

Association between neutrophil to lymphocyte ratio and Alzheimer's disease in large biobank cohorts

Journal of Alzheimer's Disease

2025, Vol. 108(3) 1302–1311

© The Author(s) 2025



Article reuse guidelines:

sagepub.com/journals-permissions

DOI: 10.1177/13872877251386813

journals.sagepub.com/home/alz



Emily Drzymalla¹, Christy Avery¹ , Priya Palta², Alexander P Reiner³, Quan Sun^{4,5} and Laura M Raffield⁶

Abstract

Background: Neutrophil to lymphocyte ratio (NLR) is an inflammatory biomarker for chronic disease that also may provide evidence for peripheral innate immune activation in Alzheimer's disease (AD) pathogenesis.

Objective: The objective of this study is to assess the association between NLR and AD as a biomarker or potential causal step for AD pathogenesis.

Methods: Cohorts used for analysis include the UK Biobank ($n = 207\,100$; $n = 2\,198$ AD cases) and the All of Us research program (AoU, $n = 45\,202$; $n = 263$ AD cases) which allowed for a larger sample size than most previous studies. Cox proportional hazard models were used to assess the association between NLR and AD, including in models adjusting for factors in the UK Biobank Dementia Risk Score. A Mendelian randomization analysis was performed to assess the potential causality between NLR and AD.

Results: NLR was associated with AD in the UK Biobank (HR: 1.03 per 1 SD, 95% CI: 1.01–1.05) but not in AoU (HR: 1.02, 95% CI: 0.92–1.14). A fixed effects model resulted in a pooled HR: 1.03 (95% CI: 1.02–1.05). These effects were robust to adjustment for C-reactive protein, APOE $\epsilon 4$ genotype status, APOE $\epsilon 2$ genotype status, and other AD risk factors. The MR analysis was performed with 214 NLR-associated variants but was not significant (IVW estimate: -0.001 , p : 0.99).

Conclusions: Findings provide evidence for NLR as a biomarker for AD but not as a causal risk factor.

Keywords

Alzheimer's disease, biobank, inflammation, Mendelian randomization, neutrophil to lymphocyte ratio

Received: 9 May 2025; accepted: 4 September 2025

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease resulting in impairments in cognition and functional abilities and is the leading cause of dementia.¹ In the United States, 6.5 million people 65 years or older are estimated to have AD and the prevalence is projected to increase to 13.8 million by 2060.² While AD is characterized by amyloid plaques and neurofibrillary tangles,¹ the complete pathogenesis of AD is not understood. Inflammation, both systemic and brain-specific, is thought to play a role in AD.³

The peripheral immune system is the portion of the immune system that resides outside of the central nervous system and is responsible for mounting an immune response including inflammation to pathogens and injury. However, even though this system is outside of the central nervous system, changes in the peripheral immune

¹Department of Epidemiology, Gillings School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

²Department of Neurology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

³Department of Epidemiology, University of Washington, Seattle, WA, USA

⁴Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

⁵Center for Computational and Genomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA

⁶Department of Genetics, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Corresponding author:

Laura Raffield, Department of Genetics, School of Medicine, University of North Carolina at Chapel Hill, 120 Mason Farm Road, 5042 Genetic Medicine Building 7264, Chapel Hill, NC 27599, USA.

Email: laura_raffield@unc.edu

system such as peripheral inflammation have been associated with neurodegenerative diseases including AD.⁴ It has been hypothesized that systemic peripheral inflammation may lead to neuroinflammation through an increase in cytokine transport across the blood brain barrier.⁵ Dysregulated cross-talk or movement of peripheral immune cells or signals crossing the blood brain barrier could lead to excessive neuroinflammation and accelerate neuron death.^{5–7} Systemic inflammation would result in an increase in the concentration of pro-inflammatory cytokines and therefore could increase the amount of pro-inflammatory cytokines that can cross the blood brain barrier.⁵ Systemic inflammation could also disrupt the blood brain barrier and allow for the increase the movement of lymphocytes, natural killer cells, and neutrophils from the peripheral immune system across the blood brain barrier into the central nervous system.⁷ Systemic inflammation markers could also correlate with much more difficult to measure neuroinflammation metrics, even if they are not causally related to AD development. Such inflammation markers have been associated with AD. For example, higher levels of the inflammatory biomarker interleukin 6 (IL-6), a cytokine with effects on multiple processes including inflammation,⁸ have been associated with AD risk in a large meta-analysis.⁹ Midlife C-reactive protein (CRP), a protein produced in response to inflammation,¹⁰ also has been associated with higher AD risk.^{9,11–13} Prolonged elevation in CRP levels may indicate chronic inflammation possibly due to certain chronic conditions.¹⁴ For example, a CRP level less than 0.3 mg/dL is considered normal for most healthy adults.¹⁴ However, a CRP level between 1.0 and 10.0 mg/dL can be considered moderate elevation that is associated with systematic inflammation, for example due to rheumatoid arthritis, autoimmune diseases, or other conditions.¹⁴ While CRP is used as a marker for inflammation, CRP, depending on the isoform, has both anti-inflammatory and pro-inflammatory effects.¹⁵

Neutrophil to lymphocyte ratio (NLR) is a marker for systemic inflammation, reflecting the balance between innate (neutrophil) and adaptive (lymphocyte) immune system cells.¹⁶ High NLR (reflecting greater innate immune activation in the periphery) has been associated with higher overall mortality and increased cardiovascular disease prevalence.^{17,18} Higher levels of NLR have also been associated with increased AD risk and age-related cognitive impairment; however, these associations have been mostly in relatively small cross-sectional case control studies which are unable to or have difficulty establishing temporality.^{19–24} One study with a longitudinal prospective design found higher NLR to be associated with incident dementia, of which 80% of cases were classified as AD.²⁵ Recent work in UK Biobank has found NLR to be associated with dementia, among other brain disorders, but it is unclear how robust this association is to adjustment for other well-known AD risk factors and important covariates such as hypertension and hypercholesterolemia.²⁶ Another study in the UK

