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Longitudinal Trajectories of Plasma Polyunsaturated Fatty Acids and Associations With Psychosis Spectrum Outcomes in Early Adulthood

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ABSTRACT

BACKGROUND: Evidence supports associations between polyunsaturated fatty acids such as docosahexaenoic acid (DHA) and psychosis. However, polyunsaturated fatty acid trajectories in the general population have not been characterized, and associations with psychosis spectrum outcomes in early adulthood are unknown.

METHODS: Plasma omega-6 to omega-3 ratio and DHA (expressed as percentage of total fatty acids) were measured by nuclear magnetic spectroscopy at 7, 15, 17, and 24 years of age in participants of ALSPAC (Avon Longitudinal Study of Parents and Children). Curvilinear growth mixture modeling evaluated body mass index–adjusted trajectories of both measures. Outcomes were assessed at 24 years. Psychotic experiences (PEs), at-risk mental state status, psychotic disorder, and number of PEs were assessed using the Psychosis-Like Symptoms interview (n = 3635; 2247 [61.8%] female). Negative symptoms score was measured using the Community Assessment of Psychic Experiences (n = 3484; 2161 [62.0%] female). Associations were adjusted for sex, ethnicity, parental social class, and cumulative smoking and alcohol use.

RESULTS: Relative to stable average, the persistently high omega-6 to omega-3 ratio trajectory was associated with increased odds of PEs and psychotic disorder, but attenuated on adjustment for covariates (PEs adjusted odds ratio [aOR] = 1.63, 95% CI = 0.92-2.89; psychotic disorder aOR = 1.69, 95% CI = 0.71-4.07). This was also the case for persistently low DHA (PEs aOR = 1.42, 95% CI = 0.84-2.37; psychotic disorder aOR = 1.14, 95% CI = 0.49-2.67). Following adjustment, persistently high omega-6 to omega-3 ratio was associated with increased number of PEs (β = 0.41, 95% CI = 0.05-0.78) and negative symptoms score (β = 0.43, 95% CI = 0.14-0.72), as was persistently low DHA (number of PEs β = 0.45, 95% CI = 0.14-0.76; negative symptoms β = 0.35, 95% CI = 0.12-0.58).

CONCLUSIONS: Optimization of polyunsaturated fatty acid status during development warrants further investigation in relation to psychotic symptoms in early adulthood.

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There is growing interest in relationships between nutrition and mental health (1), including the potential role of polyunsaturated fatty acids (PUFAs). PUFAs, which must be obtained from the diet to maintain adequate levels, comprise 2 important subtypes. Omega-6 (n-6) fatty acids, including linoleic acid and arachidonic acid, are found in nuts, eggs, and vegetable oils. Omega-3 (n-3) fatty acids, including α-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid (DHA), are found in oily fish, some green vegetables, and supplements.

Lipid mediators derived from n-6 and n-3 PUFAs have broadly opposing effects. For example, n-6 lipid mediators are generally proinflammatory, whereas n-3 lipid mediators predominantly reduce inflammation (2,3). A n-6:n-3 ratio of 1:1 to 2:1 is considered optimal for normal physiological functioning (4). However, the average Western diet typically has larger amounts of n-6 relative to n-3 PUFAs (5,6). In the brain, the most abundant n-3 PUFA is DHA, which is postulated to have neuroprotective effects via modulation of neuronal membrane integrity, inflammation, oxidative stress, and synaptogenesis (7).

Previous studies have provided evidence for associations between PUFAs and psychotic disorders. Meta-analyses have found lower erythrocyte membrane n-3 PUFA levels in people with schizophrenia (8) and lower DHA levels in individuals with first-episode psychosis (9) compared with control participants. A Mendelian randomization study reported associations between genetically predicted levels of long-chain PUFAs and reduced schizophrenia risk, suggesting a causal relationship (10). A randomized controlled trial found that n-3 supplementation reduced transitions to psychosis among individuals at clinical high risk (11). These findings were not replicated in a subsequent trial (12), although a secondary analysis found that

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increases in erythrocyte levels of n-3 and DHA predicted symptomatic and functional improvements (13).

In a general population study, higher plasma n-6:n-3 ratio and lower DHA levels were cross-sectionally associated with psychotic disorders in early adulthood (14). Higher DHA levels in late adolescence were longitudinally associated with reduced odds of incident psychotic disorder in early adulthood, though not depressive disorder or generalized anxiety disorder (14). A further study found that higher levels of n-6 PUFAs at age 7 were weakly associated with psychotic experiences (PEs) at age 18, but effects attenuated on adjustment for confounders (15). These studies focused on PUFA measurements at a single time point. Repeated measures provide a more robust assessment of PUFA status compared with single measurements, which may overlook dynamic patterns of temporal variability. However, to date, longitudinal trajectories of PUFA levels have not been characterized in the general population, and associations between such trajectories and psychosis spectrum outcomes are unknown.

