Inflammatory biomarkers and the risk of psychiatric disorders

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Introduction

- ➤ **Previous finding**
  - Inflammatory cytokines may contribute to neuropathology
  - Individuals with psychiatric disorders have been reported to have elevated levels of inflammatory biomarkers

- ➤ **Research gap**
  - Mostly cross-sectional design→the directionality and causality
  - Few cohort studies → inconsistent findings; limited sample size; reverse causation

- ➤ **Objective**
  - Investigate associations of blood inflammatory biomarkers with risk of any psychiatric disorder as well as, specifically to depression, anxiety, and stress-related disorders
  - Evaluate the causal relationship between inflammation and the studied psychiatric disorders

Study design

➢ **Part 1: The associations of inflammatory biomarkers with psychiatric disorders**

- 585 297 Exploration dataset: a prospective cohort analysis using the Swedish Apolipoprotein- Related Mortality Risk(AMORIS) study
  - Biomarkers: leukocytes, haptoglobin, immunoglobulin G(IgG), albumin, C-reactive protein, platelet, and albumin;
  - Subtypes of leukocyte: lymphocytes, monocytes, neutrophils, and eosinophils;
  - Others: lymphocyte to monocyte ratio(LMR), neutrophil to lymphocyte ratio (NLR),, platelet to lymphocyte ratio (PLR), and C-reactive protein to albumin ratio (CAR),
  - Outcomes: any psychiatric disorder, depression, anxiety, and stress-related disorders
- 485 620 Validation dataset: a prospective cohort analysis using the UK Biobank

- Sensitivity analyses
  - Repeated analysis in health check-up individuals (a sub cohort of AMORIS)
  - Excluding individuals with a history of cancer
  - Repeat analyses after excluding the first 5 years of follow-up (5 years Lag-time)
  - Stratify by sex

Main Result-Part 1

Table 1. Associations Between Inflammatory Biomarkers (Cutoff Points Set as Median Values) and Psychiatric Disorders

