



Racial Differences in Bleeding Risk: An Ecological Epidemiological Study Comparing Korea and United Kingdom Subjects

Dong-Seon Kang^{1,*} Pil-Sung Yang^{2,*} Daehoon Kim¹ Eunsun Jang¹ Hee Tae Yu¹ Tae-Hoon Kim¹
Jung Hoon Sung² Hui-Nam Pak¹ Moon-Hyoung Lee¹ Gregory Y.H. Lip^{3,4,**} Boyoung Joung^{1,**}

¹ Division of Cardiology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea

² Division of Cardiology, CHA Bundang Medical Center, CHA University, Seongnam, Republic of Korea

³ Liverpool Centre for Cardiovascular Science at University of Liverpool, Liverpool John Moores University and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom

⁴ Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Address for correspondence Boyoung Joung, MD, Division of Cardiology, Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul, Republic of Korea 03722 (e-mail: cby6908@yuhs.ac).

Gregory Y.H. Lip, MD, Liverpool Centre for Cardiovascular Science, Liverpool, England (e-mail: gregory.lip@liverpool.ac.uk).

Thromb Haemost 2024;124:842–851.

Abstract

Background This study aimed to evaluate racial differences in bleeding incidence by conducting an ecological epidemiological study using data from Korea and the United Kingdom.

Methods We included healthy participants from the Korean National Health Insurance Service-Health Screening and the UK Biobank who underwent health examinations between 2006 and 2010 and had no comorbidities or history of medication use. Finally, 112,750 East Asians (50.7% men, mean age 52.6 years) and 210,995 Caucasians (44.7% men, mean age 55.0 years) were analyzed. The primary outcome was composed of intracranial hemorrhage (ICH) and bleeding from the gastrointestinal, respiratory, and genitourinary systems.

Results During the follow-up, primary outcome events occurred in 2,110 East Asians and in 6,515 Caucasians. East Asians had a 38% lower 5-year incidence rate compared with Caucasians (3.88 vs. 6.29 per 1,000 person-years; incidence rate ratio [IRR]: 0.62, 95% confidence interval [CI]: 0.59–0.65). East Asians showed a lower incidence of major bleeding (IRR: 0.86, 95% CI: 0.81–0.91), bleeding from the gastrointestinal (IRR: 0.53, 95% CI: 0.49–0.56), and genitourinary systems (IRR: 0.49, 95% CI: 0.44–0.53) compared with Caucasians. The incidence rates of ICH (IRR: 3.20, 95% CI: 2.67–3.84) and bleeding from the respiratory system (IRR: 1.28, 95% CI: 1.11–1.47) were higher in

Keywords

- racial differences
- intracranial hemorrhage
- gastrointestinal system

* These authors contributed equally to this work.

These authors serve as joint senior authors.

The review process for this paper was fully handled by Christian Weber, Editor in Chief.

