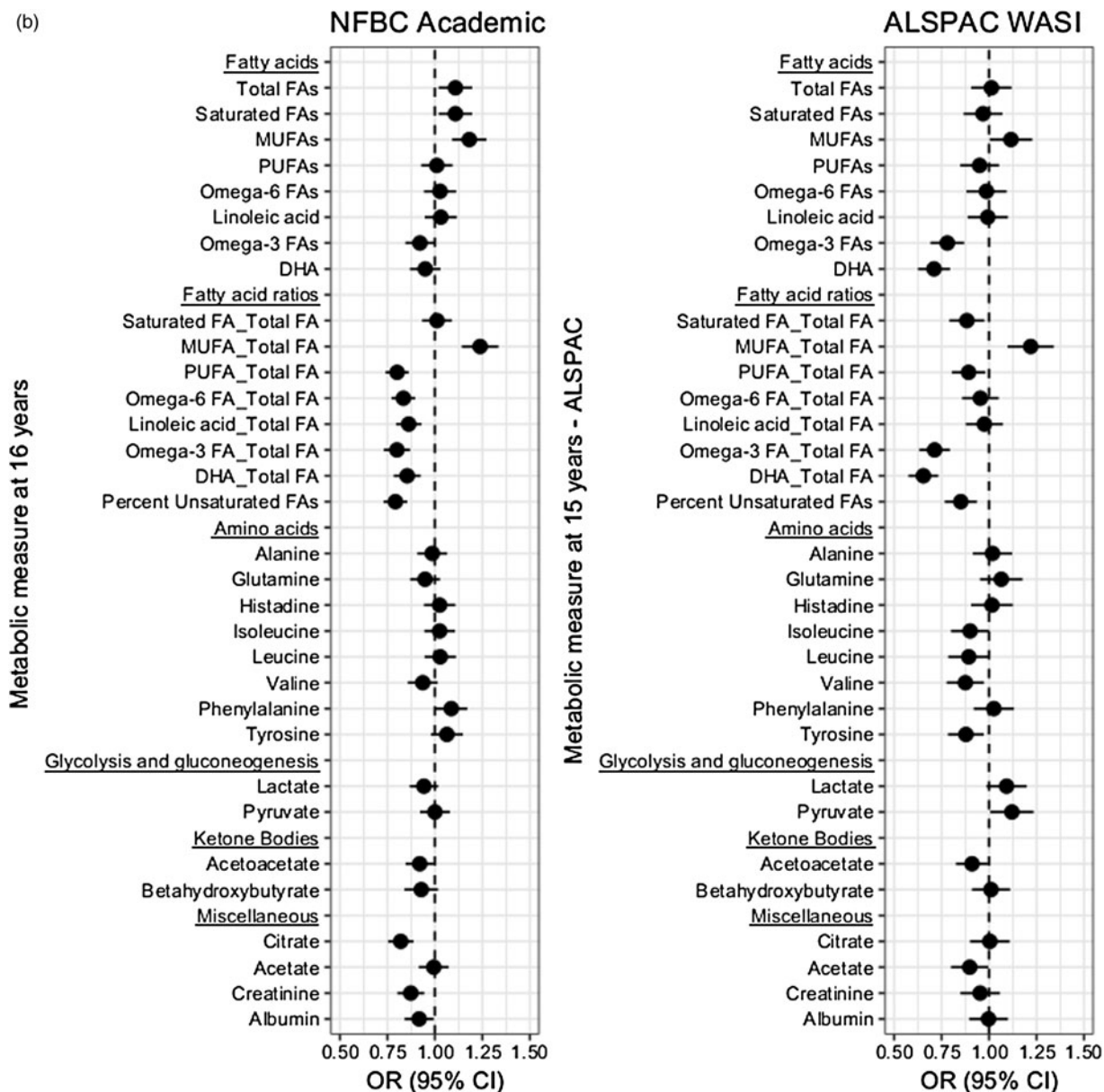


Fig. 2. Continued.

were further tested by controlling for mental health factors and physical health factors. Results of these analyses are presented in Table 5. The metabolic measures-cognitive associations were not attenuated in the NFBC 1986 sample after controlling for anxiety and depression at age 16 years. The associations were also not attenuated after controlling for psychosis risk, in either the NFBC 1986 or the ALSPAC. There were no interactions between the metabolic measures and psychosis risk in predicting cross-sectional cognitive outcomes for the NFBC 1986 or the ALSPAC.

There was no attenuation in the association between metabolic measures and academic performance after controlling for physical health factors (doctor’s visits in the previous 6 months, exercise level and healthy diet) in the NFBC 1986 (see Table 5 to compare models).