	Cutoff point	Any psychiatric disorder Outcomes (Incidence)	Hazard ratio(95%CI)	Depression Outcomes (Incidence)	Hazard ratio(95%CI)	Anxiety Outcomes (Incidence)	Hazard ratio(95%CI)	Stress-related disorder Outcomes (Incidence)	Hazard ratio(95%CI)
Inflammatory biomarkers									
Leukocyte (10**9/L)	≤6.3	19,821 (8.44)	Ref.	5,372 (2.18)	Ref.	4,411 (1.77)	Ref.	3,219 (1.29)	Ref.
Leukocyte (10**9/L)	> 6.3	18,822 (9.43)	**1.11 (1.09-1.14)**	5,166 (2.44)	**1.09 (1.05-1.14)**	4,232 (1.99)	**1.07 (1.03-1.12)**	3,073 (1.44)	1.03 (0.98-1.09)
Haptoglobin (g/L)	≤1	33,531 (5.97)	Ref.	8,761 (1.50)	Ref.	6,927 (1.18)	Ref.	5,320 (0.90)	Ref.
Haptoglobin (g/L)	> 1	32,635 (7.10)	**1.13 (1.12-1.15)**	7,987 (1.66)	**1.16 (1.12-1.19)**	5,717 (1.18)	**1.09 (1.05-1.13)**	3,849 (0.79)	**1.06 (1.02-1.10)**
Immunoglobulin G (g/L)	≤11	13,544 (7.57)	Ref.	3,306 (1.76)	Ref.	2,520 (1.33)	Ref.	1,621 (0.85)	Ref.
Immunoglobulin G (g/L)	> 11	10,406 (6.99)	**0.92 (0.89-0.94)**	2,696 (1.73)	**0.95 (0.90-0.99)**	2,089 (1.33)	**0.93 (0.88-0.99)**	1,414 (0.90)	**0.93 (0.86-1.00)**
C-reactive protein (mg/L)	≤4	32,254 (6.79)	Ref.	8,635 (1.74)	Ref.	6,942 (1.39)	Ref.	5,095 (1.02)	Ref.
C-reactive protein (mg/L)	> 4	22,494 (7.09)	**1.02 (1.00-1.04)**	5,879 (1.77)	1.02 (0.98-1.05)	4,577 (1.37)	1.00 (0.96-1.03)	3,355 (1.00)	1.01 (0.96-1.05)
Platelet (10**9/L)	≤256	18,243 (8.94)	Ref.	4,854 (2.25)	Ref.	4,045 (1.87)	Ref.	2,966 (1.36)	Ref.
Platelet (10**9/L)	> 256	18,857 (8.96)	**0.98 (0.96-1.00)**	5,265 (2.37)	1.01 (0.97-1.05)	4,262 (1.90)	**0.95 (0.91-0.99)**	3,026 (1.35)	**0.92 (0.87-0.96)**
Albumin (g/L)	≤43	43,791 (7.17)	Ref.	10,743 (1.69)	Ref.	7,948 (1.24)	Ref.	5,662 (0.88)	Ref.
Albumin (g/L)	> 43	36,492 (6.52)	**1.02 (1.01-1.04)**	10,072 (1.72)	1.03 (1.00-1.06)	8,201 (1.39)	**1.13 (1.09-1.16)**	6,233 (1.06)	**1.06 (1.02-1.10)**
Subtypes of leukocyte									
Lymphocyte (10**9/L)	≤2.07	5,257 (9.31)	Ref.	1,455 (2.44)	Ref.	1,225 (2.04)	Ref.	891 (1.48)	Ref.
Lymphocyte (10**9/L)	>2.07	5,376 (9.25)	1.01 (0.97-1.04)	1,535 (2.49)	1.01 (0.94-1.08)	1,262 (2.04)	0.97 (0.89-1.05)	982 (1.58)	1.00 (0.91-1.10)
Monocyte (10**9/L)	≤0.38	5,391 (8.76)	Ref.	1,502 (2.31)	Ref.	1,215 (1.86)	Ref.	944 (1.44)	Ref.
Monocyte (10**9/L)	>0.38	5,241 (9.88)	**1.16 (1.11-1.20)**	1,488 (2.65)	**1.17 (1.09-1.26)**	1,271 (2.25)	**1.29 (1.19-1.40)**	929 (1.63)	**1.22 (1.12-1.34)**
Neutrophil (10**9/L)	≤3.6	2,896 (10.33)	Ref.	805 (2.71)	Ref.	694 (2.32)	Ref.	539 (1.79)	Ref.
Neutrophil (10**9/L)	>3.6	2,734 (10.98)	**1.06 (1.00-1.11)**	790 (2.98)	1.08 (0.98-1.20)	683 (2.56)	1.09 (0.98-1.21)	501 (1.87)	1.00 (0.88-1.13)
Eosinophil (10**9/L)	≤0.14	5,308 (9.09)	Ref.	1,531 (2.48)	Ref.	1,303 (2.10)	Ref.	976 (1.56)	Ref.
Eosinophil (10**9/L)	>0.14	5,325 (9.48)	**1.05 (1.01-1.09)**	1,459 (2.45)	1.01 (0.94-1.09)	1,184 (1.98)	0.98 (0.91-1.06)	897 (1.49)	1.03 (0.94-1.13)
Others									
LMR	≤5.5	5,216 (9.88)	Ref.	1,476 (2.64)	Ref.	1,232 (2.19)	Ref.	904 (1.60)	Ref.
LMR	>5.5	5,317 (8.79)	**0.87 (0.84-0.91)**	1,487 (2.33)	**0.85 (0.79-0.92)**	1,236 (1.92)	**0.81 (0.75-0.88)**	955 (1.48)	**0.84 (0.76-0.92)**
NLR	≤1.86	2,821 (10.26)	Ref.	795 (2.73)	Ref.	698 (2.38)	Ref.	535 (1.82)	Ref.
NLR	> 1.86	2,809 (11.03)	**1.08 (1.02-1.13)**	800 (2.95)	1.09 (0.98-1.20)	679 (2.49)	1.05 (0.95-1.17)	505 (1.84)	1.01 (0.90-1.14)
PLR	≤126.45	4,888 (9.46)	Ref.	1,365 (2.50)	Ref.	1,136 (2.07)	Ref.	867 (1.57)	Ref.
PLR	>126.45	4,844 (9.41)	0.97 (0.93-1.01)	1,374 (2.52)	1.00 (0.93-1.08)	1,131 (2.06)	0.99 (0.91-1.08)	820 (1.49)	0.98 (0.89-1.07)
CAR	≤0.09	26,082 (6.65)	Ref.	6,958 (1.70)	Ref.	5,598 (1.36)	Ref.	4,102 (0.99)	Ref.
CAR	>0.09	25,702 (7.31)	**1.06 (1.04-1.07)**	6,720 (1.83)	**1.05 (1.01-1.09)**	5,268 (1.43)	**1.04 (1.00-1.08)**	3,833 (1.03)	**1.06 (1.01-1.11)**

