#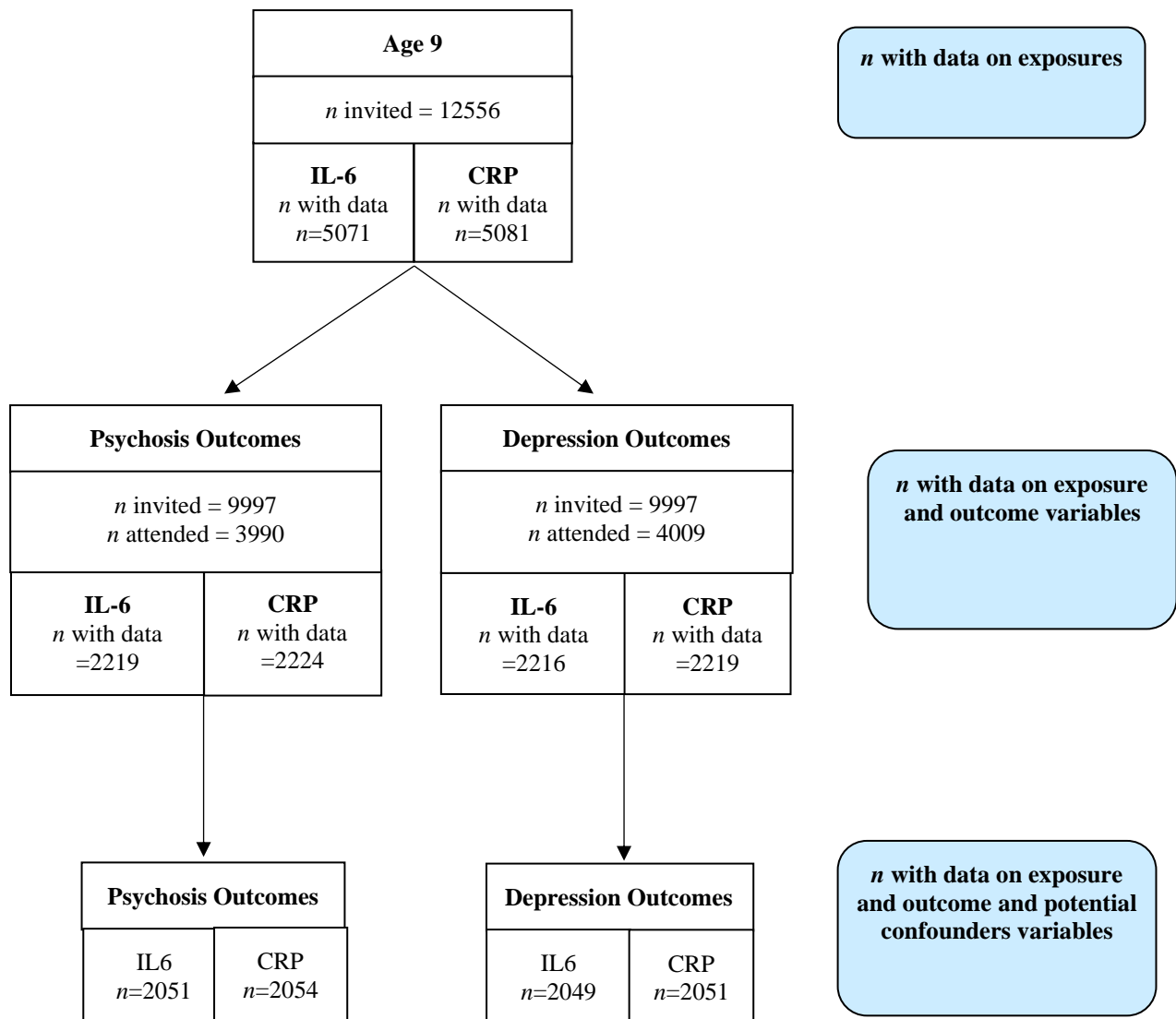 Childhood Inflammatory Markers and Risks for Psychosis and Depression at Age 24: examination of temporality and specificity of association in a population-based prospective birth cohort