Biobank with 161,968 participants found higher NLR was associated with all-cause dementia (HR: 1.03, 95% CI: 1.01–1.05).²⁷ While this study adjusted for blood pressure, other potential confounders used in existing dementia prediction models such as parental dementia history and type 2 diabetes (T2D) were not controlled.²⁷ It should also be noted that since NLR involves neutrophils, the NLR will be affected by the Duffy null variant (rs2814778-CC). Duffy null status has been associated with lower neutrophil counts and lower NLR when compared to Duffy non-null status.^{28,29} As a result, Duffy null status may be an important component to consider when assessing the association between NLR and AD. Examining the association between NLR and AD in large biobank cohorts could provide further evidence for the role of inflammation in AD pathogenesis.

Mendelian randomization (MR) may provide further insight by assessing the potential causality between NLR and incident AD. Through using genetic factors as a proxy for the exposure of interest, MR can mimic a randomized control trial and combat common concerns for observational studies including reverse causation and confounding.^{30,31} However, it should be noted that certain assumptions (genetic variant is associated with the exposure, the genetic variant only affects the outcome through the exposure, and there are no confounders between the genetic variant and outcome) are required for MR to be valid.³² We include multiple MR methods to try to address such limitations (for example variant pleiotropy).

Here, we aim to investigate the association between AD and NLR in two large cohorts (UK Biobank and All of Us (AoU)) with the hypothesis that a higher NLR would be associated with a higher risk of incident AD and that this association would be robust to adjusting for variables in the UK Biobank Dementia Risk Score (UKBDRS)³³ including age, sex, education, diabetes history, depression history, stroke history, parental history of dementia, material deprivation, hypertension, high cholesterol, and household occupancy as well as the Duffy null status (which impacts NLR)³⁴ and the *APOE* $\epsilon 4$ and *APOE* $\epsilon 2$ variants.

Methods

The UK Biobank is a prospective cohort study that began in 2006 and has continued to the present day. This cohort has phenotypic and genetic data on 502,649 participants, aged 40 to 69 years old, throughout 22 assessment centers in Wales, Scotland, and England.^{35–37} AD was defined using inpatient ICD10/9 codes and death certificates. In other cohorts, ICD-10 codes F00 and G30 have been found to have a positive predictive value (PPV) of 74.8% and a sensitivity of 71.4% in primary care.³⁸ ICD-9 code 331.0 has been found to have a 36.5% sensitivity, 99.0% specificity, and 97.9% PPV and death certificates using this ICD-9 code have been found to have a 28% sensitivity and 98% specificity.^{39,40} Follow-up time was from the date of

baseline blood draw to either date of AD diagnosis, date of death, or last date of follow-up. The blood draw measurements and covariate data were from the time of baseline in-person assessment and the last date of follow-up was based on source of hospital admission (Hospital Episode Statistics for England: September-30-2021, Scottish Morbidity Record: July-31-2021, Patient Episode Database for Wales: February-28-2018). The lymphocyte count and neutrophil count came from the blood draw at the initial assessment visit.⁴¹ Controls were restricted to individuals 65 years or older at the end of follow up.

AoU is a cohort, starting in 2018, that began recruiting participants in May 2018 at least 18 years old or older from 340 sites with the goal of creating a diverse US cohort of 1 million participants.⁴² Data for this cohort comes from questionnaires, electronic health records (EHR), physical measurements, digital technology, and biospecimen collection.⁴² AD was also defined using the same ICD10/9 codes as in UK Biobank. The time of blood draw was assigned as the time of the blood draw for the median value of lymphocyte count. Participants without neutrophil or lymphocyte information or with certain blood related disorders before or a year after the time of blood draw were excluded from the analysis (Supplemental Table 3). Time of blood draw and time of AD diagnosis (based on medical billing codes) were obtained by EHR. The last date of follow up for AoU (version 8) was October 1, 2023.⁴³ In AoU, participants could have multiple neutrophil and lymphocyte measurements over time. As a result, the lymphocyte count used for NLR was defined as the median lymphocyte count and the neutrophil count was defined as the neutrophil count taken at the time of the median lymphocyte count. Participants with a median lymphocyte count or neutrophil count equal to 0 or greater than $50 \times 10^3/\mu\text{L}$ were excluded due to lack of plausibility of the value.^{44,45} These thresholds were also applied to monocyte count, while platelet count was restricted to values greater than 0 but less than $2000 \times 10^3/\mu\text{L}$. Controls were restricted to individuals 65 years or older at the end of follow up and AD cases were restricted to individuals 65 years or older at first ICD code. We also performed a sensitivity analysis using the first instead of median lymphocyte count.

Statistical analysis

In the UK Biobank, Cox proportional hazards models were used to estimate hazard ratios (HR) adjusting for variables previously described in the UKBDRS (Supplemental Table 1)³³ as well as self-reported ethnicity (Field 21000) and assessment center (Field 54). The variables in the UKBDRS were chosen from 28 variables using a Cox LASSO regression in the UK Biobank and the Whitehall II cohorts as the strongest predictors for incident dementia.³³ Self-reported ethnicity (and self-reported race in

AoU) is adjusted for due to differential diagnosis rates of AD based on social constructs.⁴⁶ Duffy null status (defined by rs2814778-CC genotype, imputation quality = 1.0), which causes lifelong lower neutrophil counts,^{34,47} was also included as a covariate. This variant, rare in European ancestry populations but more common in populations with West African ancestry,⁴⁷ has been previously demonstrated to influence the association of NLR with mortality and CVD.³⁴ In AoU, Cox proportional hazards models were adjusted for age, sex, race and ethnicity, and Duffy null status (rs2814778-CC). AD-related risk factors used in the UK Biobank model were not adjusted for in AoU due to extensive missing data. A fixed effects model using the metafor R package was used to pool the estimates from UK Biobank and AoU with similar covariates (age, sex, race, and ethnicity).