Similar results in sensitivity analyses

Study design

> **Part 2: Longitudinal trajectories of changes in inflammatory biomarkers prior to the diagnosis of psychiatric disorders**

- AMORIS data: a nested case-control analysis
- To visualize longitudinal patterns of inflammatory biomarkers prior to the date of diagnosis (up to 30 years)
- To evaluate the associations of inflammatory biomarkers with common psychiatric disorders by each 2-years period before the diagnosis

> **Method**

- Locally weighted scatterplot smoothing: plot the mean concentrations of inflammatory biomarker by the time to index time (diagnosed time) using locally weighted scatterplot smoothing
- Conditional logistic models: calculate odds ratios (ORs) during each 2-years period of the 30 years before the diagnosis.
- Linear mixed effects model: assess the differences in inflammatory biomarker trajectories by disease status

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Main Result-Part 2
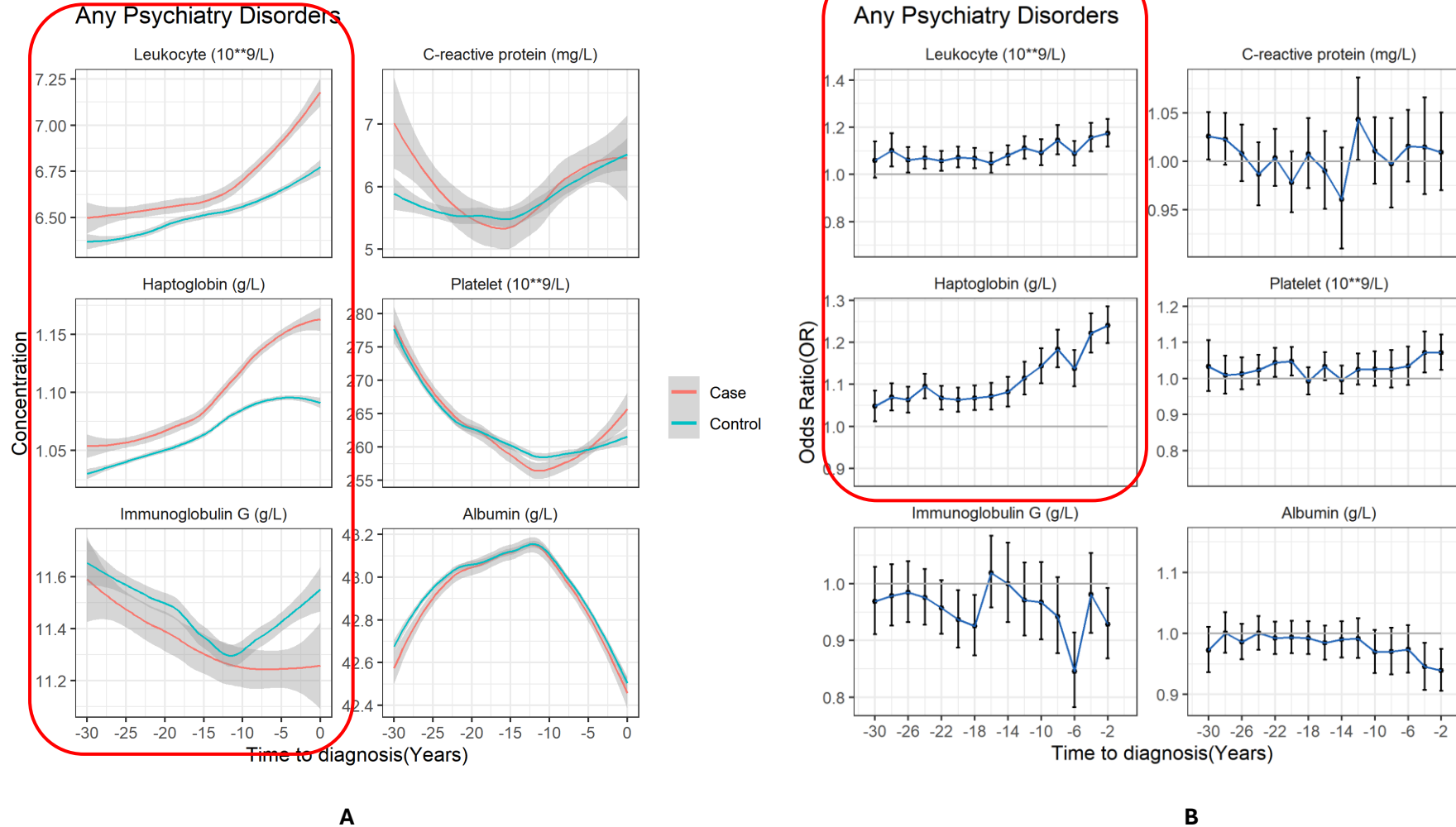
Largely similar results were observed for depression, anxiety, and stress-related disorders