In this study, we aimed to perform the first characterization to our knowledge of longitudinal trajectories of plasma PUFA measures across multiple time points in a large general population cohort and to evaluate associations between PUFA trajectories and psychosis spectrum outcomes in early adulthood. Based on previous work (14), we focused a priori on 2 plasma measures: the ratio of n-6:n-3 PUFAs and DHA levels specifically. We hypothesized that trajectories characterized by higher n-6:n-3 ratio and lower DHA levels would be associated with increased risk of psychosis spectrum outcomes.

METHODS AND MATERIALS

Participants and Study Design

ALSPAC (Avon Longitudinal Study of Parents and Children) is a prospective birth cohort study (16–18). The study website details available data through a data dictionary and variable search tool (http://www.bristol.ac.uk/alspac/researchers/our-data/). Pregnant women in Avon, United Kingdom, with expected delivery dates between April 1, 1991, and December 31, 1992, were invited. There were 14,541 pregnant women enrolled with 13,988 children alive at 1 year. When the oldest children were approximately age 7, an attempt was made to bolster the initial sample with eligible participants who did not join originally. The sample size for data from age 7 is 15,454 pregnancies with 14,901 children alive at 1 year of age. Study data were collected and managed using REDCap (https://www.project-redcap.org/) tools hosted at the University of Bristol (19,20). REDCap is a secure, web-based software platform designed to support data capture for research studies.

Participants were invited to attend clinic visits at multiple time points where questionnaires, interviews, and venipuncture were performed. For the current study, participants were included if they completed outcome assessments at age 24 and had PUFA data available for at least one time point.

Exposures

Plasma samples were collected at clinic visits when participants were approximately 7, 15, 17, and 24 years of age. Participants were requested to fast overnight or for at least 6 hours before the age 15, 17, and 24 clinic visits. Samples were collected according to a standardized protocol, centrifuged, and stored at −80 °C. The time ranges from sample collection to sending for analysis were 12.6 to 14.8 years for the age 7 clinic; 4.3 to 6.4 years for the age 15 clinic; 2.4 to 5.1 years for the age 17 clinic; and 0.3 to 2.7 years for the age 24 clinic.

Fatty acid plasma levels were measured using high-throughput nuclear magnetic resonance spectroscopy (21). Based on previous work evaluating associations between plasma PUFAs and psychotic disorders (14), we focused a priori on 2 measures: 1) the ratio of n-6:n-3 PUFAs and 2) DHA expressed as percentage of total fatty acids.

Outcomes

We examined 3 binary and 2 continuous psychosis spectrum outcomes at 24 years.

1. PEs: At the age 24 clinic visit, participants completed the Psychosis-Like Symptoms Interview (PLIKSi) (22). The PLIKSi asks 12 core questions regarding PEs comprising hallucinations, delusions, and experiences of thought interference. Participants who answered “yes” or “maybe” were cross-questioned to establish whether the experiences were psychotic. These were coded according to the Schedules for Clinical Assessment in Neuropsychiatry (23). Interviewers rated symptoms as “not present,” “suspected,” or “definite” and whether attributable to sleep or fever. Participants met criteria for this outcome if they had at least one definite PE, not attributable to sleep or fever, that occurred in the previous 6 months.
2. At-risk mental state (ARMS): ARMS cases were identified by relating PLIKSi data to Comprehensive Assessment of At-Risk Mental State and Structured Interview for Prodromal Symptoms criteria as previously described (24).
3. Psychotic disorder: In alignment with previous studies (24,25), a psychotic disorder was defined as having at least one definite PE not attributable to sleep or fever that recurred at least once per month over the previous 6 months, was associated with severe distress or marked impairment of the participant’s social or occupational functioning, or led the participant to seek professional help. This outcome also included participants who met Comprehensive Assessment of At-Risk Mental State criteria for a psychotic disorder.
4. Number of suspected/definite PEs: This was defined as the total number of suspected or definite PEs reported by the participant during the PLIKSi assessment (range, 0–11).
5. Negative symptoms score: At the same clinic visit, participants completed 10 questions from the Community Assessment of Psychic Experiences questionnaire (26) capturing interest, motivation, emotional reactivity, pleasure, and sociability. Participants rated each item as occurring never, sometimes, often, or always. These were recoded to never or sometimes (0) or often or always (1), then summed to give a total score from 0 to 10.