Benjamin I. Perry, Stanley Zammit, Peter B. Jones, Golam M. Khandaker

Supplementary Data

Supplementary Methods

Supplementary Figure 1: Flowchart of Available Sample Size for Analyses Presented

Age 9	
n invited = 12556	
IL-6 *n* with data *n*=5071	**CRP** *n* with data *n*=5081

n with data on exposures

Psychosis Outcomes	
n invited = 9997 *n* attended = 3990	
IL-6 *n* with data =2219	**CRP** *n* with data =2224

Depression Outcomes	
n invited = 9997 *n* attended = 4009	
IL-6 *n* with data =2216	**CRP** *n* with data =2219

n with data on exposure and outcome variables

Psychosis Outcomes	
IL6 *n*=2051	CRP *n*=2054

Depression Outcomes	
IL6 *n*=2049	CRP *n*=2051

n with data on exposure and outcome and potential confounders variables

Multiple Imputation for Missing Data

We used multiple imputation using chained equations (MICE) (15) to replace missing data for covariates on the sample of participants who had outcome data available, using the *MICE* package in *R* (15). Covariates were selected for multiple imputation if they had: 1) <40% missing data from the sample of participants with data on the outcome (26); 2) suitable auxiliary variables available to use as 'indicators of missingness', to reduce the impact of bias attributed by the risk of data being 'missing not at random' (27). Auxiliary variables were selected based upon their correlation with the covariate and the contribution toward reducing the fraction of missing information (28). Multiple imputation of 100 datasets was performed using the *MICE* package in *R* (15). After discounting auxiliary variables that displayed evidence of multicollinearity, over 115 auxiliary variables were included (see below). Box-and-Whisker and Density plots were used to check similarities of observed and imputed data. The covariates imputed were: IL-6 (age 9); CRP (age 9); BMI (age 9); ethnicity, and paternal social class. Following imputation, the sample size available for analyses of psychosis outcomes was *n*=3,990, and for depression outcomes *n*=4,009.

List of Auxiliary Variables for Multiple Imputation

Age	Variable
0	Gestational Age, Birthweight, Edinburgh Post-Natal Depression Scores, Partners Ethnic Group, Grandmothers Ethnic Group, Family History of Cardiovascular Disease, Perinatal Stressful Life Events Scores, Financial Difficulties Score, Smoking in Pregnancy, Paternal Education, Maternal Education
3	Vocabulary Score, Plurals Score, Past Tense Score, Word Combination Score, Language Score, Intelligibility Score, Communicative Score
5	Leptin
7	IGF-1, Triglycerides, High-Density Lipoprotein, Low-Density Lipoprotein, Body Mass Index, Waist Circumference, Heart Rate, Blood Pressure, Reading Score, Spelling Score, Phoneme Task Score
8	Weschler Intelligence Scale for Children Scores, Bullying Questionnaire Scores
9	IGF-1, Fasting Insulin, Triglycerides, High-Density Lipoprotein, Fasting Plasma Glucose, Low-Density Lipoprotein, Body Mass Index, Waist Circumference, Heart Rate, Blood Pressure, Glucose Tolerance, Leptin, Adiponectin, Apolipoprotein AI, Apolipoprotein B, Glycated Haemoglobin, Cortisol, Smoking
10	Body Mass Index, Waist Circumference, Heart Rate, Blood Pressure, Working Memory Scores
11	IGF-1
12	Alcohol Use, Simple Reaction Time, Digit Vigilance, Choice Reaction Time, Continuity of Attention, Smoking, Substance Use, Sleep Quality
13	IGF-1, Psychotic Experiences, Alcohol Use, Physical Activity
15	Adiponectin, Fasting Insulin, High Density Lipoprotein, Fasting Plasma Glucose, Low Density Lipoprotein, Triglycerides, Waist Circumference, Heart Rate, Body Mass Index, Blood Pressure, Physical Activity, Alcohol Use, Cannabis Use, C-Reactive Protein, Smoking, Sleep Quality Scores
18	Fasting Plasma Glucose, Triglycerides, High-Density Lipoprotein, Triglycerides, Low Density Lipoprotein, Waist Circumference, Fasting Insulin, Body Mass Index, Heart Rate, Blood Pressure, Alcohol Use, Cannabis Use, CRP, Smoking, Sleep Quality, Physical Activity
24	White Blood Cell Count, Neutrophils, Eosinophils, Basophils, Fasting Plasma Glucose, Triglycerides, High Density Liproprotein, Low Density Lipoprotein, Fasting Insulin, Body Mass Index, Waist Circumference, Blood Pressure, Cannabis Use, Smoking, Heart Rate

