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Association of neutrophil to high density lipoprotein cholesterol ratio with aortic dissection and aneurysm risk: epidemiological insights from prospective cohort study based on UK biobank

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Abstract

Background Neutrophil to high-density lipoprotein cholesterol ratio (NHR) is a metabolic inflammatory biomarker reflecting the balance between pro- and anti-inflammatory responses. Extensive research has revealed that NHR is an effective predictor for cardiovascular risks, such as stroke and myocardial infarction. Nevertheless, the association between NHR and incidence risks of aortic dissection (AD) and aortic aneurysm (AA) remains unclear.

Methods This research, designed as a prospective cohort study, enrolled 409,357 participants based on the UK Biobank project. The cut-off value of NHR *i.e.*, 0.205, was determined using a receiver operating characteristic curve for grouping. Participants were divided into two groups: NHR ≤ 0.205 ($n = 293,294$) and NHR > 0.205 ($n = 116,063$). The cumulative incidence of outcome, *i.e.,* AD/AA including AD and AA, was calculated using Kaplan–Meier curves. The dose–response relationship between NHR and AD/AA was evaluated using restricted cubic spline (RCS). Multivariable-adjusted Cox proportional hazards regression models, followed by sensitivity analyses and subgroup analyses, were performed to evaluate the association between NHR and AD/AA onset.

Results A total of 3,408 participants developed AD/AA, including 233 AD cases and 3,259 AA cases, with a median follow-up period of 14.8 years. The incidences of AD/AA, AD and AA were 56.34, 3.85 and 53.87 cases per 100,000 person-years, respectively. A nonlinear relationship between NHR and the incidence risk of AD/AA was documented by RCS (P for nonlinear < 0.001). Participants in the NHR > 0.205 group had a higher risk of developing AD/AA compared to those in the NHR ≤ 0.205 group, with an adjusted HR of 1.47 (95%CI 1.37–1.58). This association was further validated by sensitivity analyses and subgroup analyses.

Conclusions NHR is an independent risk factor for AD/AA. The disorder of metabolic inflammation may be a potential pathological mechanism for AD/AA. Tailored assessment and management of NHR may serve as effective strategies for the prevention and prediction of AD/AA.

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Keywords Aortic dissection, Aortic aneurysm, Neutrophil to high-density lipoprotein cholesterol ratio, Cohort study, UK Biobank, Metabolic inflammation

Background

Aortic aneurysm (AA) is a balloon-like enlargement of the aorta with an asymptomatic progression before it causes dissection or rupture, leading to sudden severe chest or abdominal pain. Globally, the prevalence of thoracic AA is estimated at 0.16%, with an incidence of rupture at 1.6 per 100,000 person-years [1]. In contrast, the prevalence of abdominal AA is 0.92%, with the highest prevalence of 1.31% in the Western Pacific region and the lowest prevalence of 0.33% in the African region [2]. According to the Global Burden of Disease Study (GBD), the global number of AA-related deaths underwent a considerable increase by more than four-fifths from 1990 to 2019 [3]. Aortic dissection (AD), a tear or separation of the layers of the aortic wall, is a rare but catastrophic disease that is partially attributed to AA. The global incidence of AD is 3.0 cases per 100,000 person-years, with a high in-hospital mortality rate of 1.3 per 100,000 person-years [4].

Inflammation and metabolic disorders are potential pathogenic mechanisms for AD and AA [5–8]. Neutrophil to high-density lipoprotein cholesterol ratio (NHR) is a composite indicator comprising neutrophil count (NC), a pro-inflammatory biomarker, and high-density lipoprotein cholesterol (HDL-c), an anti-inflammatory and metabolic biomarker [9]. NHR is calculated as NHR = NC (×10^9/L)/HDL-c (mg/dL) [10]. Due to the characteristics of NC and HDL-c, such as being cost-effective, easily measurable and well-standardized, NHR is considered as a simple and practical parameter for evaluating cardiovascular metabolic inflammation. Several studies have demonstrated that NHR is a promising indicator for conditions such as metabolic syndrome [11], ischemic stroke [12], myocardial infarction [13], Parkinson's disease [13] and cardiovascular mortality [14]. Nevertheless, the potential association between NHR and AD/AA remains unexplored. We thus aim to assess the association of NHR with the incidence risk of AD/AA using the extracted dataset from the UK Biobank.

Methods

Design, setting, ethics and participants

The UK Biobank project was designed as a prospective cohort study launched in 2006 with ethics approval number 11/NW/03820, granted by the North West Multi-Center Research Ethics Committee [15]. It provides a vast repository of de-identified health-related data from more than half a million individuals, facilitating a better understanding of a wide range of diseases, including rare and common, acute and chronic, as well as infectious and noninfectious conditions. Researchers worldwide dedicated to advancing human health can access the dataset by submitting a proposal for approval via the official link: https://www.ukbiobank.ac.uk/.

Using application number 205837, we performed a large-scale, population-based, prospective cohort study by accessing the dataset from the UK Biobank project via the Research Analysis Platform (RAP), a cloud storage and analytics platform designed to accommodate the exponentially increasing scale of data. The UK Biobank project recruited a total of 502,357 participants, aged 40 to 69 years from the United Kingdom between 2006 and 2010. After excluding participants who had a prior diagnosis of AD/AA ($n = 585$) or connective tissue disease ($n = 9{,}773$), missing NC ($n = 24{,}624$) or HDL-c values ($n = 57{,}962$), or were lost to follow-up ($n = 56$), a total of 409,357 eligible participants were included in this study. These participants were longitudinally followed up until November 30, 2023 (Fig. 1).