### Discussion

In this study, across two general population-based cohorts, we have characterised the associations between metabolic measures and broad brain function in late adolescence. The main findings were that FA metabolic measures and, to a lesser extent, apolipoprotein measures, were associated with adolescent brain function. These findings were stronger and more consistent in cross-sectional analyses and where academic scores and general intelligence were the outcomes. These findings did not appear to be related to differences in mental health factors or physical health factors between groups. Findings in the case of executive function were more nuanced, with associations between FA measures at age 15 years and one of our two tests of executive function (PR latency) at age 17 years, and weaker cross-sectional associations

**Table 2.** Cross-sectional associations between metabolic measures and cognitive performance, controlling for covariates

| Metabolic measure        | NFBC 1986 ( <i>n</i> = 5510) |                          |                          | ALSPAC ( <i>n</i> = 3022) |                          |                          |
|--------------------------|------------------------------|--------------------------|--------------------------|---------------------------|--------------------------|--------------------------|
|                          | Model 1                      | Model 2                  | Model 3                  | Model 1                   | Model 2                  | Model 3                  |
| Lipids in small VLDL     | <b>1.13 (1.04, 1.22)</b>     | 1.08 (0.99, 1.18)        | 1.08 (0.99, 1.18)        | –                         | –                        | –                        |
| Lipids in very large HDL | <b>0.88 (0.81, 0.95)</b>     | 0.92 (0.84, 1.00)        | 0.92 (0.84, 1.01)        | –                         | –                        | –                        |
| Lipids in small HDL      | –                            | –                        | –                        | <b>1.21 (1.10, 1.33)</b>  | <b>1.27 (1.14, 1.42)</b> | <b>1.32 (1.16, 1.50)</b> |
| LDL diameter             | <b>0.85 (0.79, 0.93)</b>     | <b>0.87 (0.80, 0.95)</b> | <b>0.87 (0.80, 0.95)</b> | <b>0.85 (0.076, 0.95)</b> | <b>0.83 (0.74, 0.94)</b> | <b>0.78 (0.68, 0.91)</b> |
| HDL diameter             | <b>0.84 (0.78, 0.91)</b>     | 0.89 (0.81, 0.97)        | 0.89 (0.81, 0.97)        | <b>0.85 (0.76, 0.94)</b>  | 0.87 (0.77, 0.98)        | 0.95 (0.82, 1.09)        |
| Serum TG                 | <b>1.14 (1.05, 1.23)</b>     | 1.08 (1.00, 1.18)        | 1.08 (0.99, 1.18)        | –                         | –                        | –                        |
| TG in VLDL               | <b>1.12 (1.04, 1.22)</b>     | 1.07 (0.99, 1.17)        | 1.07 (0.98, 1.17)        | –                         | –                        | –                        |
| TG in LDL                | <b>1.15 (1.06, 1.25)</b>     | 1.12 (1.02, 1.22)        | 1.12 (1.02, 1.22)        | –                         | –                        | –                        |
| PL in VLDL               | <b>1.12 (1.04, 1.21)</b>     | 1.07 (0.99, 1.17)        | 1.07 (0.98, 1.17)        | –                         | –                        | –                        |
| MUFAs                    | <b>1.18 (1.09, 1.27)</b>     | <b>1.15 (1.05, 1.25)</b> | <b>1.15 (1.05, 1.25)</b> | –                         | –                        | –                        |
| Omega-3 FAs              | –                            | –                        | –                        | <b>0.78 (0.70, 0.87)</b>  | <b>0.82 (0.73, 0.94)</b> | <b>0.76 (0.65, 0.88)</b> |
| DHA                      | –                            | –                        | –                        | <b>0.71 (0.63, 0.80)</b>  | <b>0.76 (0.66, 0.87)</b> | <b>0.74 (0.63, 0.87)</b> |
| MUFA/total FA            | <b>1.24 (1.15, 1.34)</b>     | <b>1.20 (1.11, 1.31)</b> | <b>1.20 (1.10, 1.31)</b> | <b>1.22 (1.10, 1.35)</b>  | <b>1.23 (1.10, 1.38)</b> | <b>1.29 (1.13, 1.48)</b> |
| PUFA/total FA            | <b>0.80 (0.74, 0.86)</b>     | <b>0.83 (0.76, 0.90)</b> | <b>0.83 (0.76, 0.90)</b> | –                         | –                        | –                        |
| Omega-6/total FA         | <b>0.83 (0.77, 0.90)</b>     | <b>0.87 (0.80, 0.94)</b> | <b>0.87 (0.80, 0.94)</b> | –                         | –                        | –                        |
| LA/total FA              | <b>0.86 (0.80, 0.93)</b>     | 0.89 (0.82, 0.97)        | 0.89 (0.82, 0.97)        | –                         | –                        | –                        |
| Omega-3/total FA         | <b>0.80 (0.73, 0.87)</b>     | <b>0.80 (0.73, 0.88)</b> | <b>0.80 (0.73, 0.88)</b> | <b>0.71 (0.64, 0.80)</b>  | <b>0.74 (0.65, 0.84)</b> | <b>0.65 (0.55, 0.76)</b> |
| DHA/total FA             | <b>0.85 (0.79, 0.93)</b>     | <b>0.87 (0.79, 0.95)</b> | <b>0.86 (0.79, 0.94)</b> | <b>0.65 (0.58, 0.74)</b>  | <b>0.69 (0.61, 0.79)</b> | <b>0.67 (0.57, 0.78)</b> |
| Unsaturated FA           | <b>0.79 (0.73, 0.86)</b>     | <b>0.82 (0.75, 0.89)</b> | <b>0.81 (0.75, 0.89)</b> | <b>0.85 (0.77, 0.94)</b>  | 0.86 (0.77, 0.96)        | 0.91 (0.80, 1.04)        |
| Citrate                  | <b>0.82 (0.76, 0.89)</b>     | <b>0.84 (0.77, 0.92)</b> | <b>0.84 (0.77, 0.92)</b> | –                         | –                        | –                        |
| Creatinine               | <b>0.87 (0.80, 0.95)</b>     | 0.88 (0.81, 0.96)        | <b>0.88 (0.80, 0.96)</b> | –                         | –                        | –                        |