Confounders

Based on a systematic review of nondietary factors associated with n-3 PUFA levels (27), the following available variables were considered as confounders: sex, ethnicity, body mass

index (BMI), and cumulative measures of cigarette smoking and alcohol use. We also included parental social class of the participant's mother or father (whichever was highest) measured by a questionnaire completed by mothers at 32 weeks of gestation. For negative symptoms, models were additionally adjusted for depressive symptoms at age 24. Further details regarding measurement and rationale for included covariates are in the Supplement.

Statistical Analyses

At each time point, n-6:n-3 ratio and DHA levels were standardized to *z* scores separately in male and female participants. Multiple imputation using Bayesian analysis (28,29) was used to impute missing exposure and covariate data across 10 imputed datasets. Several auxiliary variables were used as indicators of missingness to reduce the fraction of missing information, thus limiting missing not at random bias (30) (see the Supplement for further details). Tables S1 and S2 provide details on frequency of missing values for n-6:n-3 ratio and DHA, respectively.

Curvilinear growth mixture modeling was used to derive longitudinal trajectories for n-6:n-3 ratio and DHA. Modeling was performed iteratively for 1-, 2-, 3-, and 4-class solutions. The optimal number of classes was decided based on the average Bayesian information criterion (lower values indicate better fit), entropy (higher values indicate better fit), and smallest class proportion (≥1% in each class to permit further analysis with adequate sample sizes). After achieving successful convergence, checks were performed to rule out local solutions by replicating estimation using the same seed values and comparing model parameter estimates for replication. A successfully converged model with no local solutions would have the best log likelihood value repeated (31). Given recommendations to account for BMI as a potential confounder (27) and that BMI was assessed concurrently with plasma sampling at each time point, trajectories were adjusted for BMI.

Univariate multinomial logistic regression was used to characterize trajectory membership according to sociodemographic factors. Logistic regression was used to evaluate associations between trajectory membership and binary outcomes (definite PEs, ARMS, and psychotic disorder), estimating odds ratios (ORs) and 95% CI compared with the commonest trajectory. Associations of trajectory membership with number of PEs and negative symptoms score were evaluated using negative binomial and linear regression, respectively. For each outcome, results are presented for unadjusted models, models adjusted for sociodemographic confounders (ethnicity, sex, and parental social class), and models additionally adjusted for cumulative smoking and alcohol use. Statistical analyses were performed using Stata version 17 (StataCorp LLC), MPlus version 8 (32), and R version 4.2.1 (R Foundation for Statistical Computing).

Ethical Approval and Consent

Ethical approval for ALSPAC was obtained from the ALSPAC Ethics and Law Committee and local research ethics committees. Consent for biological samples was obtained in accordance with the Human Tissue Act 2004. Informed consent for use of questionnaire and clinic data was obtained following recommendations of the ALSPAC Ethics and Law Committee at the time.

RESULTS

Of 4019 participants who attended the age 24 clinic visit, 3635 had PLIKSi data available and 3484 had negative symptoms data available. PUFA data were available for 2268 participants at age 7, 1896 at age 15 (n = 1894 for n-6:n-3 ratio at age 15), 1933 at age 17, and 3163 at age 24 (Figure S1). Table 1 provides summary data for the analytical sample.

Longitudinal Trajectories of n-6:n-3 Ratio

For n-6:n-3 ratio trajectories, a 3-class solution was optimal (Table S3) comprising stable average (class 1: n = 3282, 90.3%), slightly above average (class 2: n = 61, 1.7%), and persistently high (class 3: n = 292, 8.0%). Figure 1 plots n-6:n-3 ratio trajectories after adjustment for BMI. Trajectories without adjustment are shown in Figure S2. Individual trajectories are shown in Figure S3.

Compared with the stable average class, persistently high class membership was associated with female sex. For the slightly above average and persistently high classes, membership was associated with lower parental social class, higher BMI, and higher cumulative smoking score (Table S4).

Longitudinal Trajectories of DHA

For DHA trajectories, a 3-class solution was optimal (Table S2) comprising stable average (class 1: n = 2739, 75.4%), persistently high (class 2: n = 245, 6.7%), and persistently low (class 3: n = 651, 17.9%). Figure 2 plots DHA trajectories after adjustment for BMI. Trajectories without adjustment are shown in Figure S4. Individual trajectories are shown in Figure S5.

Compared with the stable average class, persistently high class membership was associated with non-White ethnicity, higher parental social class, and higher cumulative alcohol score. Persistently low class membership was associated with female sex, non-White ethnicity, lower parental social class, higher BMI, and higher cumulative smoking score (Table S5).