Exposure

The primary measure of this study, NHR, was considered as the exposure variable and calculated using the following formula [9, 10, 12]:

$$\mathbf{NHR} = \frac{\mathbf{NC}}{\mathbf{HDL-c}}$$

Outcome

AD/AA, as defined using the 10th revision of the International Classification of Diseases (ICD-10), is a composite endpoint comprising AD (ICD-10 I71.0) and AA (ICD-10 I71.1-I71.9) [16], and was the main outcome of this study. The date when participants were diagnosed with AD or AA during the follow-up period was designated as the onset date of the endpoint. This information was sourced from death registries, primary care records, hospital data, self-reports or other sources. Participants lost to follow-up were excluded at enrollment to ensure that all individuals included in the analysis had complete follow-up data, and those who did not develop AD/AA at the end of the follow-up period were considered censored.

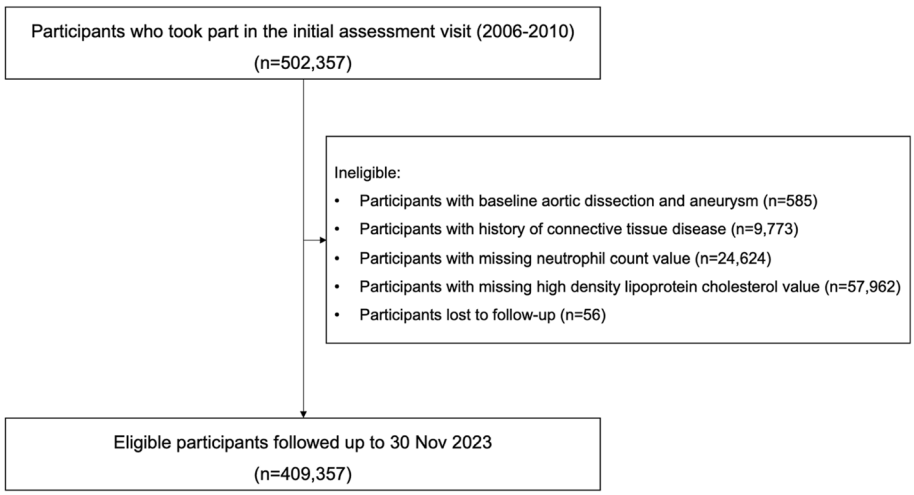

Fig. 1 Flowchart of the study participants

Covariates

The covariates in this study included demographics (age and gender), lifestyle factors (smoking and drinking statuses), anthropometric measures [body mass index (BMI), systolic blood pressure (SBP) and diastolic blood pressure (DBP)], biochemical parameters [glycated hemoglobin (HbA1c), fasting blood glucose (FBG), NC, triglyceride (TG), total cholesterol (TC), HDL-c and low-density lipoprotein cholesterol (LDL-c)], medical histories (diabetes and hypertension), and medication use (lipid-lowering drugs, antihypertensive drugs and insulin).

Statistical analysis

The receiver operating characteristic (ROC) curve was used to determine the optimal cut-off value of NHR for predicting AD/AA onset (Fig. 2). Based on the cut-off value of 0.205, participants were categorized into two groups: NHR $\leq$ 0.205 (n = 293,294) and NHR > 0.205 (n = 116,063). The normality of continuous variables was assessed using Q-Q plot. Median and interquartile range [P25, P75] were used to express variables with skewed distributions, which were evaluated using nonparametric test to compare their differences between groups; Mean ± standard deviation were used to present variables with normal distributions, which were checked using two independent samples t-tests. Numbers and percentage (%) were used to describe categorical variables, which were checked using chi-square test.

The log-rank test was applied to compare the cumulative incidence of AD/AA between groups, visualized by Kaplan–Meier plots and described as the number of cases per 100,000 person-years. Cox proportional hazards regression models were employed to evaluate the association between NHR, analyzed both as a continuous and a categorical variable, and the incidence risk of AD/AA, with results reported as hazard ratios (HRs) and 95% confidence intervals (95%CIs). Details on proportional hazards assumption testing were shown on supplemental files. Confounding factors identified by univariate Cox regression or clinical relevance were controlled in a stepwise manner using multivariable-adjusted models. Restricted cubic splines (RCS) were performed to explore potential nonlinear associations between NHR and AD/AA.

To examine the robustness of the models, sensitivity analyses was conducted in this study: sensitivity analysis 1 with adjustment for medication use, sensitivity analysis 2 with exclusion of participants affected by AD/AA in the first follow-up year, and sensitivity analysis 3 with exclusion of participants who developed AD/AA in the first two follow-up year. To investigate and compare the association of NHR with AD/AA in different populations, subgroup analyses were performed, stratified by age, gender, smoking status, diabetes, hypertension and BMI categories. Interactions between NHR and these stratifying factors were evaluated using *P*-values for interaction. RAP with the support of RStudio was used for statistical analysis.