VLDL, very low density lipoprotein; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglycerides; PL, phospholipids; FA, fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; DHA, docosahexaenoic acid.

Model 1 controlled for sex; Model 2 controlled for sex and maternal education/socioeconomic status; Model 3 controlled for sex, maternal education/socioeconomic status and BMI.

Bold =  $p < 0.004$ .

also observed for omega-3 at age 15 years. Findings for psychosis risk were fewer and weaker.

### Metabolic measures and general intelligence

While two lipoprotein metabolic measures (lipids in small HDL, LDL diameter) were associated with general intelligence, a range of FA levels and ratios were associated on both cross-sectional and longitudinal analyses. The presence of cross-sectional and longitudinal associations across two cohorts adds weight to these results. The observed associations for general intelligence are also meaningful in their strength. Each standard deviation increase in these FA measures showed reduced odds of between 0.62 and 0.87 or increased odds of between 1.15 and 1.50 of performing more than 1 standard deviation from the mean (poorest performing 15.8% of sample). While these associations are not large, they are meaningful.

There are a number of potential explanations for the findings. Firstly, there may be lifestyle factors, associated with academic performance and FA ratios that are playing a causal role. Placing these results in the context of other metabolomics work provides potential clues in this area. The pattern of FAs observed here has been noted in some other studies, particularly with regard to physical

activity (Kujala *et al.*, 2013) and cardiovascular events (Würtz *et al.*, 2015), while different patterns have been observed for other outcomes (e.g. for alcohol consumption, Würtz *et al.*, 2016). It was, therefore, possible that observed associations between metabolic measures and cognition reflected a generally healthy metabolic profile associated with cognitive performance or the effects of physical activity on cognitive performance. This study suggests this explanation is unlikely. Controlling for three significant physical health factors (doctor visits, physical exercise and diet) did not significantly impact on the associations between the four metabolic factors most consistently associated with cognitive performance. In addition, controlling for significant mental health factors that impact on cognition, anxiety and depression and psychosis risk, did not impact on the observed associations.

Secondly, the metabolic measures may be playing a causal role in terms of general cognitive ability. However, the results observed regarding omega-3 ratios provide very limited evidence in support of Bradford Hill's criteria for causality (Bradford Hill, 1965). These general guidelines suggest that strength, consistency and specificity of associations support causality, along with temporality, biological gradient, plausibility, coherence, experiment and analogy. Specifically, we have observed a moderate strength association, consistent findings between studies and limited temporal