As a sensitivity analysis, the model was further adjusted for CRP due to CRP being a more commonly measured inflammation marker, with conflicting prior evidence of association with AD.¹¹⁻¹³ Sensitivity analyses were also adjusted for *APOE* $\epsilon 4$ and *APOE* $\epsilon 2$ status (rs429358, rs7412). We also examined models with neutrophil and lymphocyte count separately to determine if ratio associations were driven by individual cell counts. Monocyte to lymphocyte ratio (MLR) and platelet to lymphocyte ratio (PLR) were also investigated as exposures in supplementary analyses due to MLR and PLR being other complete blood count derived inflammation markers.⁴⁸ Interaction between NLR and sex was also tested for in UK Biobank due to sex differences in AD and in immune function. This interaction was not tested for in AoU due to the small number of AD cases. An expanded definition of dementia was also used as a sensitivity analysis (Supplemental Table 2).⁴⁹

In addition, a two-sample Mendelian randomization (MR) analysis was performed to further assess the association of NLR with AD. While a disadvantage of MR is risk of being underpowered, MR provides insight when reverse causality is a concern. Since AD is hypothesized to begin decades before symptoms first appear, it is possible the NLR measurement may be after AD started to develop. MR can help address this concern. First, a genome wide association study (GWAS) was performed in the UK Biobank to uncover variants for the MR analysis for NLR as NLR was not included in prior large-scale UK Biobank blood cell trait GWAS.⁵⁰ Using REGENIE (v4.1), the GWAS included 9,741,125 variants (imputation quality threshold: 0.50, minor allele frequency: 1%) and 400,131 participants who had complete NLR and covariate information (age, sex, genotyping array, first 10 principal components) and were in the European ancestry cluster based on similarity to 1000G reference panel, as described previously.⁵¹ The p-value threshold for significance was 5×10^{-8} . The top variant at each locus, excluding the highly pleiotropic *APOE*, *ABO*, and *HLA* regions, was used for the MR analysis. Each locus was defined as a 1 Mb

Table 1. Population characteristics in UK Biobank and All of Us (AoU).

Cohort Characteristics	UK Biobank	All of Us
Total participants	207100	45202
Median follow-up time (y)	12.5	5.1
Alzheimer's disease (%)	2198 (1.1%)	263 (0.6%)
Mean NLR (SD)	2.33 (1.2)	3.20 (3.0)
Mean neutrophil (SD)	4.20 (1.4)	4.59 (2.5)
Mean lymphocyte (SD)	1.95 (0.6)	1.71 (0.7)
Mean CRP (SD)	2.69 (4.4)	N/A
Mean age (SD)	61.34 (4.7)	67.8 (8.3)
Female (%)	114573 (55.3%)	24557 (54.3%)
Duffy null (%)	1280 (0.6%)	3414 (7.6%)
Education (SD)	13.8 (3.1)	N/A
Hypertension (%)	98873 (47.7%)	N/A
Type 2 diabetes (%)	13394 (6.5%)	N/A
Self-reported ethnicity (UK Biobank categories)		
White (%)	193045 (93.2%)	N/A
Mixed (%)	6127 (3.0%)	N/A
Asian or Asian British (%)	5707 (2.8%)	N/A
Black or Black British (%)	705 (0.3%)	N/A
Chinese (%)	382 (0.2%)	N/A
Other ethnic group (%)	1134 (0.5%)	N/A
Self-reported race and ethnicity (AoU combined categories)*		
Non-Hispanic White (%)	N/A	34496 (76.3%)
Non-Hispanic Black or African American (%)	N/A	4361 (9.6%)
Hispanic or Latino (%)	N/A	4010 (8.9%)
Other race/ethnicity (%)	N/A	2335 (5.2%)
High cholesterol	41121 (19.9%)	N/A
Stroke (%)	5730 (2.8%)	N/A
Mean Townsend Deprivation Index (SD)	-1.59 (2.93)	N/A
Paternal dementia family history (%)	32452 (15.7%)	N/A
Household occupancy (SD)	2.14 (1.1)	N/A
Depression (%)	13302 (6.4%)	N/A

*The AoU race and ethnicity variables combined. If ethnicity variable response was "Hispanic or Latino", combined race and ethnicity was classified as Hispanic or Latino. If not, combined race and ethnicity was classified as the response to the AoU race variable.

region, 500 kb on each side of the lead SNP. The corresponding effect sizes for these SNPs with AD was obtained from the Bellenguez et al. GWAS summary statistics.⁵² We focused on inverse-variance weighted (IVW) estimator due to the lack of nominal significance ($p < 0.2$) of MR-Egger intercept to test for directional pleiotropy, though we also added MR-Egger estimator (R package: MendelianRandomization version 0.10.0) to supplemental tables for sensitivity analysis.⁵³

Results

Of the 502,539 available UK Biobank participants, 431,812 had blood cell information and did not have blood related disorders (Supplemental Table 3).^{54,55} Of these participants, 207,100 had last-day of follow-up, controls 65 years or older at the end of follow up, and covariate information. Among the 207,100 UK Biobank participants eligible for our study, mean age at baseline was 61.3 years, 55.3% were female, 0.6% were Duffy null, and most were of White self-reported ethnicity (93.2%). The mean NLR was 2.33. Over a median follow-up time of 12.5 years,

$n = 2198$ (1.1%) incident AD cases (128 cases under 65 years old at diagnosis) were identified (Table 1). For the excluded participants ($n = 295,429$) the mean age was 53.2, 53.8% were female, and 88.4% self-reported White ethnicity.