Results

Baseline characteristics of participants

A total of 409,357 participants with a median age of 58 years were included in this study. Participants were divided into two groups: NHR $\leq$ 0.205 and NHR > 0.205, based on the optimal cut-off value of NHR for identifying AD/AA (Fig. 2). There was no significant difference in age

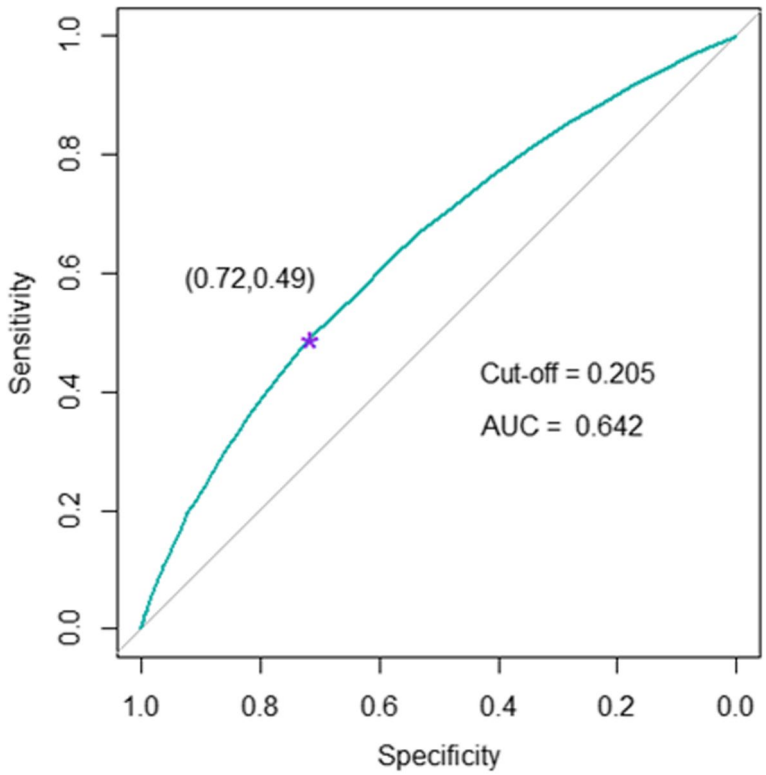

Fig. 2 ROC curve for grouping. The cut-off value was 0.205, with an area under the curve of 0.642, sensitivity of 0.49, specificity of 0.72. Abbreviation: AUC: area under the curve

between the two groups ($P=0.068$) (Table 1). Among all participants, 190,314 were males, accounting for 46.5% of the cohort. The proportion of males in the NHR > 0.205 group was significantly higher than in the NHR ≤ 0.205 group (63.0% *vs.* 40.0%, $P<0.001$).

Participants in the NHR > 0.205 group were more likely to be current smokers [21,275 (18.3%) *vs.* 21,735 (7.4%)], and never [6,105 (5.3%) *vs.* 11,623 (4.0%)] or previous drinkers [6,000 (5.2%) *vs.* 8,399 (2.9%)] (all $P<0.001$). Thery were also more likely to have a history of diabetes [11,835 (10.2%) *vs.* 9,219 (3.1%)] or hypertension [41,914 (36.1%) *vs.* 66,799 (22.8%)], and to be on medications for lipid-lowering [22,197 (19.1%) *vs.* 20,940 (7.1%)], anti-hypertension [8,599 (7.4%) *vs.* 10,245 (3.5%)], or insulin [164 (0.1%) *vs.* 200 (0.1%)], compared to those in the NHR ≤ 0.205 group (all $P<0.001$). Levels of HbA1c [36.1 (33.6,39.2) *vs.* 35.2 (32.7,37.2)], BMI [29.27 ± 5.23 *vs.* 26.67 ± 4.34], SBP [140 (129,152) *vs.* 139 (126,150)], DBP [82 (77,90) *vs.* 82 (75,88)], FBG [4.95 (4.59,5.43) *vs.* 4.92 (4.60,5.28)] and TG [1.95 (1.38,2.76) *vs.* 1.34 (0.97,1.89)] were higher in the NHR > 0.205 group than in the

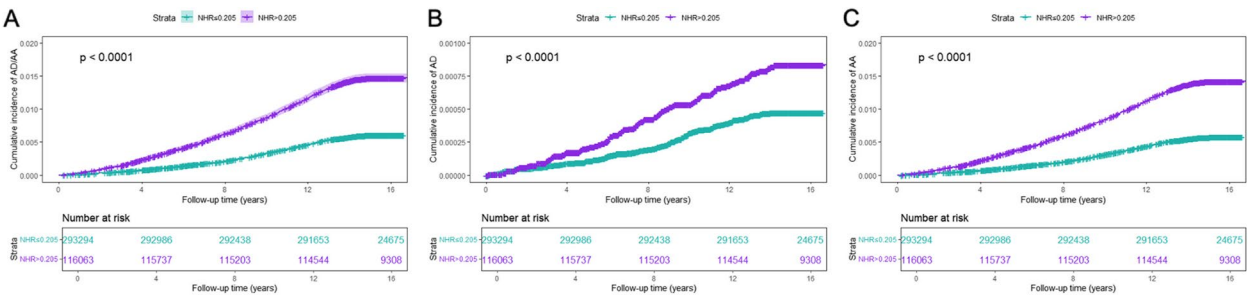

Fig. 3 Kaplan–Meier curves of cumulative incidence. NHR ≤ 0.205 was used as the reference group. **A** AD/AA. **B** AD. **C** AA