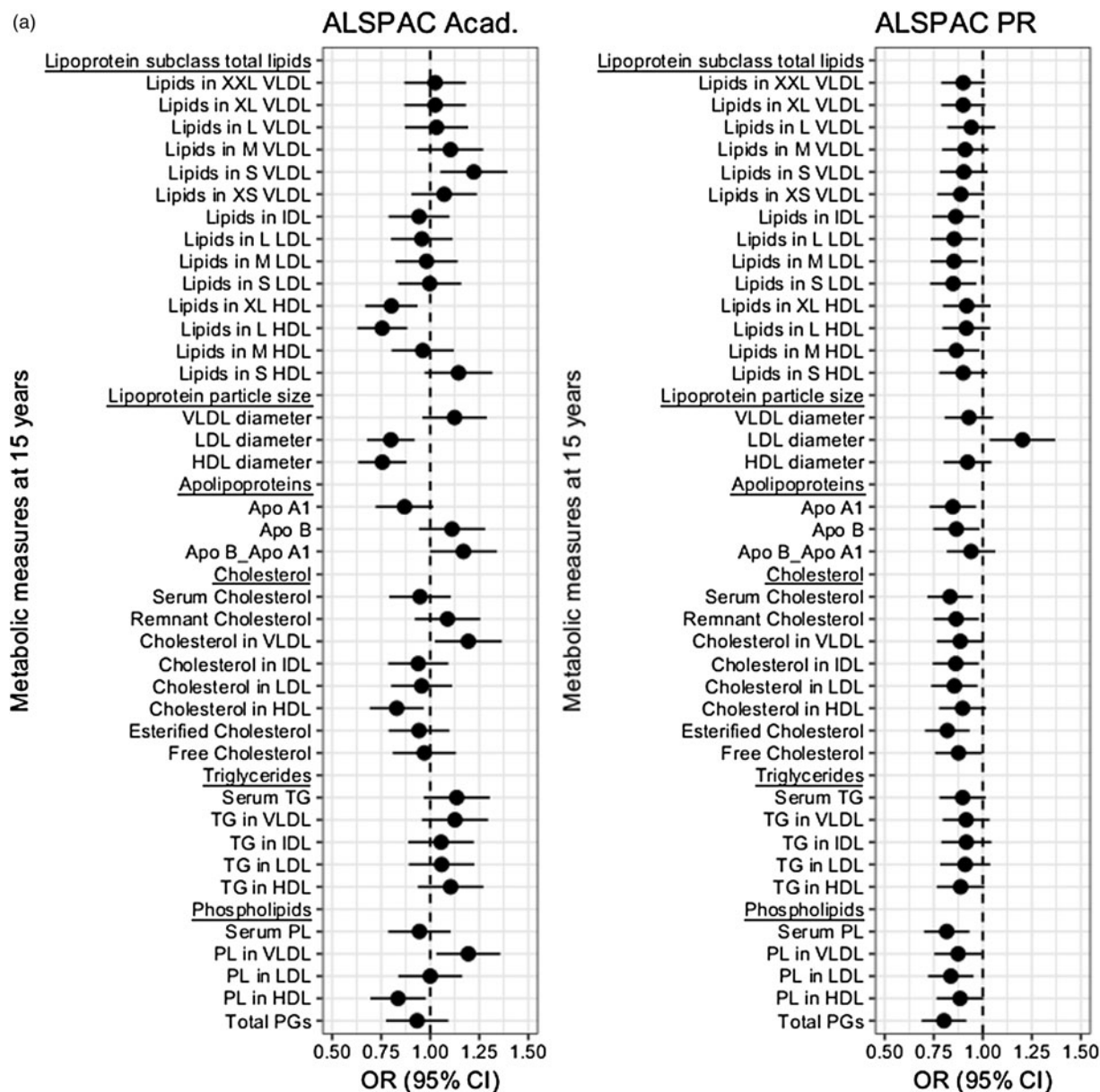


Fig. 3. Longitudinal associations between metabolic measures and cognitive performance in adolescence, controlling for sex.

associations. One plausible mechanism is that an effect on general cognitive performance could be mediated through previously identified effects of omega-3 FAs on attention (Bos *et al.*, 2015), which could enhance general cognitive development. Thirdly, higher academic performance (or a factor for which academic performance is a proxy) may precede the metabolic findings. Further longitudinal work would be needed to clarify this.

FA ratios showed more consistent associations with general cognitive performance than individual FA levels in this study. This should be considered in light of the correlation between absolute FA levels and lipoprotein lipids, particularly triglycerides. FA ratios are therefore more reflective of the individual role of these FAs than FA levels themselves. The general pattern of associations was that higher ratios of polyunsaturated FAs were associated with better performance while higher ratios of monounsaturated FAs were associated with poorer performance. Long chain PUFAs are important in cell membrane structure and

function. This role may be particularly important in adolescence, a time when psychiatric neurodevelopmental disorders associated with cognitive deficits (such as schizophrenia) begin to emerge. Lower ratios of MUFA and higher ratios of PUFA and its sub-classes may, therefore, be beneficial, or reflect a beneficial environment, in terms of adolescent neuronal membrane function.

### Metabolic markers and executive function

The findings with regard to executive function are less consistent than those for general intelligence. For one test (N-back), DHA levels and ratios showed cross-sectional associations but there were no longitudinal associations. For the other test (PR), there were no cross-sectional associations but FA levels at age 15 years (PUFAs, omega-6, linoleic acid and DHA) were associated with performance at 17 years. Once again, FA measures,