A

B

Figure 1 Trajectories of inflammatory biomarkers and the association with subsequent any psychiatric disorders. A. Mean concentrations of inflammatory biomarkers between cases and controls during the 30 years before the index date. B. Odds ratios (ORs) and 95% confidence intervals (CIs) for the associations of inflammatory biomarkers with any psychiatry disorder with the standardization by standard deviation in each 2-year period of the 30 years before the index date. Odds Ratio and 95% CIs were estimated by conditional logistic regression models, adjusting for matching factors (sex, year of birth, and calendar period of enrollment to the AMORIS Study) and fasting status at sampling.
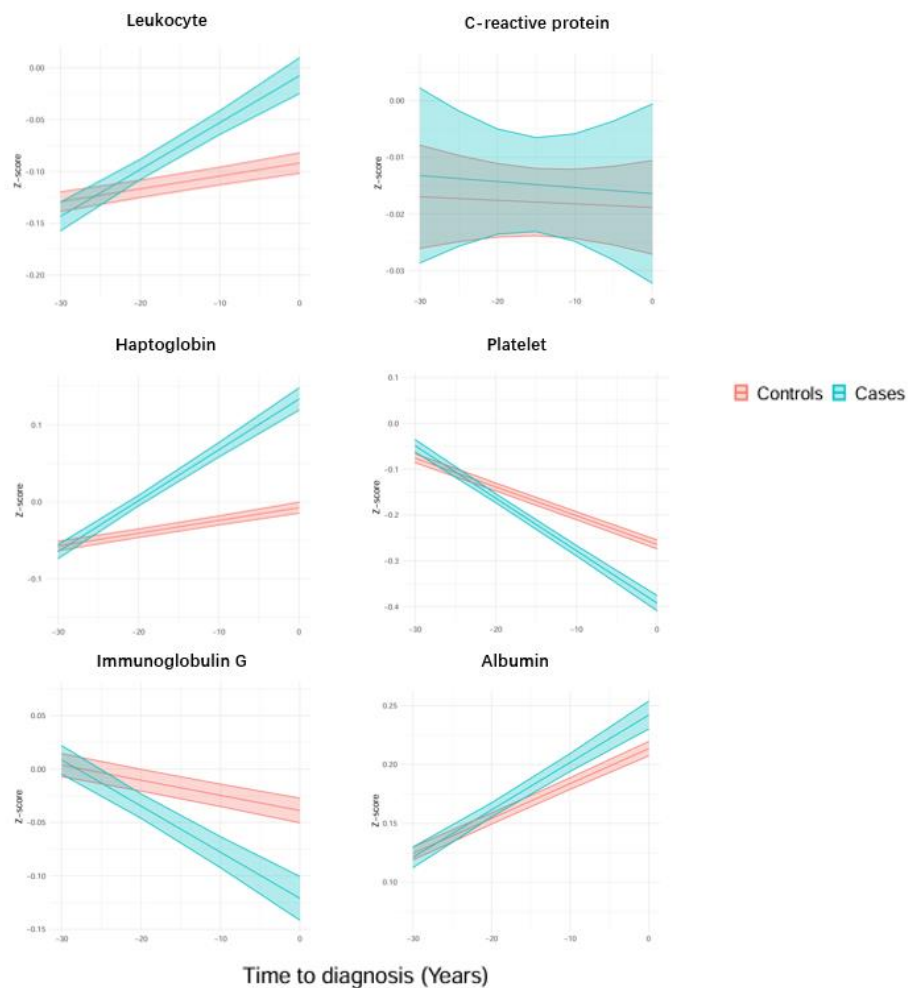
eFigure 9 T Trajectories of inflammatory biomarkers during the 30 years before diagnosis in cases of any psychiatric disorders and their individually matched controls, using linear mixed-effects models. The figure represents the associations of psychiatry disorders with trajectories of inflammatory biomarker, adjusted for time, time^2, time*disease status, time^2*disease status, sex, birth year, and fasting status at sampling