Table 1 Baseline characteristics of participants

Characteristics	Total ($n=409,357$)	NHR		*P*-value
		NHR ≤ 0.205 ($n=293,294$)	NHR > 0.205 ($n=116,063$)	
Age, years	58 (50,63)	58 (50,63)	58 (49,64)	0.068
Male, n (%)	190,314 (46.5%)	117,174 (40.0%)	73,140 (63.0%)	< 0.001
Smoking status, n (%)				< 0.001
Never smoker	225,226 (55.0%)	170,030 (58.0%)	55,196 (47.6%)	
Previous smoker	141,121 (34.5%)	101,529 (34.6%)	39,592 (34.1%)	
Current smoker	43,010 (10.5%)	21,735 (7.4%)	21,275 (18.3%)	
Dinking status, n (%)				< 0.001
Never dinking	17,728 (4.3%)	11,623 (4.0%)	6,105 (5.3%)	
Previous drinking	14,399 (3.5%)	8,399 (2.9%)	6,000 (5.2%)	
Current drinking	377,230 (92.2%)	273,272 (93.2%)	103,958 (89.6%)	
Diabetes, n (%)	21,054 (5.1%)	9,219 (3.1%)	11,835 (10.2%)	< 0.001
Hypertension, n (%)	108,713 (26.6%)	66,799 (22.8%)	41,914 (36.1%)	< 0.001
HbA1c, mmol/mol	35.5 (33.0,37.7)	35.2 (32.7,37.2)	36.1 (33.6,39.2)	< 0.001
BMI, kg/m^2	27.41 ± 4.75	26.67 ± 4.34	29.27 ± 5.23	< 0.001
BMI categories, n (%)				< 0.001
Underweight	2,075 (0.5%)	1,790 (0.6%)	285 (0.2%)	
Normal weight	132,671 (32.4%)	110,651 (37.7%)	22,020 (19.0%)	
Overweight	175,733 (42.9%)	125,400 (42.8%)	50,333 (43.4%)	
Obesity	98,878 (24.2%)	55,453 (18.9%)	43,425 (37.4%)	
SBP, mmHg	140 (127,151)	139 (126,150)	140 (129,152)	< 0.001
DBP, mmHg	82 (75,89)	82 (75,88)	82 (77,90)	< 0.001
FBG, mmol/L	4.93 (4.60,5.31)	4.92 (4.60,5.28)	4.95 (4.59,5.43)	< 0.001
Neutrophil count, $\times 10^9$/L	4.22 ± 1.42	3.67 ± 0.96	5.61 ± 1.42	< 0.001
TG, mmol/L	1.48 (1.05,2.15)	1.34 (0.97,1.89)	1.95 (1.38,2.76)	< 0.001
TC, mmol/L	5.70 ± 1.14	5.84 ± 1.11	5.34 ± 1.15	< 0.001
HDL-c, mmol/L	1.45 ± 0.38	1.57 ± 0.36	1.15 ± 0.24	< 0.001
LDL-c, mmol/L	3.56 ± 0.87	3.62 ± 0.86	3.42 ± 0.88	< 0.001
NHR, $\times 10^8$/mg	0.18 ± 0.08	0.14 ± 0.04	0.28 ± 0.08	< 0.001
Lipid-lowering drugs, n (%)	43,137 (10.5%)	20,940 (7.1%)	22,197 (19.1%)	< 0.001
Antihypertensive drugs, n (%)	18,844 (4.6%)	10,245 (3.5%)	8,599 (7.4%)	< 0.001
Insulin, n (%)	364 (0.1%)	200 (0.1%)	164 (0.1%)	< 0.001

Abbreviations: *BMI* Body mass index, *DBP* Diastolic blood pressure, *FBG* Fasting blood glucose, *HbA1c* Glycated hemoglobin, *HDL-c* High-density lipoprotein cholesterol, *LDL-c* Low-density lipoprotein cholesterol, *NHR* Neutrophil to high-density lipoprotein cholesterol ratio, *SBP* Systolic blood pressure, *TC* Total cholesterol, *TG* Triglyceride

NHR ≤ 0.205 group, except for TC, LDL-c and HDL-c (all $P < 0.001$) (Table 1).

Association between NHR and AD/AA

Figure 3 visualizes the cumulative incidences of AD/AA, AD and AA in different groups using Kaplan–Meier curves. The cumulative incidences of AD/AA, AD and AA in the NHR > 0.205 group were significantly higher than in the NHR ≤ 0.205 group, as evaluated by the log-rant test ($P < 0.001$).

There was a nonlinear correlation of NHR with risk of AD/AA and AA (P for nonlinear < 0.001) after adjusting for age, gender, smoking status, drinking status, BMI, hypertension, LDL-c and HbA1c, while a linear relationship between NHR and AD was confirmed (P for nonlinear = 0.620) (Fig. 4).