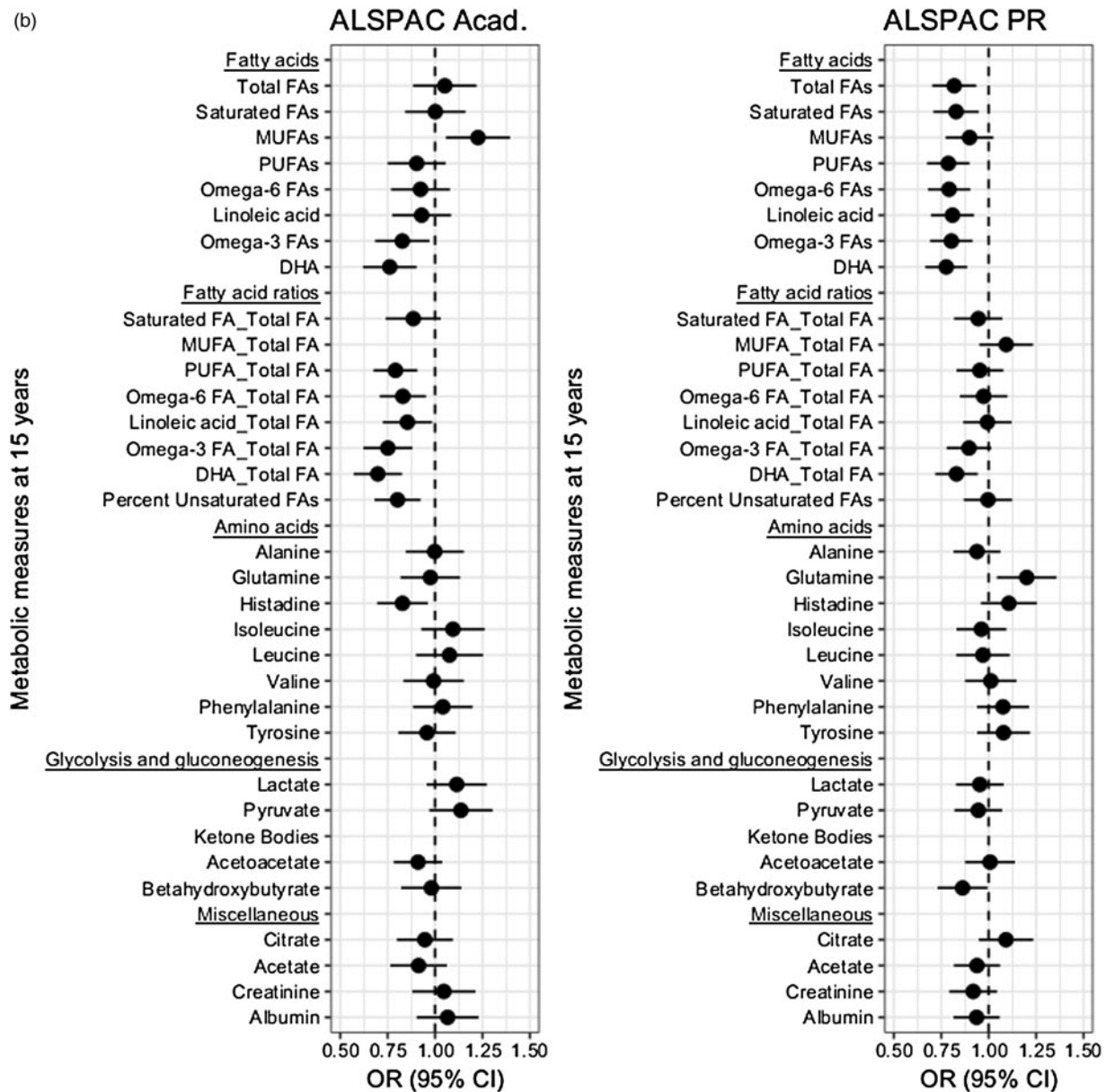


Fig. 3. Continued.

particularly DHA, showed the most noteworthy effects. This may suggest that PUFA levels in mid-adolescence are particularly important in executive function. It is interesting that the cross-sectional findings were present in the N-back task, which primarily assesses working memory, while the longitudinal findings were present for the PR task, which assesses learning following a rule change. This aspect of executive function is evolving rapidly during adolescence (Blakemore and Choudhury, 2006) and this may partly explain the differences in longitudinal and cross-sectional findings between the tests. However, given the variability in the findings, further replication is warranted.

**Metabolic markers and psychosis risk**

While we observed one cross-sectional association between acetate and psychosis risk in ALSPAC, this finding was not evident

in the NFBC sample or in ALSPAC longitudinally. Other findings were weak and not consistent between samples or between cross-sectional and longitudinal analyses. One possible reason for differences in findings between the NFBC 1986 and ALSPAC is that the measures used were quite different. The PROD-screen is a screening questionnaire and has limited evidence of either sensitivity or specificity at the cut-off used here (around 6% of the NFBC 1986 sample). It is therefore likely that among those who scored positive, there were many without psychosis risk as well as those with it. The PLIKS interview was more specific for psychosis risk but the outcome was, therefore, rarer (only 5% of the ALSPAC group). Ideally, studies would utilise the same measures to allow for potential replication.