eTable 12 β coefficient and 95% confidence intervals of the association between inflammatory biomarkers and risk of any psychiatric disorders - analysis using linear mixed-effects model

	β Coefficient and 95% confidence intervals [a]	
Biomarker	Difference at the biomarkers level between case and control	Difference at the biomarkers change rate between case and control
Leukocyte	0.084 (0.076-0.093)	0.003 (0.003-0.004)
Haptoglobin	0.141 (0.134-0.148)	0.005 (0.005-0.005)
Immunoglobulin G	-0.082 (-0.092--0.073)	-0.003 (-0.003--0.002)
C-reactive protein	0.002 (-0.006-0.011)	-0.000 (-0.001-0.000)
Platelet	-0.128 (-0.136--0.120)	-0.005 (-0.006--0.005)
Albumin	0.029 (0.023-0.035)	0.001 (0.001-0.001)

Both the level and change rate of **leukocytes, haptoglobin and IgG** significantly differed between patients with any psychiatric disorder and controls

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Study design

➢ **Part 3: Genetic correlation and causal relationship between inflammatory biomarkers and common psychiatric disorders**

- GWAS summary statistics: Genetic correlation analysis and MR analysis

- Linkage disequilibrium score regression(LDSC) and genetic covariance analyzer approach(GNOVA) to detect the pleiotropic effect

- Inverse variance–weighted method (IVW method), MR-Egger, the weighted median regression method and MR with correlated horizontal pleiotropy unraveling shared etiology and Confounding(MR-CUE) to estimate the causal associations

Main Result-Part 3

eTable 13 The genetic correlations between inflammatory biomarkers and depression, anxiety, and stress-related disorders