Supplementary Table 1: Baseline Characteristics of Sample

Characteristic	IL-6 Tertiles		
	Bottom	**Middle**	**Top**
Male Sex, *n* (column %)	995 (58.8)	837 (51.0)	728 (42.0)
White British Ethnicity, *n* (column %)	1545 (98.4)	1476 (98.2)	1534 (97.8)
Social Class, *n* (column %)			
I	47 (3.1)	65 (4.3)	53 (3.4)
II	422 (26.9)	502 (33.4)	507 (32.3)
III - non manual & manual	733 (46.7)	679 (45.2)	739 (47.1)
IV & V	366 (23.3)	212 (14.1)	270 (17.2)
BMI at age 9, mean (SD)	16.75 (1.91)	17.53 (2.56)	18.49 (3.39)
CRP (mg/L) at age 9, mean (SD)	0.26 (0.63)	0.42 (0.90)	1.69 (1.21)

IL-6 = Interleukin-6; CRP=C-Reactive Protein.

Supplementary Table 2: ORs (95% CI) and *p*-values for Quadratic Terms for IL-6 and CRP (IL-6^2 and CRP^2) in Logistic Regression Models Testing Associations of IL-6 and CRP Levels at Age 9 and Risks for Psychosis and Depression at Age 24

Outcome (Binary Variable)	Quadratic term for risk factor	OR (95% C.I.) adjusted for sex, ethnicity, social class and BMI	*p*-value for quadratic term
Definite PEs	IL-6-squared	1.04 (0.97-1.12)	0.300
	CRP-squared	1.03 (0.93-1.14)	0.596
Psychotic Disorder	IL-6-squared	0.94 (0.71-1.23)	0.638
	CRP-squared	1.11 (0.91-1.36)	0.295
Depressive Episode	IL-6-squared	0.95 (0.86-1.05)	0.327
	CRP-squared	1.06 (0.96-1.16)	0.251

Supplementary Table 3: Beta-coefficients (95% CIs) and *p*-values for Quadratic Terms for IL-6 and CRP (IL-6^2 and CRP^2) in the Linear Regression Models Testing Associations of IL-6 and CRP Levels at Age 9 and Risks for Negative and Depressive Symptoms at Age 24

Outcome (Binary Variable)	Risk Factor	β (95% C.I.)	*p*-value for adjusted model
		Adjusted for sex, ethnicity, social class, BMI	
Negative Psychotic Symptoms	IL-6-squared	-0.01 (-0.01, 0.01)	0.597
	CRP-squared	0.00 (0.00, 0.00)	0.825
Depressive Symptom Score	IL-6-squared	0.01 (-0.02, 0.03)	0.475
	CRP-squared	0.00 (-0.01, 0.01)	0.276

Supplementary Table 4: ORs (95% CI) and *p*-values for Risk of Psychosis and Depression at Age 24 for Participants in Middle and Top Thirds of CRP Distributions, Compared with Bottom Third, at Age 9