In AoU, 45,202 participants were included (Table 1). Only 0.6% ($n = 263$) developed incident AD and 7.6% were Duffy null. The mean NLR was 3.20 and mean age was 67.8 years. Most participants were female (54.3%) and self-reported White race (76.3%). Participants had a median follow-up time of 5.1 years.

In UK Biobank, after adjusting for age and sex, a 1 standard deviation (SD) higher NLR level was associated with a 3% higher risk of AD (HR = 1.03, 95% CI = 1.02–1.05). This association was robust to adjustment for AD-related risk factors from the UKBDRS in UK Biobank³³ and the Duffy variant (Table 2) as well as *APOE* status (HR = 1.03, 95% CI: 1.01–1.05) to prediction models (Table 3, Figure 1). The NLR association with AD was also robust to the addition of CRP (NLR HR = 1.03 for NLR, NLR 95% CI: 1.02–1.05) after adjusting for the UKBDRS variables, age, sex, assessment center, self-reported ethnicity, and Duffy (Table 4). CRP was associated with AD after

Table 2. Association of neutrophil-lymphocyte ratio (NLR) with incident Alzheimer's disease in UK Biobank and All of Us.

Model	Hazards Ratio	95% Confidence Interval	p
UK Biobank (AD cases: 2198, controls: 204902)			
AD ~ NLR	1.05	1.03–1.06	1.93×10^{-12}
AD ~ NLR + age + sex	1.03	1.02–1.05	0.0001
AD ~ NLR + age + sex + assessment center + self-reported ethnicity	1.04	1.02–1.05	7.07×10^{-5}
AD ~ NLR + age + sex + assessment center + self-reported ethnicity + diabetes + depression + stroke + hypertension + high cholesterol + Townsend deprivation index + education + household occupancy + parental dementia history + Duffy null status (rs2814778)	1.03	1.01–1.05	0.0005
All of Us (AD cases: 263, controls: 44939)			
AD ~ NLR + age + sex + race/ethnicity	1.02	0.92–1.14	0.662
AD ~ NLR + age + sex + race/ethnicity + Duffy null status (rs2814778)	1.02	0.92–1.14	0.682

Table 3. Results for addition of APOE4 variant to models in UK Biobank, with hazards ratio reported per standard deviation (sd) of NLR.

Model	Hazards Ratio	95% Confidence Interval	p
UK Biobank (AD cases: 2198, controls: 204902)			
AD ~ NLR + APOE4 (rs429358) status + APOE2 (rs7412) status	1.05	1.03–1.06	6.07×10^{-13}
AD ~ NLR + age + sex + APOE4 (rs429358) status + APOE2 (rs7412) status	1.04	1.02–1.06	8.84×10^{-5}
AD ~ NLR + age + sex + assessment center + self-reported ethnicity + APOE4 (rs429358) status + APOE2 (rs7412) status	1.04	1.02–1.06	6.99×10^{-5}
AD ~ NLR + age + sex + assessment center + self-reported ethnicity + diabetes + depression + stroke + hypertension + high cholesterol + Townsend deprivation index + education + household occupancy + parental dementia history + Duffy null status (rs2814778) + APOE4 (rs429358) status + APOE2 (rs7412) status	1.03	1.01–1.05	0.0004

adjustment for the UKBDRS variables, age, sex, assessment center, self-reported ethnicity, Duffy, and NLR (HR: 0.90, 95% CI: 0.86–0.95) (Table 4, Figure 1). There was not a significant interaction between sex and NLR in the model adjusting for sex and age (sex NLR interaction term $p = 0.70$). We did not observe a statistically significant association between NLR (per 1 SD higher) and AD in All of Us (HR = 1.02, 95% CI: 0.92–1.14) (Table 2). Using the first lymphocyte measurement, increasing the number of incident AD cases to 374, the association between NLR and AD was not statistically significant (HR = 1.03, 95% CI: 0.94–1.13) (Supplemental Table 4). The pooled HR from UK Biobank adjusting for age, sex, assessment center, and self-reported ethnicity and AoU adjusting for age, sex, and race and ethnicity was 1.03 with a 95% CI of 1.02–1.05.

In the UK Biobank, neutrophil count was associated with AD, robust to adjustment for potential confounders, while the lymphocyte count was not statistically significant in any model (Supplemental Tables 5 and 6). In the AoU, neither neutrophil count nor lymphocyte count was statistically significant for AD (Supplemental Tables 5 and 6).

When a more expansive definition of all-cause dementia (including AD, vascular dementia frontotemporal dementia, unspecified dementia) (Supplemental Table 2) was used,

NLR was associated with dementia in the UK Biobank (HR 1.05, 95% CI 1.05–1.06) but still not in AoU (Supplemental Table 7). Monocyte to lymphocyte ratio (MLR) and platelet to lymphocyte ratio (PLR) were both not significantly associated with AD in the UK Biobank or AoU (Supplemental Tables 8 and 9).

GWAS of NLR in European ancestry UK Biobank participants resulted in 214 lead variants (all from distinct 1 Mb regions, clumping based on distance) also present in the AD summary statistics for the MR analysis (Supplemental Table 10). The MR analysis resulted in an F-statistic of 67.7. In two-sample MR, the results of the IVW and, as a sensitivity analysis, MR-Egger were both not significant (IVW beta: -0.001 , 95% CI: -0.077 – 0.076 , $p = 0.99$, Egger intercept $p = 0.15$, Egger estimate: -0.129 , 95% CI: -0.318 – 0.056 , $p = 0.18$) (Supplemental Table 11, Supplemental Figures 1 and 2).