	Depression		Anxiety		Stress related-disorders	
	LDSC	GNOVA	LDSC	GNOVA	LDSC	GNOVA
Biomarker	r_g (95%CI)	r_g (95%CI)	r_g (95%CI)	r_g (95%CI)	r_g (95%CI)	r_g (95%CI)
Inflammatory biomarkers						
Leukocyte	0.03 (-0.03-0.09)	0.08 (-0.01-0.17)	0.12 (-0.07-0.30)	**0.19 (0.05-0.33)**	-0.01 (-0.09-0.08)	-0.01 (-0.09-0.08)
Haptoglobin	0.08 (-0.08-0.24)	0.10 (-0.06-0.25)	0.10 (-0.17-0.38)	0.22 (-0.04-0.49)	0.09 (-0.21-0.38)	0.12 (-0.15-0.40)
Immunoglobulin G	-0.06 (-0.31-0.20)	-0.11 (-0.28-0.06)	0.01 (-0.71-0.74)	-0.22 (-0.57-0.14)	-0.26 (-0.58-0.06)	-0.18 (-0.35--0.01)
C-reactive protein	**0.14 (0.09-0.19)**	**0.12 (0.07-0.16)**	0.07 (-0.07-0.21)	0.02 (-0.10-0.13)	**0.24 (0.14-0.34)**	**0.22 (0.14-0.30)**
Platelet	-0.02 (-0.08-0.03)	-0.01 (-0.06-0.03)	-0.00 (-0.15-0.14)	0.03 (-0.07-0.12)	-0.07 (-0.15-0.01)	**-0.06 (-0.12--0.00)**
Albumin	0.03 (-0.03-0.08)	-0.03 (-0.07-0.01)	0.04 (-0.12-0.20)	0.02 (-0.08-0.11)	**-0.10 (-0.17--0.02)**	**-0.08 (-0.12--0.03)**
Subtypes of leukocyte						
Neutrophil	0.07 (0.01-0.13)	0.05 (-0.00-0.11)	0.07 (-0.09-0.22)	-0.03 (-0.15-0.08)	0.02 (-0.06-0.09)	-0.04 (-0.10-0.02)
Lymphocyte	0.00 (-0.05-0.06)	0.08 (-0.02-0.17)	0.03 (-0.12-0.17)	**0.16 (0.04-0.29)**	0.01 (-0.06-0.08)	0.06 (-0.02-0.14)
Monocyte	0.05 (-0.01-0.10)	0.10 (0.03-0.18)	0.07 (-0.09-0.24)	0.18 (0.06-0.30)	0.03 (-0.06-0.12)	0.05 (-0.03-0.13)
Eosinophil	-0.06 (-0.11-0.01)	-0.02 (-0.10-0.05)	-0.02 (-0.17-0.12)	0.05 (-0.06-0.15)	-0.01 (-0.08-0.06)	0.01 (-0.05-0.07)
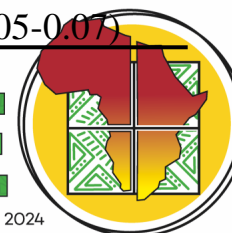
Main Result-Part 3

Table 3 The associations of inflammatory biomarkers with depression, anxiety, and stress-related disorders according to the Mendelian Randomization analysis