Psychosis risk did not appear to play a major role in the cognitive findings. Controlling for psychosis risk did not impact on cognitive findings. This may be due to the relatively low

**Table 3.** Longitudinal associations between metabolic measures and cognitive performance, controlling for covariates

| Metabolic measure   | Academic scores ( <i>n</i> = 2893) |                          |                          | PR latency ( <i>n</i> = 2040) |                          |                          |
|---------------------|------------------------------------|--------------------------|--------------------------|-------------------------------|--------------------------|--------------------------|
|                     | Model 1                            | Model 2                  | Model 3                  | Model 1                       | Model 2                  | Model 3                  |
| Lipids in large HDL | <b>0.75 (0.64, 0.89)</b>           | 0.86 (0.70, 1.05)        | 0.77 (0.58, 1.04)        | –                             | –                        | –                        |
| LDL diameter        | <b>0.80 (0.68, 0.93)</b>           | <b>0.70 (0.59, 0.84)</b> | <b>0.62 (0.48, 0.80)</b> | –                             | –                        | –                        |
| HDL diameter        | <b>0.76 (0.64, 0.89)</b>           | 0.83 (0.68, 1.01)        | 0.74 (0.56, 0.98)        | –                             | –                        | –                        |
| MUFA                | <b>1.23 (1.07, 1.41)</b>           | <b>1.36 (1.16, 1.60)</b> | <b>1.47 (1.18, 1.83)</b> | –                             | –                        | –                        |
| PUFA                | –                                  | –                        | –                        | <b>0.79 (0.69, 0.91)</b>      | <b>0.75 (0.64, 0.88)</b> | <b>0.74 (0.63, 0.87)</b> |
| Omega-6             | –                                  | –                        | –                        | <b>0.79 (0.69, 0.91)</b>      | <b>0.77 (0.65, 0.90)</b> | <b>0.76 (0.65, 0.89)</b> |
| Linoleic acid       | –                                  | –                        | –                        | <b>0.81 (0.70, 0.93)</b>      | <b>0.79 (0.68, 0.92)</b> | <b>0.79 (0.67, 0.92)</b> |
| Omega-3             | –                                  | –                        | –                        | <b>0.80 (0.70, 0.92)</b>      | <b>0.75 (0.64, 0.89)</b> | <b>0.74 (0.63, 0.87)</b> |
| DHA                 | <b>0.76 (0.63, 0.92)</b>           | 0.91 (0.73, 1.13)        | 0.91 (0.68, 1.21)        | <b>0.71 (0.63, 0.80)</b>      | <b>0.72 (0.61, 0.85)</b> | <b>0.72 (0.61, 0.85)</b> |
| MUFA/total FA       | <b>1.35 (1.16, 1.56)</b>           | <b>1.32 (1.11, 1.58)</b> | <b>1.50 (1.18, 1.90)</b> | –                             | –                        | –                        |
| PUFA/total FA       | <b>0.79 (0.68, 0.91)</b>           | <b>0.77 (0.65, 0.92)</b> | 0.71 (0.56, 0.90)        | –                             | –                        | –                        |
| Omega-3/total FA    | <b>0.75 (0.63, 0.89)</b>           | 0.84 (0.68, 1.03)        | 0.76 (0.57, 1.01)        | –                             | –                        | –                        |
| DHA/total FA        | <b>0.70 (0.58, 0.84)</b>           | 0.74 (0.59, 0.93)        | <b>0.75 (0.56, 1.01)</b> | –                             | –                        | –                        |

HDL, high density lipoprotein; LDL, low density lipoprotein; FA, fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; DHA, docosahexaenoic acid. Model 1 controlled for sex; Model 2 controlled for sex and maternal education/socioeconomic status; Model 3 controlled for sex, maternal education/socioeconomic status and BMI. Bold =  $p < 0.004$ .

numbers with psychosis risk (5–6% of the samples). However, the findings suggest that, at a population level at least, metabolic measures do not influence cognition differentially according to psychosis risk. Further studies with enriched psychosis risk samples may be useful to consider this further.

### Future research implications

We have observed cross-sectional and longitudinal associations between metabolic markers and cognition. Future research should examine other specific cognitive domains outside of the executive function. Future studies could add to these findings by further exploring for evidence in support of causality, for example by considering potential biological mechanisms through experimental animal studies. In addition, consideration of the role of other covariates, such as exercise, would be helpful, even if this is on the same causal pathway to the outcome.