Discussion

NLR was associated with AD in the UK Biobank after accounting for multiple lifestyle, environmental, and clinical risk factors as well as Duffy null status. However, this association was not significant in AoU, though effect direction was concordant, likely due to small number of

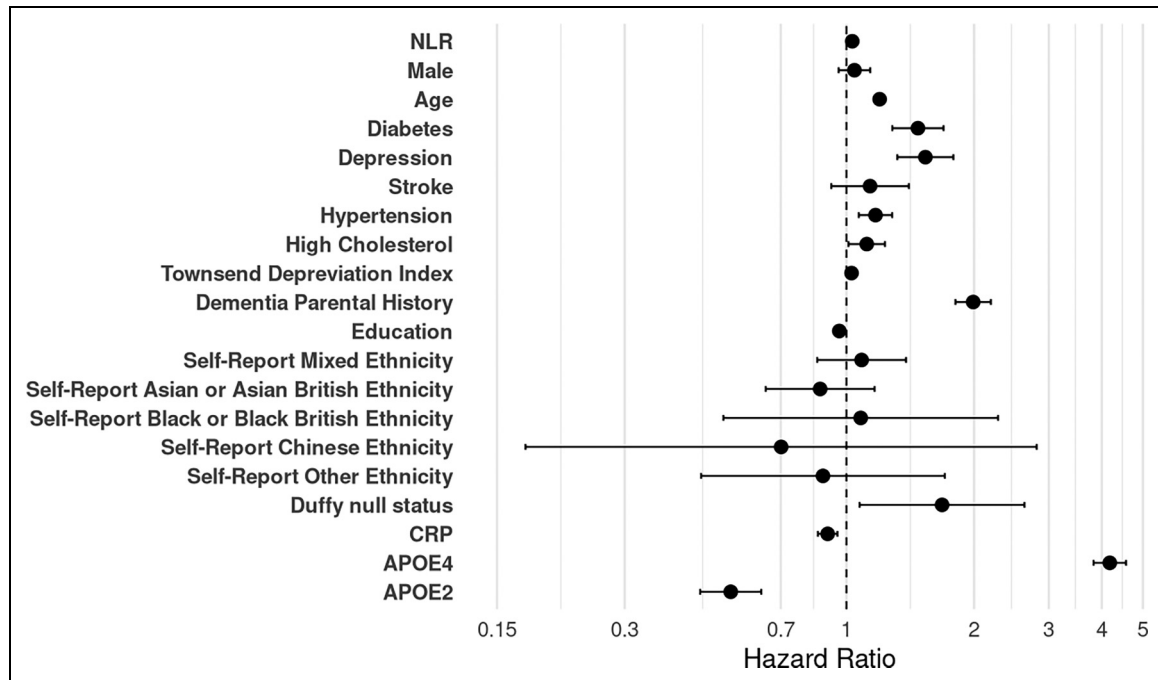


Figure 1. UK Biobank hazards ratios for NLR, UKBDRS variables, self-reported ethnicity, Duffy null status, CRP, APOE4, and APOE2. White self-reported ethnicity is reference group for Mixed, Asian or Asian British, Black or Black British, Chinese, or other ethnic group self-reported ethnicity. Hazards ratios for NLR, UKBDRS variables, self-reported ethnicity, and Duffy null status obtained from model adjusting for UKBDRS variables, self-reported ethnicity, Duffy null status, and assessment center. CRP and APOE variants hazards ratios obtained by adding the respective variable to the previous model.

Table 4. Association of C-reactive protein (CRP) and neutrophil-lymphocyte ratio (NLR) with incident Alzheimer's disease in UK Biobank.

Model	CRP			NLR		
	Hazards Ratio	95% Confidence Interval	p	Hazards Ratio	95% Confidence Interval	p
UK Biobank (AD cases: 2198, controls: 204902)						
AD ~ CRP	0.96	0.91–1.00	0.0694	NA	NA	NA
AD ~ CRP + NLR	0.95	0.90–1.00	0.0344	1.05	1.03–1.06	1.43×10^{-13}
AD ~ CRP + NLR + age + sex	0.93	0.88–0.97	0.0029	1.04	1.02–1.05	8.75×10^{-6}
AD ~ CRP + NLR + age + sex + assessment center + self-reported ethnicity	0.92	0.88–0.97	0.0023	1.04	1.02–1.05	4.94×10^{-6}
AD ~ CRP + NLR + age + sex + assessment center + self-reported ethnicity + diabetes + depression + stroke + hypertension + high cholesterol + Townsend deprivation index + education + household occupancy + parental dementia history + Duffy null status (rs2814778)	0.90	0.86–0.95	0.0002	1.03	1.02–1.05	2.46×10^{-5}

detected cases and short total available follow-up time. MR results do not support a causal role for NLR in AD; this suggests NLR may instead be correlated with other true causal risk factors for AD unmeasured in this study.

Previous studies have investigated the association between NLR and AD. Multiple cross-sectional case-

control studies, including a meta-analysis, found AD patients to have a higher mean NLR compared to patients with normal cognition.^{19,21–23} A systematic review has also been performed for NLR and AD with 12 studies, where they found a higher NLR to be associated with AD compared to healthy controls and compared to participants

with mild cognitive impairment, again based on mostly cross-sectional data.⁵⁶ A previously mentioned study in the Framingham Heart Study found NLR to be associated with incident all-cause dementia.²⁵ This study had the strength of being a prospective study while many previous studies have had a cross-sectional design, but number of cases was small ($n = 51$). There have also been previous studies looking at incident AD and dementia with NLR in the UK Biobank.^{26,27} These studies found a higher NLR to be associated with AD and all-cause dementia similar to our study. However, a weakness of these studies is not adjusting for important covariates such as Duffy null status, CRP, and variables included in UKBDRS,^{26,27} and MR was not considered. Our study also had a longer median follow up time (12.5 versus 8.99 years) and more AD cases (2198 versus 1896 cases) than one study²⁶ and a greater overall sample size (207,100 versus 161,968 participants), longer median follow up time (12.5 versus 9.66 years), and more dementia cases in our supplementary analysis (5048 all-cause dementia versus 2958 dementia cases) than another study.²⁷ The use of the UKBDRS is an important addition to our study compared to previous studies since this allows for adjusting for variables that have been shown to be strong predictors in the UK Biobank for dementia.³³ However, contrary results for NLR with dementia have also been reported.⁵⁷ Compared to these previous studies, our study utilizes incident cases with longer follow up, accounts for time of follow-up from time of white blood cell measures, helps clarify the likely noncausal role of NLR in AD development using MR analysis, examines the constituent components of NLR, and also has the advantage of having an increased sample size for AD cases.