Overlap Between n-6:n-3 Ratio and DHA Trajectory Classes

As expected, there was substantial overlap between n-6:n-3 ratio and DHA trajectory classes. For example, 75.7% of participants in the persistently high n-6:n-3 ratio class were in the persistently low DHA class (Table S6).

Psychosis Spectrum Outcomes at Age 24 Years

Of 3635 participants with PLIKSi data available, 116 (3.2%) met criteria for definite PEs, 23 (0.6%) met criteria for ARMS, and 46 (1.3%) met criteria for a psychotic disorder. At least one suspected/definite PE was reported by 450 participants, among whom the median was 1 (interquartile range = 1). Of 3484 participants with negative symptoms data available, 1724 had a score of at least 1, among whom the median was 2 (interquartile range = 4).

Table 1. Summary Data for Sample Characteristics

Characteristic	Analytical Sample, *n* = 3635	Missing Data, *n* (%)
Sex, *n* (%)		0 (0%)
Female	2247 (61.8%)	
Male	1388 (38.2%)	
Ethnicity, *n* (%)		404 (11.1%)
Non-White	128 (4.0%)	
White	3103 (96.0%)	
BMI, Mean (SD)		
Age 7	16.2 (2.0)	542 (14.9%)
Age 15	21.3 (3.4)	896 (24.6%)
Age 17	22.6 (3.9)	832 (22.9%)
Age 24	24.8 (4.9)	34 (0.9%)
Parental Social Class at 32 Weeks' Gestation Based on Occupation, *n* (%)		487 (13.4%)
I	627 (19.9%)	
II	1444 (45.9%)	
III	717 (22.8%)	
IV	258 (8.2%)	
V	92 (2.9%)	
VI	10 (0.3%)	
Cumulative Smoking Score, *n* (%)		1542 (42.4%)
0	1786 (85.3%)	
1	173 (8.3%)	
2	98 (4.7%)	
3	36 (1.7%)	
Cumulative Alcohol Score, *n* (%)		2574 (70.8%)
0	38 (3.6%)	
1	204 (19.2%)	
2	589 (55.5%)	
≥3	230 (21.7%)	
Plasma Omega-6 to Omega-3 Ratio, Mean (SD)		
Age 7	10.5 (1.8)	1367 (37.6%)
Age 15	10.9 (2.2)	1741 (47.9%)
Age 17	10.2 (1.9)	1702 (46.8%)
Age 24	10.0 (1.6)	472 (13.0%)
Plasma DHA % Total Fatty Acids, Mean (SD)		
Age 7	1.1 (0.2)	1367 (37.6%)
Age 15	1.1 (0.3)	1739 (47.8%)
Age 17	1.1 (0.3)	1702 (46.8%)
Age 24	1.3 (0.3)	472 (13.0%)
Definite Psychotic Experiences at Age 24, *n* (%)		0 (0%)
No	3519 (96.8%)	
Yes	116 (3.2%)	
Psychotic Disorder at Age 24, *n* (%)		0 (0%)
No	3589 (98.7%)	
Yes	46 (1.3%)	
ARMS at Age 24, *n* (%)		0 (0%)
No	3612 (99.4%)	
Yes	23 (0.6%)	
Number of Psychotic Experiences at Age 24, *n* (%)		0 (0%)
0	3185 (87.6%)	
1	310 (8.5%)	
2	90 (2.5%)	
3	27 (0.7%)	
4	12 (0.3%)	
≥5	11 (0.3%)	
Negative Symptoms Score at Age 24, *n* (%)		151 (4.2%)
0	1760 (50.5%)	
1	575 (16.5%)	
2	312 (9.0%)	
3	225 (6.5%)	
4	176 (5.1%)	
5	140 (4.0%)	
≥6	296 (8.5%)	

ARMS, at-risk mental state; BMI, body mass index; DHA, docosahexaenoic acid.

Associations Between n-6:n-3 Ratio Trajectories and Psychosis Spectrum Outcomes

Table 2 presents details of associations between n-6:n-3 ratio trajectories and psychosis spectrum outcomes. There was evidence for association of the persistently high n-6:n-3 ratio trajectory with PEs and a psychotic disorder, which attenuated on adjustment for covariates (PEs fully adjusted OR = 1.63, 95% CI = 0.92-2.89; psychotic disorder fully adjusted OR = 1.69, 95% CI = 0.71-4.07). There was little evidence for associations between n-6:n-3 trajectories and ARMS. There was evidence that the persistently high n-6:n-3 ratio trajectory was associated with number of PEs (fully adjusted β = 0.41, 95% CI = 0.05-0.78) and negative symptoms (fully adjusted β = 0.43, 95% CI = 0.14-0.72).