Outcome (Binary Variable)	Risk Factor (vs Bottom Tertile)	OR (95% C.I.)		*p*-value for adjusted model
		Unadjusted	Adjusted for sex, ethnicity, social class, BMI	
Definite PEs	Bottom Tertile	1 [Reference]	1 [Reference]	-
	Middle Tertile	1.27 (0.85-1.90)	1.31 (0.85-2.01)	0.217
	Top Tertile	1.18 (0.80-1.76)	1.13 (0.70-1.83)	0.612
Psychotic Disorder	Bottom Tertile	1 [Reference]	1 [Reference]	-
	Middle Tertile	1.00 (0.65-1.56)	1.04 (0.40-2.66)	0.942
	Top Tertile	1.02 (0.43-2.43)	1.43 (0.54-3.82)	0.471
Depressive Episode	Bottom Tertile	1 [Reference]	1 [Reference]	-
	Middle Tertile	1.06 (0.74-1.52)	0.89 (0.61-1.31)	0.554
	Top Tertile	1.03 (0.43-2.43)	1.00 (0.67-1.49)	0.990

Supplementary Table 5: Beta Coefficients (95% CI) and *p*-values for the SD Increase in Negative and Depressive Symptoms for Participants in Middle and Top Thirds of IL-6 Distributions, Compared with Bottom Third, at Age 9

Outcome	Risk Factor (vs Bottom Tertile)	Beta Coefficient (95% C.I.)		*p*-value for adjusted model
		Unadjusted	**Adjusted for sex, ethnicity, social class, BMI**	
Negative Symptoms	Bottom Tertile	1 [Reference]	1 [Reference]	-
	Middle Tertile	0.04 (-0.03, 0.09)	0.02 (-0.03, 0.06)	0.304
	Top Tertile	0.24 (0.01, 0.48)	0.20 (0.04, 0.31)	0.021
Depressive Symptoms	Bottom Tertile	1 [Reference]	1 [Reference]	-
	Middle Tertile	0.10 (-0.09, 0.20)	0.07 (-0.11, 0.23)	0.522
	Top Tertile	0.65 (0.01, 1.31)	0.43 (0.00, 1.15)	0.049

Supplementary Table 6: Beta Coefficients (95% CI) and *p*-values for the SD Increase in Negative and Depressive Symptoms for Participants in Middle and Top Thirds of CRP Distributions, Compared with Bottom Third, at Age 9

Outcome	Risk Factor (vs Bottom Tertile)	Beta Coefficient (95% C.I.)		*p*-value for adjusted model
		Unadjusted	Adjusted for sex, ethnicity, social class, BMI	
Negative Symptoms	Bottom Tertile	1 [Reference]	1 [Reference]	-
	Middle Tertile	0.01 (-0.19, 0.21)	0.02 (-0.20, 0.18)	0.708
	Top Tertile	-0.03 (-0.26, 0.20)	0.09 (-0.18, 0.36)	0.521
Depressive Symptoms	Bottom Tertile	1 [Reference]	1 [Reference]	-
	Middle Tertile	0.05 (-0.22, 0.29)	-0.01 (-0.25, 0.23)	0.887
	Top Tertile	0.32 (-0.34, 0.98)	0.02 (-0.76, 0.81)	0.955

Supplementary Table 7: Commonality of Associations for IL-6 and CRP at Age 9 with PEs or Depressive Episode at Age 24

Risk Factor	Odds Ratio (95% C.I.)			LRT[1] Comparing Specific vs. Common Effect
	Specific Effect on Definite PEs	Specific Effect on Depressive Episode	Common Effect on Both Outcomes	χ^2-statistic, *p*-value[2]
IL-6	1.10 (0.97-1.25)	1.14 (1.01-1.28)	1.12 (1.02-1.23)	χ^2=0.15; 0.701
CRP	1.06 (0.93-1.21)	1.08 (0.97-1.21)	1.07 (0.98- 1.19)	χ^2=0.03; 0.853

[1]Likelihood Ratio Test comparing a model assuming outcome-specific effect for each model vs model where the risk factor is common (i.e. constrained to be the same across outcomes)

[2]Small *p*-values indicate evidence of differences in fit between the two models, whereby the shared-effect model does not provide adequate fit for the data and an outcome-specific model provides a better fit.