CRP is another commonly used marker for chronic inflammation¹⁰ and has been examined for associations with AD in multiple prior efforts.^{10,58,59} While CRP was not associated with AD incidence in the UK Biobank when categorized into $CRP < 8$ mg/L and $CRP \geq 8$ mg/L,⁵⁸ higher CRP (modeled as continuous) adjusted for NLR, age, sex, assessment center, self-reported ethnicity UKBDRS factors, Duffy null status (rs2814778) was associated with lower AD incidence (HR: 0.87, 95% CI: 0.82–0.91) in our study. Differences in reported effect sizes may be due to higher CRP having been associated with higher AD risk in midlife and lower AD risk at older ages.^{11–13} In this study, the association between NLR and AD incidence remained after adjusting for CRP. The association between CRP and AD also remained after adjustment for NLR. This suggests NLR may be an important inflammation marker to investigate for predictive value for AD, apart from the more commonly studied CRP biomarker.

While these previous studies found similar associations between NLR and AD or dementia in the UK Biobank as our study,^{26,27} the use of MR in our study provides further insight into whether NLR is a biomarker of AD development or a step along the causal pathway, and our more complete

modelling strategy provides additional information on independence of this association from known or related risk factors. The association between NLR and AD provides evidence for systemic inflammation as either having a role in or being a biomarker for AD pathogenesis. While measured NLR had an association with AD, the MR analysis did not have a significant result. This suggests that NLR may be a biomarker for AD development but is not a causal step in AD pathogenesis. A recent MR publication suggested that lymphocyte counts may be a causal risk factor for vascular, as opposed to Alzheimer's, dementia, based on summary statistics from FinnGen, suggesting that the putative causal role of both leukocyte subpopulations and their ratios (not examined in this prior publication) should be further investigated for additional dementia subtypes in future work.⁵⁹ As previously mentioned, strengths of this study include the number of AD cases available in the UK Biobank, adjustment for known dementia risk factors, inclusion of the novel AoU dataset, as well as the prospective design of the study. However, a limitation of this analysis is missing AD cases due to low sensitivity to detect AD³⁹ from health records and death certificates. Another limitation, specifically for AoU, is a lack of sufficient power to detect a significant effect size due to a smaller number of incident AD cases. A power analysis in R (R package: survivalpwr) for Cox proportional hazards model assuming an HR of 1.03, standard deviation of 3.04, AD probability of 0.6%, and R^2 of about 0.02 results in a power of 0.30. Also, different social and environmental exposures could play a role in population heterogeneity resulting in a lack of generalizability. Finally, use of a standardized baseline visit NLR, with standardized methods across all participants, in UK Biobank, versus electronic health record derived measures for NLR which may have a higher rate of noise or error in AoU, may also impact results. Our cohort in the AoU is currently too small to assess. Based on prior analyses of administrative record-based AD case adjudication,⁶⁰ we are possibly underestimating the true number of AD cases in both AoU and UK Biobank, which biases our results towards the null. The use of ICD-9/ICD-10 codes for AD may also include dementia cases that are not truly AD cases such as vascular dementia cases.

NLR was associated with AD in UK Biobank but not in AoU, though MR analyses suggest NLR may not be a causal biomarker for AD. These findings provide further evidence for the association between NLR and AD as well as the possible role of systemic inflammation in AD development.


Acknowledgements


This research has been conducted using the UK Biobank Resource under Application Number 25953. The All of Us Research Program was made possible by the partnership of its participants. The All of Us Research Program is supported by the National

Institutes of Health, Office of the Director: Regional Medical Centers: 1 OT2 OD026549; 1 OT2 OD026554; 1 OT2 OD026557; 1 OT2 OD026556; 1 OT2 OD026550; 1 OT2 OD026552; 1 OT2 OD026553; 1 OT2 OD026548; 1 OT2 OD026551; 1 OT2 OD026555; IAA #: AOD 16037; Federally Qualified Health Centers: HHSN 263201600085U; Data and Research Center: 5 U2C OD023196; Biobank: 1 U24 OD023121; The Participant Center: U24 OD023176; Participant Technology Systems Center: 1 U24 OD023163; Communications and Engagement: 3 OT2 OD023205; 3 OT2 OD023206; and Community Partners: 1 OT2 OD025277; 3 OT2 OD025315; 1 OT2 OD025337; 1 OT2 OD025276.

ORCID iDs

Quan Sun  <https://orcid.org/0000-0001-8324-2803>

Laura M Raffield  <https://orcid.org/0000-0002-7892-193X>

Christy Avery  <https://orcid.org/0000-0002-1044-8162>

Ethical considerations

Data for analysis was obtained from the UK Biobank and the All of Us database.

Consent to participate

Informed consent was obtained from these participants at study recruitment for either the UK Biobank or the All of Us database.

Author contribution(s)

Emily Drzymalla: Formal analysis; Methodology; Writing – original draft.

Christy Avery: Writing – review & editing.

Priya Palta: Writing – review & editing.

Alexander P Reiner: Writing – review & editing.

Quan Sun: Writing – review & editing.

Laura M Raffield: Methodology; Supervision; Writing – review & editing.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by R01 AG075884.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability statement

The data supporting the findings of this study are available in the UK Biobank and the All of Us databases.

Supplemental material

Supplemental material for this article is available online.