A total of 3,408 participants developed AD/AA during a median follow-up of 14.8 (14.1, 15.5) years, with an incidence of 56.34 cases per 100,000 person-years. The incidence of AD/AA in the NHR > 0.205 group was higher than that in the NHR ≤ 0.205 group (97.59 cases per 100,000 person-years *vs.* 40.08 cases per 100,000 person-years). Especially, 223 participants developed AD, with an incidence of 3.85 cases per 100,000 person-years, and 3,259 participants were affected by AA, with an incidence of 53.87 cases per 100,000 person-years.

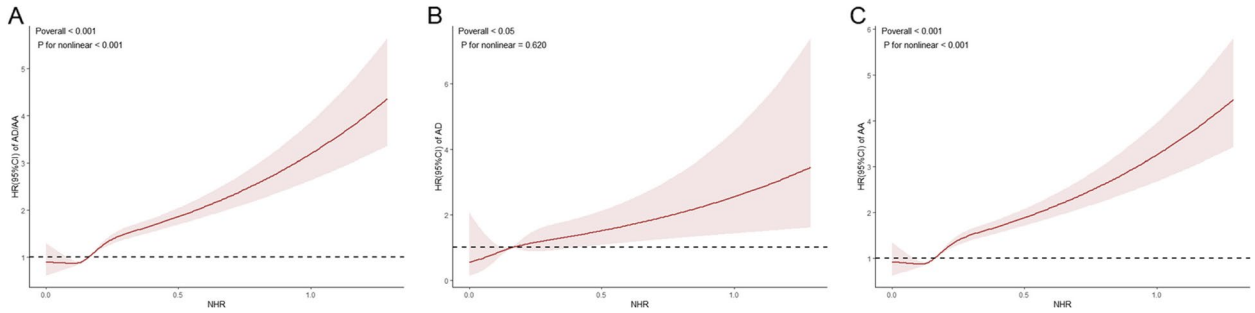

Fig. 4 Nonlinear relationship between NHR and incidence risk of outcomes evaluated by RCS. All covariates in model 3 including age, gender, smoking status, drinking status, BMI, hypertension, LDL-c and HbA1c were adjusted in this analysis. The RCS analysis utilized 4 knots placed at the 5th, 35th, 65th and 95th percentiles of the NHR distribution, corresponding to NHR values of 0.08, 0.13, 0.19 and 0.33, respectively. Solid lines in the figure represent the aHRs, and the shaded regions represent the 95%CIs of aHRs. Dashed lines in the figure represent the reference value of the association, which was set at 1.0. **A** Nonlinear relationship between NHR and AD/AA. **B** Nonlinear relationship between NHR and AD. **C** Nonlinear relationship between NHR and AA

The incidence of AD and AA in the NHR > 0.205 group was higher than in the NHR ≤ 0.205 group (5.56 AD cases per 100,000 person-years *vs.* 3.18 AD cases per 100,000 person-years; 94.02 AA cases per 100,000 person-years *vs.* 38.05 AA cases per 100,000 person-years) (Table 2).

Compared with the NHR ≤ 0.205 group, the HR (95%CI) for AD/AA in the NHR > 0.205 group without adjustment was 2.44 (2.28–2.61) ($P < 0.001$). After adjusting for age and gender, the NHR-related incidence risk of AD/AA underwent a considerable drop, with an adjusted HR (aHR) (95%CI) of 1.78 (1.66–1.91) in the NHR > 0.205 group (Model 1, $P < 0.001$). The magnitude of the association reduced when further adjusting for smoking and drinking statuses [aHR 1.56 (95%CI 1.45–1.67), Model 2, $P < 0.001$)] and additional covariates including BMI, hypertension, LDL-c and HbA1c [aHR 1.47 (95%CI 1.37–1.58), Model 3, $P < 0.001$].

Compared with the NHR ≤ 0.205 group, the unadjusted HR (95%CI) for AD in the NHR > 0.205 group was 1.75 (1.35–2.27) ($P < 0.001$). After adjusting for age and gender, the incidence risk of AD associated with NHR declined substantially, with an aHR (95%CI) of 1.51 (1.15–1.97) in the NHR > 0.205 group (Model 1, $P = 0.003$). The magnitude of the association further decreased when adjusting for smoking and drinking statuses [aHR 1.36 (95%CI 1.03–1.79), Model 2, $P = 0.029$], but it was no longer significant when additional covariates including BMI, hypertension, LDL-c and HbA1c were adjusted for [aHR 1.26 (95%CI 0.95–1.68), Model 3, $P = 0.110$].

In the unadjusted analysis, participants with NHR > 0.205 had a HR (95%CI) for AA of 2.47 (2.31–2.65) compared to those with NHR ≤ 0.205 ($P < 0.001$). After adjusting for age and gender (Model 1), the risk associated with NHR dropped markedly to an aHR (95%CI) of 1.79 (1.67–1.92) ($P < 0.001$). Further adjustment for smoking and drinking statuses (Model 2) reduced the aHR to 1.56 (95%CI 1.45–1.68) ($P < 0.001$), and additional adjustment for BMI, hypertension, LDL-c and HbA1c (Model 3) resulted in an aHR of 1.47 (95%CI 1.37–1.59) ($P < 0.001$).

When NHR was treated as a continuous variable, the aHRs (95%CIs) for the incidence risks of AD/AA, AD and AA were of 3.68 (3.18–4.25), 2.70 (1.24–5.87) and 3.75 (3.24–4.34), respectively. These findings were consistent with the results of sensitivity analysis 1 (adjusting for the effects of medications), sensitivity analysis 2 (excluding those developing AD/AA within the first year), and sensitivity analysis 3 (excluding those developing AD/AA within the first two years) (Table 2).