Associations Between DHA Trajectories and Psychosis Spectrum Outcomes

Table 3 presents details of associations between DHA trajectories and psychosis spectrum outcomes. There was evidence for association of the persistently low DHA trajectory with PEs and a psychotic disorder, which attenuated on adjustment for covariates (PEs fully adjusted OR = 1.42, 95% CI = 0.84-2.37; psychotic disorder fully adjusted OR = 1.14, 95% CI = 0.49-2.67). There was little evidence for associations between DHA trajectories and ARMS. There was evidence that the persistently low DHA trajectory was associated with number of PEs (fully adjusted β = 0.45, 95% CI = 0.14-0.76) and negative symptoms (fully adjusted β = 0.35, 95% CI = 0.12-0.58).

DISCUSSION

To our knowledge, this is the first characterization of longitudinal trajectories of plasma PUFA measures across childhood, adolescence, and early adulthood in a large general population

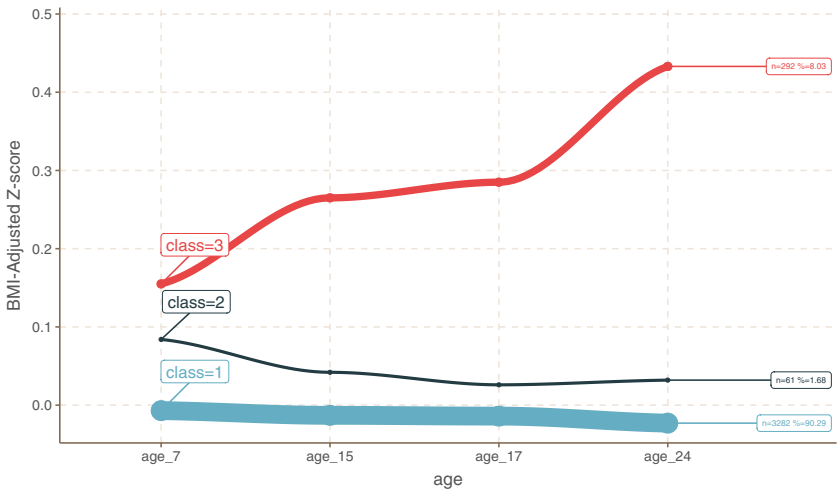

Figure 1. Trajectories of omega-6 to omega-3 ratio after adjustment for body mass index (BMI).

cohort. For both n-6:n-3 ratio and DHA, we found evidence for 3 longitudinal trajectories. Compared with stable average trajectories, persistently high n-6:n-3 ratio and persistently low DHA were associated with increased odds of PEs and a psychotic disorder, with these associations explained by included covariates. Conversely, there was strong evidence for associations of high n-6:n-3 ratio and persistently low DHA with increased number of PEs and increased negative symptoms at age 24, which persisted on adjustment.

Higher levels of DHA at age 17 have previously been associated with reduced odds of incident psychotic disorder in early adulthood (14). A further study found that higher levels of n-6 PUFAs at age 7 were weakly associated with PEs at age 18, but effects attenuated after adjustment for confounders (15). In this study, unadjusted analyses provided evidence of an association between persistently low DHA and increased odds of definite PEs and a psychotic disorder, although these associations were explained by included confounders. One possibility is that longitudinal PUFA status is not associated with psychosis risk. However, this contrasts with the analyses of symptom-level outcomes. The relatively small number of individuals who met criteria for the binary outcomes examined (particularly ARMS or psychotic disorder) in this general population study may have limited statistical power, increasing the risk of type II error. There was comparatively stronger evidence for associations between persistently high n-6:n-3 ratio and persistently low DHA in relation to number of PEs and negative symptoms score. The continuous nature of these symptom-level outcomes may have afforded greater power. It is also possible that the longitudinal effects of PUFAs are subtle and thus detectable in relation to symptom-level dimensions rather than binary outcomes criteria.

The number of PEs outcome included suspected and definite PEs and reflects the broadest examined outcome based on positive PEs. n-3 PUFA levels have been inversely associated with psychotic symptoms in individuals at clinical high risk for psychosis (13), and n-3 supplementation has modest effects on general psychopathology and positive symptoms in