### Limitations and advantages

A number of limitations of this study must be acknowledged. Firstly, much of the data was cross-sectional, making it difficult to more closely examine the directions of relationships. However, longitudinal associations between FA metabolic measures and academic performance and executive performance in the ALSPAC study add considerably to the cross-sectional findings. Secondly, we could control for only a limited number of potential confounders in the ALSPAC group. However, those chosen (maternal education, BMI) at least partly address a wide variety of potential confounders such as diet and exercise levels. Furthermore, controlling for physical health, diet and exercise did not impact on observed associations in the case of the NFBC 1986 sample. Thirdly, the main outcome of interest,

academic performance, has limitations. In addition to reflecting a variety of cognitive processes (Rohde and Thompson, 2007), academic performance reflects self-discipline (Duckworth and Seligman, 2005), sex and home cultural factors, including socioeconomic context. This could also be regarded as a strength, as academic achievement reflects a variety of personality and cognitive processes that are important for success into adulthood. In addition, this data was augmented with more specific measures of executive function, a key cognitive skill that advances rapidly during late adolescence. Fourthly, the psychosis risk outcomes had limitations, particularly in the case of the PROD-screen items, which has limited validity in identifying psychosis risk. Fifthly, the use of BMI in adolescence has limitations, as it is likely to fluctuate in adolescence in response to growth spurts. However, the use of other physical measures in the NFBC 1986 sample partly addresses this limitation. Finally, the conversion of measurements, including cognitive performance, from continuous into categorical will result in some loss of information. However, this loss of information is justified by the measures being more meaningful and easier to interpret.

This study also has a number of important strengths. The data is derived from two large general population-based birth cohorts. Despite this, the findings were similar across the studies. Furthermore, the two samples come from different genetic contexts and different social contexts, including with regard to diet, which reduces the chances of uncontrolled confounding. As mentioned, information was both cross-sectional and longitudinal. We were also fortunate to have data on a large number of metabolic measures and sufficient participants to truly examine associations across two samples. Finally, we were fortunate that for the NFBC 1986 sample, we had rich data on physical and mental health factors that may have impacted on the results.

**Table 4.** Cross-sectional associations between metabolic measures and various markers of brain function from age 15 to 17 years and longitudinal associations between metabolic measures at age 15 years and markers of brain function at age 16–17 years in ALSPAC only

| Variable                  | Cross-sectional  |                    |                          |                    |                |                            | Longitudinal  |             |         |                     |
|---------------------------|------------------|--------------------|--------------------------|--------------------|----------------|----------------------------|---------------|-------------|---------|---------------------|
|                           | ALSPAC WASI (15) | NFBC academic (16) | NFBC psychosis risk (16) | ALSPAC N-back (17) | ALSPAC PR (17) | ALSPAC psychosis risk (17) | Academic (16) | N-back (17) | PR (17) | Psychosis risk (17) |
| Lipoprotein subclass      |                  |                    |                          |                    |                |                            |               |             |         |                     |
| total lipids              |                  |                    |                          |                    |                |                            |               |             |         |                     |
| Lipids in small HDL       | 1.32**           | 1.10*              | 1.04                     | 0.96               | 1.01           | 0.82                       | 1.34*         | 0.99        | 0.92    | 1.03                |
| Lipoprotein particle size |                  |                    |                          |                    |                |                            |               |             |         |                     |
| LDL diameter              | 0.78**           | 0.87**             | 0.99                     | 1.01               | 1.05           | 1.11                       | 0.62**        | 0.95        | 1.21*   | 0.98                |
| Fatty acids               |                  |                    |                          |                    |                |                            |               |             |         |                     |
| MUFA                      | 1.17*            | 1.15**             | 1.09*                    | 0.92               | 0.97           | 0.93                       | 1.47**        | 0.95        | 0.88    | 1.07                |
| PUFA                      | 0.98             | 1.00               | 1.07*                    | 0.94               | 0.91           | 0.99                       | 1.04          | 1.07        | 0.74**  | 1.04                |
| Omega-6                   | 1.03             | 1.02               | 1.07*                    | 0.96               | 0.93           | 1.00                       | 1.06          | 1.10        | 0.76**  | 1.05                |
| Linoleic acid             | 1.02             | 1.03               | 1.07*                    | 0.99               | 0.92           | 0.98                       | 1.03          | 1.10        | 0.79**  | 1.04                |
| Omega-3                   | 0.76**           | 0.91*              | 1.07*                    | 0.82*              | 0.86*          | 0.94                       | 0.95          | 0.91        | 0.74**  | 0.95                |
| DHA                       | 0.74**           | 0.94               | 1.07*                    | 0.77**             | 0.90           | 0.81                       | 0.91          | 0.90        | 0.72**  | 0.93                |
| Fatty acid ratios         |                  |                    |                          |                    |                |                            |               |             |         |                     |
| MUFA                      | 1.29**           | 1.20**             | 1.06                     | 0.94               | 1.04           | 0.93                       | 1.50**        | 0.93        | 1.14    | 1.06                |
| PUFA                      | 0.90             | 0.83**             | 0.97                     | 1.11               | 0.97           | 1.08                       | 0.71*         | 1.23*       | 0.96    | 0.95                |
| Omega-3                   | 0.65**           | 0.80**             | 1.02                     | 0.83               | 0.84*          | 0.94                       | 0.76          | 0.90        | 0.85*   | 0.90                |
| DHA                       | 0.67**           | 0.86**             | 1.03                     | 0.76               | 0.89           | 0.78*                      | 0.75          | 0.88        | 0.79**  | 0.88                |

HDL, high density lipoprotein; LDL, low density lipoprotein; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; DHA, docosahexaenoic acid; NFBC 1986, Northern Finland Birth Cohort 1986; ALSPAC, Avon Longitudinal Study of Parents and Children.