Supplementary Table 8: The ORs (95% CI) and *p*-values for Mild and Moderate/Severe Depressive Episode at age 24 per SD Increase in IL-6 and CRP Levels at Age 9

Risk Factor	Adjusted Odds Ratio (95% C.I.)			
	No Depressive Episode	Mild Depressive Episode	Moderate/Severe Depressive Episode	Likelihood Ratio Test (χ^2, *p*-value)
IL-6	1 [Reference]	1.12 (0.86-1.46)	1.20 (1.05-1.36)	9.43, 0.014
CRP	1 [Reference]	1.01 (0.76-1.33)	1.09 (0.92-1.29)	0.87, 0.648

Supplementary Table 9: Odds Ratios for Psychosis and Depression (Binary Outcomes) at Age 24 per SD Increase in IL-6 and CRP Levels at Age 9 After Multiple Imputation

Outcome	Risk Factor	OR (95% C.I.)		*p*-value for adjusted model
		Unadjusted	Adjusted for sex, ethnicity, social class, BMI	
Definite PEs	IL-6	1.08 (0.94-1.25)	1.05 (0.90-1.21)	0.540
	CRP	1.07 (0.93-1.23)	1.00 (0.85-1.17)	0.924
Psychotic Disorder	IL-6	1.30 (1.01-1.80)	1.41 (1.12-2.25)	0.012
	CRP	0.96 (0.69-1.34)	0.97 (0.68-1.39)	0.858
Depressive Episode	IL-6	1.12 (1.00-1.27)	1.08 (0.98-1.21)	0.091
	CRP	1.09 (0.96-1.24)	0.98 (0.85-1.14)	0.826

Supplementary Table 10: Odds Ratios for Psychosis and Depression (Binary Outcomes) at Age 24 for Participants in Top and Middle Tertiles of IL-6 Distribution Compared with Bottom Tertile at Age 9 After Multiple Imputation

Outcome (Binary Variable)	Risk Factor (vs Bottom Tertile)	OR (95% C.I.)		p-value for adjusted model
		Unadjusted	Adjusted for sex, ethnicity, social class, BMI	
Definite PEs	Bottom Tertile	1 [Reference]	1 [Reference]	-
	Middle Tertile	0.96 (0.66-1.39)	0.91 (0.63-1.33)	0.641
	Top Tertile	1.23 (0.88-1.73)	1.14 (0.81-1.62)	0.453
Psychotic Disorder	Bottom Tertile	1 [Reference]	1 [Reference]	-
	Middle Tertile	0.82 (0.32-2.11)	0.83 (0.32-2.14)	0.693
	Top Tertile	1.82 (0.98-3.03)	1.54 (1.02-3.11)	0.035
Depressive Episode	Bottom Tertile	1 [Reference]	1 [Reference]	-
	Middle Tertile	1.19 (0.86-1.64)	1.11 (0.80-1.53)	0.535
	Top Tertile	1.36 (1.00-1.85)	1.19 (0.98-1.44)	0.068

Supplementary Table 11: ORs (95% CI) and *p*-values for Risk of Psychosis and Depression at Age 24 for Participants in Middle and Top Thirds of CRP Distributions, Compared with Bottom Third, at Age 9 After Multiple Imputation