Biomarker	N_SNP	PVE	F	MR-IVW ß (95%CI)	P	MR-Egger ß (95%CI)	P	MR-Weighted median ß (95%CI)	P	MR-CUE ß (95%CI)	P
Depression											
Inflammatory biomarkers											
Leukocyte	222	8.61%	73.05	**0.06 (0.013-0.107)**	**0.013**	**0.135 (0.025-0.245)**	**0.016**	**0.088 (0.013-0.163)**	**0.021**	**0.080 (0.042-0.119)**	**4.64E-05**
Haptoglobin	26	47.71%	374.89	-0.005 (-0.024-0.013)	0.571	0.015 (-0.025-0.055)	0.475	-0.012 (-0.037-0.014)	0.366	0.004 (-0.002-0.009)	0.183
Immunoglobulin G	2	1.23%	66.59	-0.015 (-0.149-0.119)	0.825	--	--	--	--	-0.008 (-0.032-0.016)	0.514
C-reactive protein	440	9.19%	132.33	**0.059 (0.014-0.104)**	**0.010**	0.032 (-0.038-0.103)	0.371	0.032 (-0.039-0.103)	0.373	**0.091 (0.050-0.131)**	**9.32E-07**
Platelet	329	17.15%	104.31	-0.004 (-0.036-0.028)	0.804	-0.068 (-0.135-0.000)	0.050	-0.017 (-0.067-0.033)	0.504	0.011 (-0.020-0.042)	0.478
Albumin	382	7.83%	79.57	-0.023 (-0.077-0.032)	0.417	-0.065 (-0.172-0.042)	0.237	-0.065 (-0.148-0.018)	0.125	-0.004 (-0.052-0.043)	0.864
Subtypes of leukocyte											
Neutrophil	188	7.92%	77.96	-0.002 (-0.050-0.045)	0.927	-0.059 (-0.172-0.053)	0.301	-0.007 (-0.078-0.063)	0.839	0.008 (-0.035-0.051)	0.711
Lymphocyte	221	9.10%	77.62	0.012 (-0.033-0.058)	0.597	**0.118 (0.011-0.224)**	**0.030**	0.006 (-0.062-0.074)	0.857	0.044 (0.004-0.083)	0.030
Monocyte	304	16.55%	111.20	0.02 (-0.016-0.055)	0.278	0.027 (-0.040-0.095)	0.428	0.014 (-0.039-0.066)	0.604	0.036 (0.003-0.069)	0.033
Eosinophil	240	10.27%	82.08	0.025 (-0.017-0.066)	0.246	0.004 (-0.093-0.101)	0.933	0.019 (-0.044-0.081)	0.559	0.005 (-0.036-0.046)	0.820
Anxiety											
Inflammatory biomarkers											
Leukocyte	211	8.53%	76.12	-0.02 (-0.161-0.120)	0.776	**0.415 (0.061- 0.768)**	**0.022**	0.131 (-0.090-0.352)	0.247	0.083 (-0.047-0.212)	0.210
Haptoglobin	15	37.47%	427.22	-0.001 (-0.068-0.066)	0.972	-0.043 (-0.169-0.083)	0.503	0.009 (-0.077-0.095)	0.840	0.010 (-0.035-0.054)	0.669
Immunoglobulin G	2	1.23%	66.59	-0.589 (-1.528-0.349)	0.218	--	--	--	--	0.014 (-0.065-0.093)	0.725
C-reactive protein	378	8.02%	132.63	0.056 (-0.083-0.196)	0.429	0.056 (-0.181-0.293)	0.642	-0.005 (-0.241-0.232)	0.969	0.062 (-0.063-0.188)	0.330
Platelet	305	16.46%	107.07	-0.027 (-0.128-0.073)	0.591	0.101 (-0.120-0.323)	0.370	0.041 (-0.126-0.207)	0.633	-0.064 (-0.161-0.033)	0.196
Albumin	356	6.87%	74.16	-0.006 (-0.189-0.178)	0.950	-0.203 (-0.650-0.244)	0.374	-0.116 (-0.408-0.176)	0.436	0.046 (-0.100-0.191)	0.537
Subtypes of leukocyte											
Neutrophil	179	7.60%	78.38	0.035 (-0.107-0.178)	0.626	-0.080 (-0.427-0.267)	0.651	0.143 (-0.090-0.377)	0.228	-0.028 (-0.163-0.106)	0.681
Lymphocyte	212	9.01%	80.05	-0.071 (-0.211-0.069)	0.317	0.114 (-0.251-0.479)	0.539	0.017 (-0.196-0.229)	0.876	-0.028 (-0.148-0.092)	0.647
Monocyte	279	14.87%	106.71	0.05 (-0.054-0.154)	0.342	0.261 (0.045- 0.476)	0.018	0.140 (-0.036-0.316)	0.120	0.039 (-0.072-0.151)	0.489
Eosinophil	220	9.78%	84.77	0.035 (-0.094-0.164)	0.594	0.034 (-0.277-0.345)	0.829	0.032 (-0.170-0.234)	0.758	0.019 (-0.099-0.137)	0.752
Stress-related disorders											
Inflammatory biomarkers											
Leukocyte	216	8.44%	73.47	0.067 (-0.023-0.156)	0.144	**0.213 (0.003-0.423)**	**0.047**	0.107 (-0.040-0.253)	0.154	0.074 (-0.004-0.153)	0.063
Haptoglobin	24	44.91%	362.87	-0.023 (-0.062-0.016)	0.248	0.022 (-0.063-0.107)	0.613	-0.039 (-0.091-0.013)	0.145	0.013 (-0.016-0.042)	0.374
Immunoglobulin G	2	0.64%	34.24	-0.18 (-0.562-0.201)	0.354	--	--	--	--	-0.009 (-0.065-0.046)	0.741

Summary

- **Question:** Are inflammatory biomarkers associated with subsequent risk of psychiatric disorders? Whether such associations represent causal relationships?

- **Findings:** Leveraging large-scale data from the Swedish AMORIS cohort, the UK Biobank, and GWAS summary statistics, we <u>found inflammatory biomarkers including leukocytes, haptoglobin, C-reactive protein, and immunoglobulin G</u> were associated with the risk of psychiatric disorders using cohort and nested case-control study analysis. Moreover, mendelian randomization analyses suggested <u>a possible causal link between leukocytes and depression</u>.

- **Meaning:** These findings provide supportive evidence on the role of inflammatory alternations in the development of psychiatric disorders and may aid in identifying individuals at high risk.

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Research

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Inflammatory Biomarkers and Risk of Psychiatric Disorders

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Thank you for listening!