received

January 15, 2024

accepted after revision

February 13, 2024

accepted manuscript online

February 15, 2024

article published online

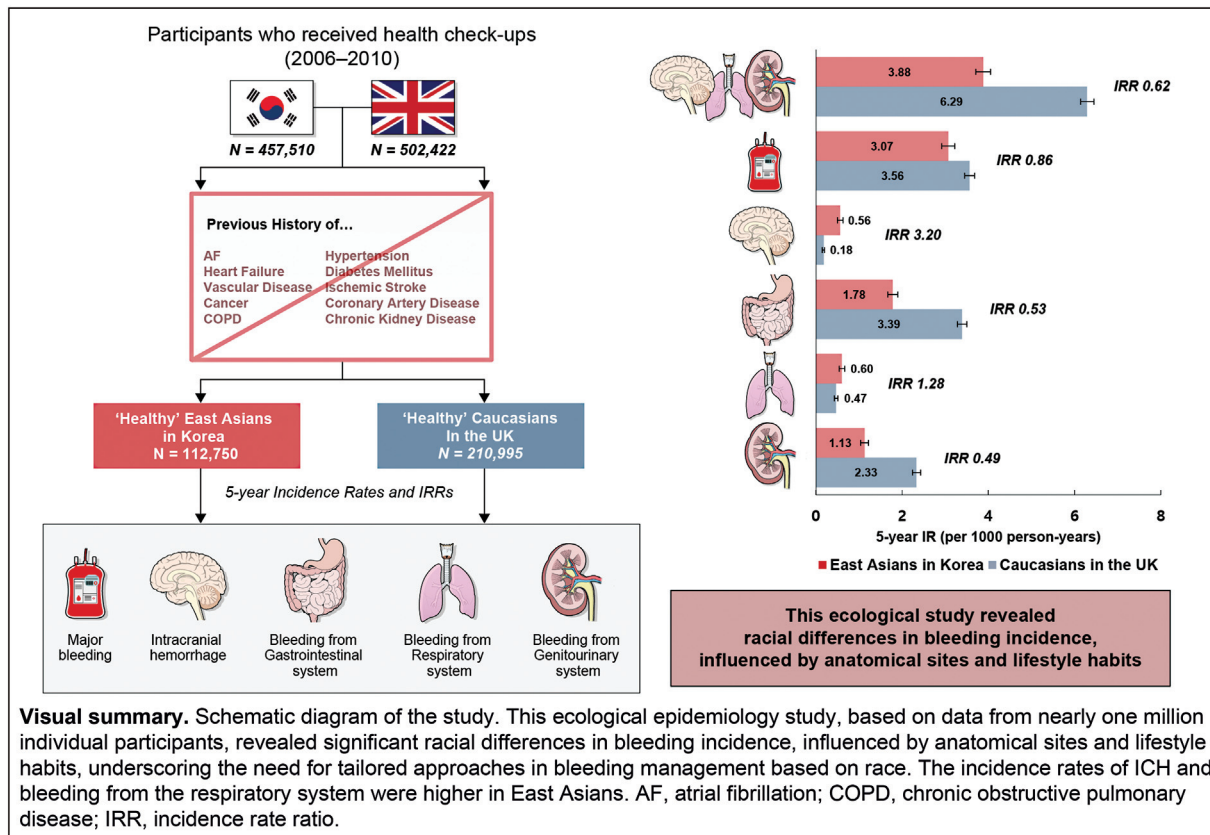
March 8, 2024

DOI <https://doi.org/10.1055/a-2269-1123>.
ISSN 0340-6245.

© 2024. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany



East Asians. Notably, East Asians consuming alcohol ≥ 3 times/week showed a higher incidence of the primary outcome than Caucasians (IRR: 1.12, 95% CI: 1.01–1.25).

Conclusion This ecological study revealed significant racial differences in bleeding incidence, influenced by anatomical sites and lifestyle habits, underscoring the need for tailored approaches in bleeding management based on race.

Introduction

Various bleeding events across all anatomical sites can frequently necessitate modifications to existing treatment plans and adversely affect patient prognosis.^{1,2} Race plays a major role in predicting the bleeding risk. For example, East Asians, especially when on anticoagulant therapy, are known to have a significantly higher risk of major bleeding and intracranial hemorrhage (ICH) compared with non-East Asians,³ leading to Japanese guidelines recommending a lower target international normalized ratio range of 1.6 to 2.6 to prevent bleeding events.⁴ However, since the burden of the major causes of bleeding at different anatomical sites varies by race (i.e., colorectal cancer and/or angiodysplasia for bleeding from the gastrointestinal system), the relative risk of bleeding based on its origin can differ between races.^{5,6} This suggests the need to consider race-specific characteristics in effective public health care planning and allocation for each region/country. Nevertheless, with East Asia being one of the most populous regions with over 1.5 billion people, its underrepresentation in major clinical trials

often complicates extrapolating their conclusions, and evidence directly comparing differences between races using patient-level data and consistent statistical methods is even scarcer.⁷

In this study, we analyzed nearly one million individual patient data extracted from cohorts conducted in South Korea and the United Kingdom to understand bleeding occurrences in East Asians and identify differences with Caucasians. We designed an ecological epidemiological study to investigate the overall bleeding incidence within the two cohorts, validate differences using various analyses, and assess the risk of bleeding by anatomical site and the temporal trends of bleeding occurrences. Thus, this ecological study bears the characteristics of an observational epidemiological study that associates exposure and disease at a population level, rather than an individual level.

Methods

The data for this retrospective study were collected from the Korean National Health Insurance Service-Health Screening

(K-NHIS-HealS) and the UK Biobank. The detailed information of these cohorts has been reported previously and is also demonstrated in ► **Supplementary Methods** (available in the online version).^{8,9} This study was approved by the Institutional Review Board of the Yonsei University Health System (4-2022-1241). The requirement for informed consent was waived for the K-NHIS-HealS because personal de-identification proceeded after the cohort was generated. The UK Biobank study was approved by the North West Multicenter Research Ethics Committee (REC approval 21/NM/0157) and was conducted using the UK Biobank resource under application 77793. Informed consent was obtained from all the participants in the UK Biobank.