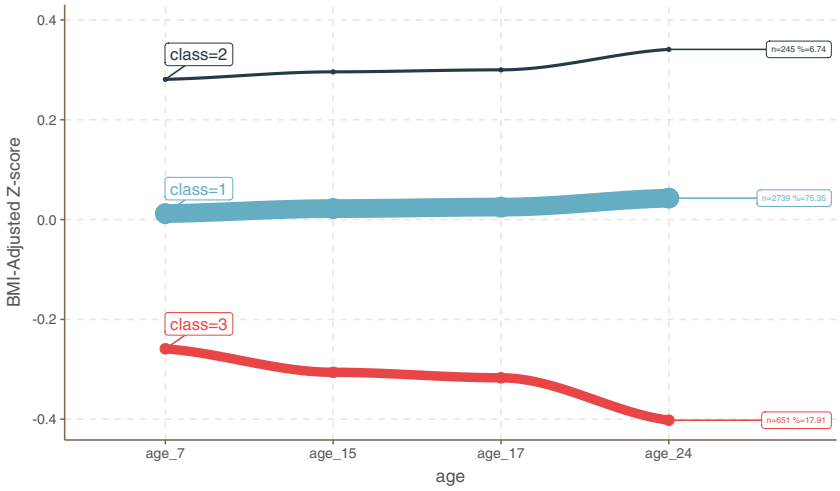

Figure 2. Trajectories of docosahexaenoic acid (percentage of total fatty acids) after adjustment for body mass index (BMI).

Table 2. Associations Between Omega-6 to Omega-3 Ratio Trajectories and Psychosis Spectrum Outcomes in Early Adulthood

Outcome	Trajectory (Reference: Stable Average)	Unadjusted			Adjusted for Sex, Ethnicity, and Parental Social Class			Further Adjusted for Smoking and Alcohol Use[a]		
Binary Outcomes		OR	95% CI	*p* Value	OR	95% CI	*p* Value	OR	95% CI	*p* Value
PEs	Slightly above average	1.77	0.56 to 4.25	.341	2.51	0.35 to 18.22	.362	1.94	0.27 to 14.20	.511
	Persistently high	2.52	1.63 to 3.77	<.001	2.15	1.25 to 3.68	.006	1.63	0.92 to 2.89	.092
ARMS	Slightly above average	6.51	1.46 to 19.47	.014	2.80	0.26 to 29.65	.392	3.83	0.31 to 47.61	.297
	Persistently high	2.67	0.96 to 6.25	.079	2.52	0.79 to 8.05	.118	2.19	0.61 to 7.91	.231
Psychotic Disorder	Slightly above average	3.06	0.70 to 8.71	.130	2.49	0.22 to 28.02	.459	2.05	0.18 to 23.07	.561
	Persistently high	2.54	1.26 to 4.69	.019	2.29	0.99 to 5.30	.053	1.69	0.71 to 4.07	.237
Continuous Outcomes		β	95% CI	*p* Value	β	95% CI	*p* Value	β	95% CI	*p* Value
Number of Suspected/Definite PEs	Slightly above average	0.34	−0.42 to 1.13	.378	0.38	−0.65 to 1.40	.473	0.24	−0.77 to 1.25	.637
	Persistently high	0.71	0.38 to 1.06	<.001	0.68	0.32 to 1.03	<.001	0.41	0.05 to 0.78	.026
Negative Symptoms	Slightly above average	0.26	−0.33 to 0.86	.384	0.17	−0.59 to 0.94	.660	0.05	−0.66 to 0.76	.887
	Persistently high	0.69	0.41 to 0.98	<.001	0.69	0.39 to 0.98	<.001	0.43	0.14 to 0.72	.004

ARMS, at-risk mental state; OR, odds ratio; PE, psychotic experiences.
[a]Models evaluating associations with negative symptoms were additionally adjusted for depressive symptoms.

people with schizophrenia (33). However, trials of PUFA supplementation for psychosis prevention in the clinical high-risk population have produced mixed results (11,12,34). In relation to negative symptoms, we found strong evidence for associations of persistently high n-6:n-3 ratio and persistently low DHA with negative symptoms at age 24. In the setting of psychotic disorders, negative symptoms are frequently associated with a high degree of disability and functional impairment and are less responsive to standard treatments compared with positive symptoms (35). A previous meta-analysis found no improvement in negative symptoms associated with n-3 supplementation in schizophrenia (33). However, a secondary analysis of a randomized controlled trial in clinical high-risk individuals found increases in n-3 PUFA levels associated with improvement in negative symptoms (13).

Potential effects of PUFAs on subsequent risk of psychotic symptoms may not be adequately captured by the relatively short supplementation periods common in trials. Furthermore, existing trials of PUFAs for psychosis prevention focus on the clinical high-risk population (usually greater than 14 years of age). It is possible that early neurodevelopmental periods exist during which PUFA status is especially pertinent in relation to risk of psychotic symptoms, whether in childhood or adolescence [in keeping with the pruning hypothesis for schizophrenia (36)], or even prenatally. Evidence from animal studies suggests that chronic n-3 deficiency is associated with disturbances in synaptic function (37), while offspring from maternal mice fed an n-3–deficient diet show increased synaptic elimination in the developing hippocampus (38). The earliest PUFA measurement available for analysis in the current study occurred at age 7, such that earlier time points could not be captured in our analysis. Notably, there was no crossover between PUFA trajectories across the examined exposure time frame, suggesting that trajectories were broadly fixed by age 7 years. Longitudinal patterns of prenatal and early childhood PUFA levels warrant exploration in further studies to determine whether an early critical period exists in relation to PUFA effects on psychosis risk.