\*\* $p < 0.004$ ; \* $0.004 < p < 0.05$ .



**Table 5.** Cross-sectional associations between metabolic measures and academic performance at age 16 years, controlling for mental health factors and physical health factors

| Variable         | Model 3 OR (95% CI) | Model 4 (Model 3 + anxiety and depression) OR (95% CI) | Model 5 (Model 4 <sup>a</sup> + psychosis risk) OR (95% CI) | P for interaction (model 5 v. model with interaction) | Model 6 (Model 3 + doctor visits, exercise and diet) OR (95% CI) |
|------------------|---------------------|--|---|---|--|
| NFBC sample      |                     |  |   |   |  |
| LDL diameter     | 0.87 (0.80–0.95)    | 0.83 (0.75–0.92)                                       | 0.81 (0.73–0.90)  | 0.120   | 0.85 (0.77–0.94)   |
| MUFA/total FA    | 1.20 (1.10–1.31)    | 1.22 (1.11–1.35)                                       | 1.22 (1.11–1.35)  | 0.502   | 1.23 (1.11–1.36)   |
| Omega-3/total FA | 0.80 (0.73–0.88)    | 0.82 (0.74–0.91)                                       | 0.83 (0.74–0.93)  | 0.683   | 0.81 (0.73–0.91)   |
| DHA/total FA     | 0.86 (0.79–0.95)    | 0.88 (0.79–0.97)                                       | 0.89 (0.80–0.99)  | 0.918   | 0.87 (0.78–0.96)   |
| ALSPAC sample    |                     |  |   |   |  |
| LDL diameter     | 0.78 (0.68–0.91)    | NA   | 0.80 (0.69–0.93)  | 0.417   | NA   |
| MUFA/total FA    | 1.29 (1.13–1.48)    | NA   | 1.26 (1.10–1.45)  | 0.909   | NA   |
| Omega-3/total FA | 0.65 (0.55–0.76)    | NA   | 0.66 (0.56–0.78)  | 0.300   | NA   |
| DHA/total FA     | 0.67 (0.57–0.78)    | NA   | 0.67 (0.57–0.79)  | 0.496   | NA   |

OR, odds ratio; 95% CI, 95% confidence interval; LDL, low density lipoprotein; HDL, high density lipoprotein; MUFA, monounsaturated fatty acid; FA, fatty acid; DHA, docosahexaenoic acid. Model 3 controlling for sex, maternal education level and BMI.

<sup>a</sup>Model 3 in the case of the ALSPAC sample.

## Conclusion

In conclusion, we have identified differences in FA ratios associated with academic and cognitive performance in adolescence. These were strongest for general cognitive ability and were not explained by mental or physical health factors. Further analysis of these FA ratios may further our understanding of cognitive development at this key age, particularly in groups that are especially vulnerable to psychiatric co-morbidity and longer-term functional deficits.

**Supplementary material.** The supplementary material for this article can be found at <https://doi.org/10.1017/S0033291718001794>.

**Acknowledgements.** The authors are extremely grateful to all the families who took part in these studies and the whole NFBC 1986 and ALSPAC teams, which include interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. They thank professor Anna-Liisa Hartikainen (who launched the NFBC 1986), the NFBC project center and the University of Oulu.

**Financial support.** The UK Medical Research Council and Wellcome (Grant ref: 102215/2/13/2) and the University of Bristol provide core support for ALSPAC, while ALSPAC metabolomics data generation was funded by the UK Medical Research Council (MRC – MC\_UC\_12013/1). This research was also supported by funding from the EU (QLG1-CT-2000-01643 (EUROBLCS) grant no. E51560), NorFA (grant nos. 731, 20056, 30167), the NIH (USA) 2000 (G DF682 grant no. 50945), and the researchers' own funding. JM was supported by the Academy of Finland (Grant no. 268336). MAK was supported by the Sigrid Juselius Foundation, Finland. MAK and GDS work in a Unit that was supported by the University of Bristol and UK Medical Research Council (MC\_UU\_12013/1). GDS works in the Medical Research Council Integrative Epidemiology Unit at the University of Bristol (MC\_UU\_00011/1).

**Conflict of interest.** None.

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