References

- DeTure MA and Dickson DW. The neuropathological diagnosis of Alzheimer's disease. *Mol Neurodegener* 2019; 14: 32.
- Alzheimer's Association. 2024 Alzheimer's disease facts and figures. *Alzheimers Dement* 2024; 20: 3708–3821.
- Kinney JW, Bemiller SM, Murtishaw AS, et al. Inflammation as a central mechanism in Alzheimer's disease. *Alzheimers Dement (N Y)* 2018; 4: 575–590.
- Berriat F, Lobsiger CS and Boillée S. The contribution of the peripheral immune system to neurodegeneration. *Nat Neurosci* 2023; 26: 942–954.
- Sun Y, Koyama Y and Shimada S. Inflammation from peripheral organs to the brain: how does systemic inflammation cause neuroinflammation? *Front Aging Neurosci* 2022; 14: 903455.
- Zhang S, Gao Y, Zhao Y, et al. Peripheral and central neuroimmune mechanisms in Alzheimer's disease pathogenesis. *Mol Neurodegener* 2025; 20: 22.
- Galea I. The blood–brain barrier in systemic infection and inflammation. *Cell Mol Immunol* 2021; 18: 2489–2501.
- Tanaka T, Narazaki M and Kishimoto T. IL-6 in inflammation, immunity, and disease. *Cold Spring Harb Perspect Biol* 2014; 6: a016295.
- Shen XN, Niu LD, Wang YJ, et al. Inflammatory markers in Alzheimer's disease and mild cognitive impairment: a meta-analysis and systematic review of 170 studies. *J Neurol Neurosurg Psychiatry* 2019; 90: 590–598.
- Sproston NR and Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. *Front Immunol* 2018; 9: 754.
- Hegazy SH, Thomassen JQ, Rasmussen IJ, et al. C-reactive protein levels and risk of dementia-observational and genetic studies of 111,242 individuals from the general population. *Alzheimers Dement* 2022; 18: 2262–2271.
- Schmidt R, Schmidt H, Curb JD, et al. Early inflammation and dementia: a 25-year follow-up of the Honolulu-Asia aging study. *Ann Neurol* 2002; 52: 168–174.
- Gong C, Wei D, Wang Y, et al. A meta-analysis of C-reactive protein in patients with Alzheimer's disease. *Am J Alzheimers Dis Other Dement* 2016; 31: 194–200.
- Singh B, Goyal A and Patel BC. *C-reactive protein: clinical relevance and interpretation*. StatPearls. Treasure Island, FL: StatPearls Publishing LLC., 2025.
- Olson ME, Hornick MG, Stefanski A, et al. A biofunctional review of C-reactive protein (CRP) as a mediator of inflammatory and immune responses: differentiating pentameric and modified CRP isoform effects. *Front Immunol* 2023; 14: 1264383.
- Zahorec R. Ratio of neutrophil to lymphocyte counts—rapid and simple parameter of systemic inflammation and stress in critically ill. *Bratisl Lek Listy* 2001; 102: 5–14.
- Song M, Graubard BI, Rabkin CS, et al. Neutrophil-to-lymphocyte ratio and mortality in the United States general population. *Sci Rep* 2021; 11: 464.