The findings of this study are compatible with the idea that optimizing PUFA status during development (whether through supplementation or dietary interventions) may be associated with reduction in psychotic symptoms in early adulthood. Clinically, minimally invasive methods such as dried blood spot testing are available to measure and monitor n-3 PUFA levels without need for cold temperature storage (39). Targeting interventions toward children and young people with measured n-3 deficiencies may prove fruitful. However, the optimal developmental stage for and duration and form of such interventions are not known. Furthermore, it is unclear whether targeting specific subpopulations (such as high-risk groups or people with established n-3 deficiencies) or the general population at large would yield optimal preventive benefits. Adequately powered trials of PUFA supplementation and/or dietary interventions in early childhood (or prenatally) with long-term follow-up into early adulthood would be helpful. An additional challenge related to supplementation concerns the variable oxidation of fish oil products, which could affect their efficacy (40). n-3 PUFAs, including DHA (41,42), are capable of crossing the blood-brain barrier by passive diffusion or facilitated transport, but these processes are likely influenced by

Table 3. Associations Between Docosahexaenoic Acid Trajectories and Psychosis Spectrum Outcomes in Early Adulthood

Outcome	Trajectory (Reference: Stable Average)	Unadjusted			Adjusted for Sex, Ethnicity, and Parental Social Class			Further Adjusted for Smoking and Alcohol Use[a]		
		OR	95% CI	*p* Value	OR	95% CI	*p* Value	OR	95% CI	*p* Value
Binary Outcomes										
PEs	Persistently high	0.44	0.14 to 1.03	.166	0.45	0.14 to 1.44	.179	0.48	0.15 to 1.54	.214
	Persistently low	2.20	1.56 to 3.07	<.001	2.06	1.26 to 3.36	.004	1.42	0.84 to 2.37	.188
ARMS	Persistently high	0.70	0.07 to 2.78	.727	0.71	0.09 to 5.48	.746	0.98	0.12 to 7.82	.981
	Persistently low	1.58	0.68 to 3.37	.339	1.20	0.38 to 3.76	.760	0.90	0.26 to 3.18	.873
Psychotic Disorder	Persistently high	0.36	0.04 to 1.37	.313	0.36	0.05 to 2.64	.312	0.39	0.05 to 2.94	.362
	Persistently low	1.92	1.10 to 3.23	.045	1.79	0.81 to 3.93	.149	1.14	0.49 to 2.67	.756
Continuous Outcomes		β	95% CI	*p* Value	β	95% CI	*p* Value	β	95% CI	*p* Value
Number of Suspected/Definite PEs	Persistently high	−0.35	−0.83 to 0.12	.151	−0.30	−0.77 to 0.17	.213	−0.25	−0.72 to 0.22	.300
	Persistently low	0.62	0.37 to 0.87	<.001	0.70	0.40 to 1.01	<.001	0.45	0.14 to 0.76	.004
Negative Symptoms	Persistently high	−0.12	−0.42 to 0.19	.456	−0.08	−0.39 to 0.22	.585	−0.08	−0.36 to 0.20	.584
	Persistently low	0.63	0.43 to 0.83	<.001	0.70	0.45 to 0.95	<.001	0.35	0.12 to 0.58	.003

ARMS, at-risk mental state; OR, odds ratio; PE, psychotic experiences.
[a]Models evaluating associations with negative symptoms were additionally adjusted for depressive symptoms.

individual-level factors including age and health status (43). Further research in younger samples would be helpful to determine optimal age-appropriate dosing, bioavailability, administration, and formulation strategies [for example, using PUFA-enriched meat rather than fish oil (44)]. In the absence of sufficient trial evidence, existing guidance on PUFA intake should be followed (45,46).