Subgroup analyses

The association of NHR with AD/AA, AD, and AA across stratified participant groups was also investigated by subgroup analyses (Fig. 5). NHR, analyzed as a continuous parameter, was found to increase the risk of AD/AA and AA in subgroups defined by age, gender, smoking status, diabetes, hypertension and BMI categories. Significant interactions of NHR with age, gender, smoking status, diabetes, hypertension and BMI categories were identified (P for interaction < 0.05). The relationship between NHR and AD/AA onset was more prominent in participants aged over 60 years compared to those younger than 60 years [aHR 7.55 (95%CI 5.72–9.97) *vs.* aHR 2.81 (95%CI 1.99–3.97)], in males compared to females [aHR 6.63 (95%CI 4.98–8.83) *vs.* aHR 3.01 (95%CI 2.23–4.07)], in current smokers compared to previous and never smokers [aHR 22.92 (95%CI 13.37–39.30) *vs.* aHR 3.31 (95%CI 2.63–4.17) *vs.* aHR 2.73 (95%CI 1.37–5.44)], in participants with diabetes compared to those without diabetes [aHR 8.10 (95%CI 2.93–22.41) *vs.* aHR 3.70 (95%CI 3.19–4.30)], in participants with hypertension compared to those without hypertension [aHR 8.62

Table 2 Baseline NHR and incidence risks of AD/AA

	NHR, HRs (95%CIs)		*P-value*	Per SD	*P*-value
	NHR ≤ 0.205	NHR > 0.205			
Outcome: AD/AA					
Number of events	1,739	1,669			
Persons	293,294	116,063			
Person-years	4,339,066	1,710,292			
Incidence	40.08	97.59			
Unadjusted model	Reference	2.44 (2.28–2.61)	< 0.001	3.51 (3.27–3.77)	< 0.001
Model 1	Reference	1.78 (1.66–1.91)	< 0.001	4.24 (3.84–4.68)	< 0.001
Model 2	Reference	1.56 (1.45–1.67)	< 0.001	3.70 (3.26–4.19)	< 0.001
Model 3	Reference	1.47 (1.37–1.58)	< 0.001	3.68 (3.18–4.25)	< 0.001
Sensitivity analysis 1	Reference	1.45 (1.35–1.56)	< 0.001	3.63 (3.14–4.22)	< 0.001
Sensitivity analysis 2	Reference	1.48 (1.37–1.59)	< 0.001	3.67 (3.17–4.26)	< 0.001
Sensitivity analysis 3	Reference	1.48 (1.37–1.59)	< 0.001	3.62 (3.10–4.23)	< 0.001
Outcome: AD					
Number of events	138	95			
Persons	293,294	116,063			
Person-years	4,339,066	1,710,292			
Incidence	3.18	5.56			
Unadjusted model	Reference	1.75 (1.35–2.27)	< 0.001	3.17 (2.20–4.56)	< 0.001
Model 1	Reference	1.51 (1.15–1.97)	0.003	3.30 (2.07–5.27)	< 0.001
Model 2	Reference	1.36 (1.03–1.79)	0.029	2.86 (1.56–5.24)	0.001
Model 3	Reference	1.26 (0.95–1.68)	0.110	2.70 (1.24–5.87)	0.012
Sensitivity analysis 1	Reference	1.27 (0.96–1.69)	0.097	2.75 (1.28–5.87)	0.009
Sensitivity analysis 2	Reference	1.34 (1.00–1.80)	0.048	2.66 (1.18–5.99)	0.019
Sensitivity analysis 3	Reference	1.31 (0.98–1.77)	0.073	2.55 (1.06–6.18)	0.037
Outcome: AA					
Number of events	1,651	1,608			
Persons	293,294	116,063			
Person-years	4,339,066	1,710,292			
Incidence	38.05	94.02			
Unadjusted model	Reference	2.47 (2.31–2.65)	< 0.001	3.53 (3.29–3.79)	< 0.001
Model 1	Reference	1.79 (1.67–1.92)	< 0.001	4.31 (3.90–4.76)	< 0.001
Model 2	Reference	1.56 (1.45–1.68)	< 0.001	3.76 (3.32–4.28)	< 0.001
Model 3	Reference	1.47 (1.37–1.59)	< 0.001	3.75 (3.24–4.34)	< 0.001
Sensitivity analysis 1	Reference	1.46 (1.35–1.57)	< 0.001	3.71 (3.20–4.30)	< 0.001
Sensitivity analysis 2	Reference	1.48 (1.37–1.60)	< 0.001	3.74 (3.22–4.34)	< 0.001
Sensitivity analysis 3	Reference	1.48 (1.37–1.60)	< 0.001	3.70 (3.16–4.32)	< 0.001

NHR was analyzed as both a categorical (left) and a continuous variable (right)

The incidence is per 100,000 person-years

Model 1: adjusted for age and gender

Model 2: additionally adjusted for smoking status and drinking status

Model 3: additionally adjusted for BMI, hypertension, LDL-c and HbA1c

Sensitivity analysis 1: additionally adjusted for lipid-lowering drugs, antihypertensive drugs and insulin