Outcome (Binary Variable)	Risk Factor (vs Bottom Tertile)	OR (95% C.I.)		*p*-value for adjusted model
		Unadjusted	Adjusted for sex, ethnicity, social class, BMI	
Definite PEs	Bottom Tertile	1 [Reference]	1 [Reference]	-
	Middle Tertile	1.17 (0.83-1.67)	1.20 (0.79-1.60)	0.534
	Top Tertile	1.15 (0.82-1.64)	1.01 (0.69-1.47)	0.975
Psychotic Disorder	Bottom Tertile	1 [Reference]	1 [Reference]	-
	Middle Tertile	0.96 (0.42-2.19)	0.95 (0.42-2.17)	0.902
	Top Tertile	1.00 (0.46-2.14)	1.01 (0.44-2.28)	0.988
Depressive Episode	Bottom Tertile	1 [Reference]	1 [Reference]	-
	Middle Tertile	1.03 (0.74-1.45)	0.92 (0.65-1.30)	0.644
	Top Tertile	1.14 (0.83-1.55)	0.90 (0.64-1.26)	0.536

Supplementary Table 12: Increase in Negative and Depressive Symptoms (SDs) at age 24 per SD increase in IL-6 and CRP Levels at Age 9 After Multiple Imputation

Outcome	Risk Factor	Beta Coefficient (95% C.I.)		*p*-value for adjusted model
		Unadjusted	**Adjusted for sex, ethnicity, social class, BMI**	
Negative Symptoms	IL-6	0.04 (-0.06, 0.13)	0.04 (0.00, 0.07)	0.039
	CRP	0.00 (-0.09, 0.10)	-0.01 (-0.11, 0.10)	0.944
Depressive Symptoms Score	IL-6	0.10 (-0.06, 0.21)	0.03 (-0.11, 0.16)	0.726
	CRP	0.03 (-0.11, 0.16)	-0.07 (-0.21, 0.08)	0.359

Supplementary Table 13: Beta Coefficients (95% CI) and *p*-values for the SD Increase in Negative and Depressive Symptoms for Participants in Middle and Top Thirds of IL-6 Distributions, Compared with Bottom Third, at Age 9, After Multiple Imputation

Outcome	Risk Factor (vs Bottom Tertile)	Beta Coefficient (95% C.I.)		*p*-value for adjusted model
		Unadjusted	**Adjusted for sex, ethnicity, social class, BMI**	
Negative Symptoms	Bottom Tertile	1 [Reference]	1 [Reference]	-
	Middle Tertile	-0.01 (-0.23, 0.21)	-0.01 (-0.22, 0.21)	0.939
	Top Tertile	0.13 (-0.08, 0.34)	0.14 (0.00, 0.29)	0.023
Depressive Symptoms	Bottom Tertile	1 [Reference]	1 [Reference]	-
	Middle Tertile	0.17 (-0.14, 0.49)	0.11 (-0.20, 0.43)	0.493
	Top Tertile	0.22 (-0.09, 0.53)	0.12 (-0.20, 0.43)	0.470

Supplementary Table 14: Beta Coefficients (95% CI) and *p*-values for the SD Increase in Negative and Depressive Symptoms for Participants in Middle and Top Thirds of CRP Distributions, Compared with Bottom Third, at Age 9, After Multiple Imputation

Outcome	Risk Factor (vs Bottom Tertile)	Beta Coefficient (95% C.I.)		*p*-value for adjusted model
		Unadjusted	Adjusted for sex, ethnicity, social class, BMI	
Negative Symptoms	Bottom Tertile	1 [Reference]	1 [Reference]	-
	Middle Tertile	0.09 (-0.23, 0.41)	0.03 (-0.26, 0.28)	0.754
	Top Tertile	0.13 (-0.18, 0.43)	0.02 (-0.25, 0.27)	0.845
Depressive Symptoms	Bottom Tertile	1 [Reference]	1 [Reference]	-
	Middle Tertile	-0.05 (-0.27, 0.17)	-0.01 (-0.33, 0.31)	0.955
	Top Tertile	-0.02 (-0.23, 0.20)	-0.07 (-0.40, 0.27)	0.697