While Mendelian randomization analyses support protective effects of long-chain PUFAs on schizophrenia risk (10), the underlying mechanisms are unclear. There is evidence for low-grade inflammation during and preceding the onset of psychosis (47). Modulation of inflammation and the innate immune system is one potential mechanism by which PUFAs may influence psychosis outcomes (48,49), although effects on oxidative stress and neurotransmission have also been suggested (50). n-3 PUFAs such as DHA promote neurite growth and synaptogenesis and thus may limit the dysregulated synaptic pruning during adolescence that is hypothesized to underlie at least part of the pathophysiology of schizophrenia (36). Regarding brain morphology, deficits in right hippocampal growth during adolescence have been observed in young people who experienced PEs compared with control participants (51). Higher hippocampal volume has been associated with higher n-3 levels in cognitively healthy older adults (52), although whether a similar relationship underscores development of psychotic symptoms in young people is unconfirmed. Abnormalities in PUFA levels in individuals with or at risk of psychosis spectrum outcomes could arise due to an underlying dysregulation of PUFA metabolism associated with liability to psychosis rather than from nutritional deficits alone. For example, genetic variation of fatty acid desaturase enzymes, elevated phospholipase A_2 activity, and abnormalities of fatty acid binding protein have been proposed in the setting of schizophrenia (50). This is potentially in keeping with the early dysregulation of wider lipid metabolism noted in some individuals at clinical high risk of psychosis (53) and preceding the onset of PEs (54).

The present findings relate to a general population sample. While positive PEs have been extensively studied in this context (55), the extent to which the construct of negative symptoms applies to the general population is debated (56). Negative symptoms have been most prominently associated with chronic schizophrenia, but evidence from transdiagnostic studies suggests that negative symptoms are prevalent to varying degrees in people with non–schizophrenia spectrum disorders and high-risk groups as well as in the general population (57–59). It is possible that the findings in the present study reflect associations between PUFAs and a nonspecific latent factor of psychopathology more generally [akin to the *p* factor (60)]. This will require further elucidation in diverse cohorts with repeated measures of PUFA levels.

Our findings suggest that substantial proportions of the United Kingdom population evidence trajectories characterized by persistently high plasma n-6:n-3 ratio (approximately 8%) and persistently low DHA levels (approximately 18%) compared with the population average. Average n-3 PUFA intake in the United Kingdom is already suboptimal compared with World Health Organization recommendations (61,62). Given several reported health benefits associated with n-3

PUFAs (63,64), these findings have implications beyond psychosis. Notably, several sociodemographic factors were associated with trajectories characterized by persistently high n-6:n-3 ratio and low DHA levels. These patterns likely reflect effects of social determinants on diet and health (65,66). The observed trajectories did not overlap following the first measurement at age 7, underscoring the importance of addressing social determinants in early life.

Limitations

Several limitations should be noted. Given the observational nature of this study, causality cannot be inferred, and residual confounding is possible. PUFA levels may be a marker of dietary quality more broadly, and other associated dietary factors may confound observed associations. PUFA levels were measured in plasma rather than erythrocyte cell membranes. Plasma has the advantages of being less subject to degradation and greater stability in long-term storage (67). However, erythrocyte membrane levels have slower turnover and thus better reflect PUFA status in the preceding months, whereas plasma levels reflect a shorter time frame of approximately 1 to 2 weeks (68,69). While participants were requested to fast before the age 15, 17, and 24 clinic visits, this did not apply to the age 7 clinic visit. Our analyses were limited to participants who attended and completed assessments for psychosis spectrum outcomes at age 24. In common with most longitudinal cohorts, participants had varying amounts of missing data, and attrition occurred in association with socioeconomic status. We used multiple imputation to avoid potential biases of complete case analyses. The ALSPAC cohort is largely White and of higher socioeconomic status compared with the general population in the United Kingdom. This may limit the generalizability of our findings due to selection bias, particularly since dietary patterns can differ by ethnicity (70) and socioeconomic characteristics (71). Replication studies in more diverse and representative samples are thus warranted. Finally, the PLIKSi does not generate diagnoses according to DSM or ICD classifications, but it is likely that individuals who fulfilled the definition of a psychotic disorder would also meet such criteria based on the frequency of psychotic symptoms and associated functional impairment.

Conclusions

We found evidence of 3 longitudinal trajectories for plasma n-6:n-3 ratio and DHA levels across childhood, adolescence, and early adulthood in a large general population cohort. Trajectories characterized by persistently high n-6:n-3 ratio and persistently low DHA were associated with increased odds of PEs and a psychotic disorder in early adulthood, with these associations explained by included covariates. Persistently high n-6:n-3 ratio and persistently low DHA trajectories were associated with increased number of PEs and negative symptoms in early adulthood. Further evidence, including replication in diverse cohorts with repeated PUFA measurements and trials with long-term follow-up into adulthood, would be helpful to further evaluate the longitudinal effects of PUFAs on psychosis spectrum outcomes.

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Requests for access to ALSPAC data may be submitted to the ALSPAC executive committee as detailed on the study website: http://www.bristol.ac.uk/alspac/researchers/access/.

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