Sensitivity analysis 2: excluded follow-up time less than 1 years, remaining 409,248 participants with 3,307 AD/AA cases, 220 AD cases and 3,164 AA cases

Sensitivity analysis 3: excluded follow-up time less than 2 years, remaining 409,115 participants with 3,191 AD/AA cases, 211 AD cases and 3,052 AA cases

Per SD: risk per unit increment in NHR

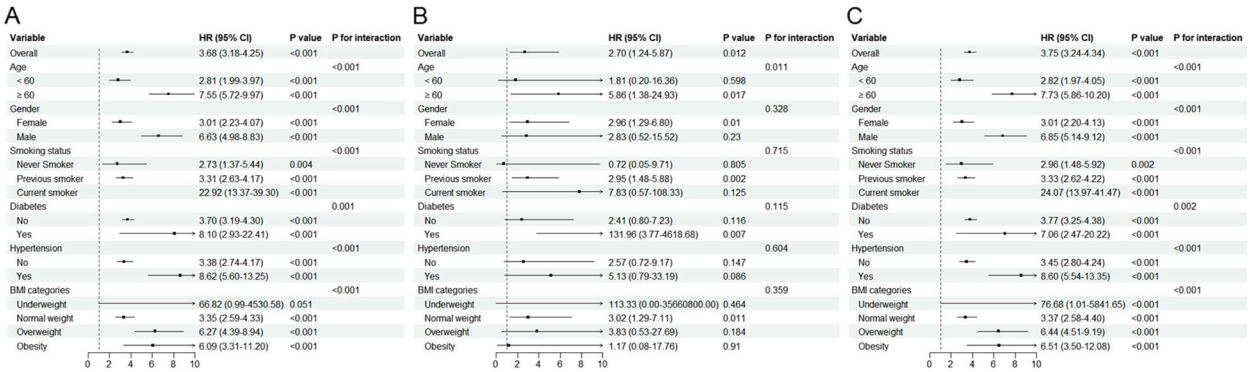

Fig. 5 Subgroup analyses of the association between NHR and incidence risk of AD/AA. The covariates in model 3 including age, gender, smoking status, drinking status, BMI, hypertension, LDL-c and HbA1c were controlled. **A** AD/AA. **B** AD. **C** AA

(95%CI 5.60–13.25) *vs.* aHR 3.38 (95%CI 2.74–4.17)], in overweight and obese participants compared to those with normal weight [aHR 6.27 (95%CI 4.39–8.94) *vs.* aHR 6.09 (95%CI 3.31–11.20) *vs.* aHR 3.35 (95%CI 2.59–4.33)]. A consistent relationship was also observed between NHR and AA. In contrast, a significant interaction between NHR and age was found in predicting the risk of AD (P for interaction < 0.05), whereas no significant interactions were observed for gender, smoking status, diabetes, hypertension and BMI categories (all P for interaction > 0.05).

Discussion

This study, involving 409,357 individuals from the general population based on the UK Biobank, reported incidences of AD and AA of 3.85 and 53.87 cases per 100,000 person-years, respectively. An independent nonlinear association of NHR with the incidence risk of AD/AA within a nearly 15-year follow-up period was also confirmed. The NHR-related incidence risk for AD/AA, particularly for AA, was obviously higher in the NHR > 0.205 group compared to the NHR ≤ 0.205 group, even after stepwise adjustment for potential confounding factors (such as age, gender, smoking status, drinking status, BMI, hypertension, LDL-c and HbA1c), although the association for AD was attenuated. This finding was further validated by sensitivity analyses and subgroup analyses, suggesting that NHR could serve as a useful biomarker in identifying patients at elevated risk, particularly for AA, enabling clinicians to classify patients into high- and low-risk groups. Additionally, patients with an elevated NHR might benefit from more intensive lifestyle modifications and aggressive management of blood pressure, lipid levels, and metabolic parameters to mitigate the risk of AA.

Age, gender, smoking and hypertension are well-documented risk factors for AD/AA [17–19]. Consistent with these studies, we demonstrated that the association of NHR with incident cases of AD/AA was more pronounced in specific stratified participants groups, such as older age, males, current smokers and patients with hypertension, suggesting a significant interplay between these well-known factors and NHR in the onset of AD/AA. Insulin resistance has been considered a risk factor for AD/AA, with an aHR (95%CI) of 1.15 (1.08–1.23) [16]. Similar to this study, the interaction between diabetes and NHR was significant in increasing the incidence risk of AD/AA. The NHR-related risk of AD/AA sharply raised more than twice in participants with diabetes. A significant correlation between NHR and AD/AA onset was also investigated in the overweight and obese population. This is because overweight or obese individuals are more likely to develop metabolic disorders, such as diabetes and fatty liver disease, which further aggravate the progression of AD/AA [20, 21].

Consistent with our findings, extensive research has substantiated that inflammation responses contribute to the progression of aortic disease. Inflammatory cells infiltration, particularly driven by neutrophils, is responsible for dysfunction of the aortic endothelial layer and the inflammatory microenvironment of aortic tissues [22]. Neutrophil extracellular traps (NETs), DNA structures generated and released by activated neutrophils upon recognizing stimuli, have been demonstrated to be associated with the progression of AA [23]. Ibrahim et al. identified that inhibiting NETs with peptidyl arginine deiminase 4 (PAD4) inhibitors effectively attenuated aneurysmal growth in an angiotensin II (Ang II)-induced AD mouse model [22, 24]. The above evidence underlines the significance of inhibiting the NET induction process in aortic pathologies.