18. Angkananard T, Anothaisintawee T, McEvoy M, et al. Neutrophil lymphocyte ratio and cardiovascular disease risk: a systematic review and meta-analysis. *Biomed Res Int* 2018; 2018: 2703518.
19. Huang LT, Zhang CP, Wang YB, et al. Association of peripheral blood cell profile with Alzheimer's disease: a meta-analysis. *Front Aging Neurosci* 2022; 14: 888946.
20. Hou JH, Ou YN, Xu W, et al. Association of peripheral immunity with cognition, neuroimaging, and Alzheimer's pathology. *Alzheimers Res Ther* 2022; 14: 29.
21. Kuyumcu ME, Yesil Y, Oztürk ZA, et al. The evaluation of neutrophil-lymphocyte ratio in Alzheimer's disease. *Dement Geriatr Cogn Disord* 2012; 34: 69–74.
22. Rembach A, Watt AD, Wilson WJ, et al. An increased neutrophil-lymphocyte ratio in Alzheimer's disease is a function of age and is weakly correlated with neocortical amyloid accumulation. *J Neuroimmunol* 2014; 273: 65–71.
23. Kalelioglu T, Yuruyen M, Gultekin G, et al. Neutrophil and platelet to lymphocyte ratios in people with subjective, mild cognitive impairment and early Alzheimer's disease. *Psychogeriatrics* 2017; 17: 506–508.
24. Li JQ, Zhang YR, Wang HF, et al. Exploring the links among peripheral immunity, biomarkers, cognition, and neuroimaging in Alzheimer's disease. *Alzheimers Dement (Amst)* 2023; 15: e12517.
25. Ramos-Cejudo J, Johnson AD, Beiser A, et al. The neutrophil to lymphocyte ratio is associated with the risk of subsequent dementia in the Framingham Heart Study. *Front Aging Neurosci* 2021; 13: 773984.
26. Zhang YR, Wang JJ, Chen SF, et al. Peripheral immunity is associated with the risk of incident dementia. *Mol Psychiatry* 2022; 27: 1956–1962.
27. Zhong X, Qiang Y, Wang L, et al. Peripheral immunity and risk of incident brain disorders: a prospective cohort study of 161,968 participants. *Transl Psychiatry* 2023; 13: 382.
28. Merz LE, Story CM, Osei MA, et al. Absolute neutrophil count by Duffy status among healthy Black and African American adults. *Blood Adv* 2023; 7: 317–320.
29. Hysong MR, Shuey MM, Huffman JE, et al. Characterization of the phenotypic consequences of the Duffy-null genotype. *Blood Adv* 2025; 9: 1452–1462.
30. Davey Smith G and Ebrahim S. Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol* 2003; 32: 1–22.
31. Richmond RC and Davey Smith G. Mendelian randomization: concepts and scope. *Cold Spring Harb Perspect Med* 2022; 12: a040501.
32. Sanderson E, Glymour MM, Holmes MV, et al. Mendelian randomization. *Nat Rev Methods Primers* 2022; 2: 6.
33. Anatiürk M, Patel R, Ebmeier KP, et al. Development and validation of a dementia risk score in the UK Biobank and Whitehall II cohorts. *BMJ Ment Health* 2023; 26: e300719.
34. Kim S, Eliot M, Koestler DC, et al. Association of neutrophil-to-lymphocyte ratio with mortality and cardiovascular disease in the Jackson Heart Study and modification by the Duffy antigen variant. *JAMA Cardiol* 2018; 3: 455–462.
35. Mutz J, CJ R and Lewis CM. Exploring health in the UK Biobank: associations with sociodemographic characteristics, psychosocial factors, lifestyle and environmental exposures. *BMC Med* 2021; 19: 240.
36. Conroy MC, Lacey B, Bešević J, et al. UK Biobank: a globally important resource for cancer research. *Br J Cancer* 2023; 128: 519–527.
37. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med* 2015; 12: e1001779.
38. Ponjoan A, Garre-Olmo J, Blanch J, et al. How well can electronic health records from primary care identify Alzheimer's disease cases? *Clin Epidemiol* 2019; 11: 509–518.
39. Macera CA, Sun RK, Yeager KK, et al. Sensitivity and specificity of death certificate diagnoses for dementing illnesses, 1988–1990. *J Am Geriatr Soc* 1992; 40: 479–481.
40. Pippenger M, Holloway RG and Vickrey BG. Neurologists' use of ICD-9CM codes for dementia. *Neurology* 2001; 56: 1206–1209.
41. Elliott P and Peakman TC. The UK Biobank sample handling and storage protocol for the collection, processing and archiving of human blood and urine. *Int J Epidemiol* 2008; 37: 234–244.
42. Denny JC, Rutter JL, Goldstein DB, et al. The "All of Us" Research program. *N Engl J Med* 2019; 381: 668–676.
43. All of Us Research Program. Curated Data Repository (CDR) version 8 Release Notes, <https://support.researchallofus.org/hc/en-us/articles/30294451486356-Curated-Data-Repository-CDR-version-8-Release-Notes> (accessed 25 April 2025).
44. Tahir N and Zahra F. *Neutrophilia*. StatPearls. Treasure Island, FL: StatPearls Publishing LLC., 2025.
45. National Heart, Lung, and Blood Institute. Lymphopenia: Diagnosis, <https://www.nhlbi.nih.gov/health/lymphopenia/diagnosis> (accessed July 3 2025).
46. Shiekh SI, Cadogan SL, Lin LY, et al. Ethnic differences in dementia risk: a systematic review and meta-analysis. *J Alzheimers Dis* 2021; 80: 337–355.
47. Reich D, Nalls MA, Kao WH, et al. Reduced neutrophil count in people of African descent is due to a regulatory variant in the Duffy antigen receptor for chemokines gene. *PLoS Genet* 2009; 5: e1000360.
48. Masoumi M, Bozorgi M, Nourmohammadi Z, et al. Evaluation of hematological markers as prognostic tools in rheumatoid arthritis. *BMC Rheumatol* 2024; 8: 75.
49. Zeng C, Schlueter DJ, Tran TC, et al. Comparison of phenomic profiles in the All of Us research program against the US general population and the UK Biobank. *J Am Med Inform Assoc* 2024; 31: 846–854.
50. Vuckovic D, Bao EL, Akbari P, et al. The polygenic and monogenic basis of blood traits and diseases. *Cell* 2020; 182: 1214–1231.e1211.

51. Sun Q, Graff M, Rowland B, et al. Analyses of biomarker traits in diverse UK biobank participants identify associations missed by European-centric analysis strategies. *J Hum Genet* 2022; 67: 87–93.
52. Bellenguez C, Küçükali F, Jansen IE, et al. New insights into the genetic etiology of Alzheimer's disease and related dementias. *Nat Genet* 2022; 54: 412–436.
53. Bowden J, Davey Smith G and Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol* 2015; 44: 512–525.
54. Rowland B, Venkatesh S, Tardaguila M, et al. Transcriptome-wide association study in UK Biobank Europeans identifies associations with blood cell traits. *Hum Mol Genet* 2022; 31: 2333–2347.
55. Sun Q, Rowland B, Wang W, et al. Genetic examination of hematological parameters in SARS-CoV-2 infection and COVID-19. *Blood Cells Mol Dis* 2023; 103: 102782.
56. Mohammadi A, Mohammadi M, Almasi-Dooghaee M, et al. Neutrophil to lymphocyte ratio in Alzheimer's disease: a systematic review and meta-analysis. *PLoS One* 2024; 19: e0305322.
57. Kara SP, Altunan B and Unal A. Investigation of the peripheral inflammation (neutrophil-lymphocyte ratio) in two neurodegenerative diseases of the central nervous system. *Neurol Sci* 2022; 43: 1799–1807.
58. Huang J, Tao Q, Ang TFA, et al. The impact of increasing levels of blood C-reactive protein on the inflammatory loci SPI1 and CD33 in Alzheimer's disease. *Transl Psychiatry* 2022; 12: 523.
59. Liu S, Zhang C, Zhang Y, et al. Causal association between blood leukocyte counts and vascular dementia: a two-sample bidirectional Mendelian randomization study. *Sci Rep* 2024; 14: 19582.
60. Chow EPF, Hsu B, Waite LM, et al. Diagnostic accuracy of linked administrative data for dementia diagnosis in community-dwelling older men in Australia. *BMC Geriatr* 2022; 22: 858.