Cholesterol metabolism considerably affects NC in circulation. Extensive animal studies have revealed that a high-fat diet causes substantial circulating neutrophilia

[25–28], which gradually returns to normal levels after cessation of the high-fat diet [29]. A cross-sectional study involving 10,866 hypertensive patients showed a negative association of HDL-c with NC [30], which was also confirmed by other studies [31–33]. Several studies have reported the effects of cholesterol on NC homeostasis. Impaired cholesterol homeostasis promotes the migration and degranulation of granulocytes [34] and the formation of NETs in a dose-dependent manner [35]. Moreover, diet-induced dyslipidemia impairs the chemotaxis of neutrophils [36]. Thus, NHR, reflecting the imbalance between pro- and anti-inflammatory responses, could serve as a feasible indicator of metabolic inflammation in aortic disease.

Numerous studies have investigated the association between NHR and cardiovascular diseases and confirmed the promising potential of NHR as an effective metabolic inflammatory biomarker [37–40]. However, these studies are limited by retrospective or cross-sectional designs, relatively small sample sizes, and a specific patient population. Importantly, few studies have evaluated the correlation between NHR and the incidence risk of aortic disease, a gap that the present study addresses.

Strengths and limitations

Several strengths of this study merit attention. For the first time, we identified the epidemiological relationship between the metabolic inflammatory biomarker NHR and the incidence of AD/AA, strongly supporting the essential role of inflammation and metabolic disorders in cardiovascular diseases. Additionally, to avoid bias from confounding factors or pre-existing outcomes, most covariates identified by univariate Cox regression models and those well-known in clinical practice were controlled. Those who developed outcomes during the first year or the first two years of follow-up were also excluded. Lastly, the prospective study design, large sample size, long follow-up duration and high follow-up retention rate are commendable.

Some limitations of this study should be addressed. Firstly, detailed classification of type A and type B AD failed to be achieved owing to incomplete data and the rare incidence of these outcomes. Secondly, the study population were recruited in the United Kingdom, limiting the generalizability of the results to other geographic regions. Thirdly, the impact of potential unmeasured confounders on the observed association between NHR and the incidence risk of AD/AA, such as genetic predisposition and medication use, could not be ruled out. Family history of aortic diseases, including rare conditions like Marfan syndrome, can elevate an individual's risk of developing AD/AA. The use of anti-inflammatory drugs, such as antibiotics and non-steroidal anti-inflammatory drugs, can alter the body's inflammatory states. By reducing inflammation, these medications may lower the NHR value, potentially masking or exaggerating the true relationship between NHR and AD/AA. Fourthly, although participants lost to follow-up were already excluded at enrollment, those who died prior to AD/AA onset were not accounted for. The potential competing risks could affect the interpretation of the results. Additionally, the association between NHR and the progression or worsening of AD/AA was not investigated, which could be explored in future research.

Conclusion

This study showed a significant and independent association between NC and HDL-c-derived metabolic inflammatory biomarkers and the incidence of AD/AA. Subclinical metabolic inflammation, evaluated by NHR, may be a potential pathogenic mechanism for AD/AA, especially for AA. Tailored surveillance and management of NHR in individuals at high risk for AA represent promising strategies to prevent its onset.

Abbreviations

AA	Aortic aneurysm
AD	Aortic dissection
aHR	Adjusted hazard ratio
BMI	Body mass index
CI	Confidence interval
DBP	Diastolic blood pressure
FBG	Fasting blood glucose
GBD	Global Burden of Disease Study
HbA1c	Glycosylated hemoglobin
HDL-c	High-density lipoprotein cholesterol
HR	Hazard ratio
ICD-10	International Classification of Diseases, 10th revision
LDL-c	Low-density lipoprotein cholesterol
NC	Neutrophil count
NET	Neutrophil extracellular traps
95%CI	95% confidence interval
NHR	Neutrophil to high-density lipoprotein cholesterol ratio
RAP	Research Analysis Platform
RCS	Restricted cubic spline
ROC	Receiver operating characteristic
SBP	Systolic blood pressure
TC	Total cholesterol
TG	Triglyceride

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-025-22061-3.

Supplementary Material 1.

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Authors' contributions

Prof. X.T., serving as the principal investigator, contributed to the design of this study. Dr. C.T. performed the statistical analysis and was responsible for the conception, literature review and drafting of this manuscript. Prof. Y.C. were

responsible for the results interpretation. Dr X.W. and Prof. L.T. reviewed the manuscript. All authors approved the final manuscript.

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Data availability
This work was conducted using the UK Biobank dataset with application number of 205837. All international researchers whether from academic, commercial, or charitable affiliation are accessible to the dataset upon application (http://www.ukbiobank.ac.uk/register-apply).

Declarations

Ethics approval and consent to participate
This study adhered to the Declaration of Helsinki (1975). Participants provided their informed consent and ethical approval was obtained from the North West Multi-center Research Ethics Committee (MREC) (No. 11/NW/03820).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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