Assessment of Baseline Characteristics

Definitions of comorbidities in the K-NHIS-HealS and UK Biobank are presented in ► **Supplementary Table S1** (available in the online version), which have been validated in previous studies.^{10,11} Sex and race were defined by using self-reported data.¹² To determine the comorbidities at baseline, diagnostic and procedural codes associated with hospital encounters were utilized. Information on medication use for the treatment of cardiovascular diseases was collected from linked general practitioner electronic health records, which were obtained through either self-report or prescription data.¹³ The frequency of moderate-to-vigorous-intensity physical activity was assessed using a short-form survey derived from the International Physical Activity Questionnaire during health check-ups.¹⁴ Participants were classified into three groups based on their exercise habits: not engaged, 1 to 3 days/week, and 4 to 7 days/week. Questionnaires were used to obtain information on smoking and alcohol intake. Participants were categorized as non-, ex-, and current smokers, and their alcohol consumption was classified as non-, 1 to 3 times/month, 1 to 2 times/week, and ≥ 3 times/week.⁹

Study Outcomes

The primary outcome was a composite of ICH and bleeding from the gastrointestinal, respiratory, and genitourinary systems. Additionally, as a secondary outcome, we analyzed not only each component of the primary outcome but also major bleeding, defined as a composite of ICH, bleeding from the gastrointestinal system, anemia caused by bleeding, and bleeding-related death, and compared between racial groups. Outcomes were defined using established ICD-10 (International Classification of Diseases, 10th Revision) codes from the K-NHIS-HealS and UK Biobank claims data. Related death records were utilized to define the outcomes (► **Supplementary Table S2** [available in the online version]).¹³ These codes were in the primary position, and procedure codes for concomitant brain imaging were required in cases of ICH. We investigated the risk of initial bleeding events rather than that of recurrent events in these participants.¹⁵

Selection of Participants

The process of selecting participants is detailed in ► **Supplementary Methods** (available in the online version)

and ► **Fig. 1**. We identified 457,510 and 502,422 participants aged ≥ 18 years in the K-NHIS-HealS and UK Biobank, respectively. To match the timing and age of enrollment of participants within the two cohorts, we included individuals who had health check-ups between 2006 and 2010 and were between 40 and 69 years old at the time of enrollment. Participants were also excluded from the analysis if they had missing information on comorbidities, medications, physical activity, alcohol intake, or smoking habits. Based on previous studies, we excluded participants who had underlying comorbidities or were taking medications related to these conditions.⁹

Statistical Analysis

The participants' baseline characteristics were described using descriptive statistics. To account for the varying follow-up duration in the two cohorts, the age- and sex-adjusted 5-year incidence rates (5-year IRs) of the primary and secondary outcomes were calculated by dividing the number of first-ever events by the sum of person-years during the 5 years from enrollment and reported per 1,000 person-years by race. To compare IRs between the two racial groups, we estimated IR ratios (IRRs) with 95% confidence intervals (CIs) for Caucasians in the United Kingdom as a reference. To identify temporal trends in the incidence of the primary outcome within each racial group, IRs were calculated independently for participants in each year of enrollment. Cox regression analysis was used to estimate the hazard ratios and 95% CIs for participants in each year, which were compared with those enrolled in 2006. The model was adjusted for age, sex, body mass index (BMI), physical activity, alcohol intake, and smoking habits.

In the sensitivity analyses, we first calculated the 1- and 3-year IRs and the IRRs for those time periods. Second, to address the imbalance in age, sex, and enrollment date distribution between the two cohorts, one-to-one propensity score matching (PSM) was used. Standardized mean differences were used to assess balance, with a value of 0.1 or higher set as the threshold to indicate imbalance. Third, for Caucasians in the United Kingdom, we only used ICD-10 codes to define comorbidities at enrollment, similar to East Asians in Korea. Fourth, given the impact of antithrombotic agents (i.e., oral anticoagulants, aspirin, and P₂Y₁₂ inhibitors) on bleeding events, we censored the data according to the time of antithrombotic prescription. Finally, subgroup analyses were conducted considering age, sex, BMI, physical activity, alcohol intake, and smoking habits. All tests were two-tailed, and statistical significance was set at $p < 0.05$. We used R version 4.2.1 (The R Foundation, www.R-project.org) for all analyses.

Results

Baseline Characteristics

After exclusions, our final sample was 112,750 "healthy" East Asians in Korea and 210,995 Caucasians in the United Kingdom at baseline, with mean (standard deviation) ages of 52.6 (6.5) and 55.0 (7.9) years, respectively (► **Table 1**). Men accounted

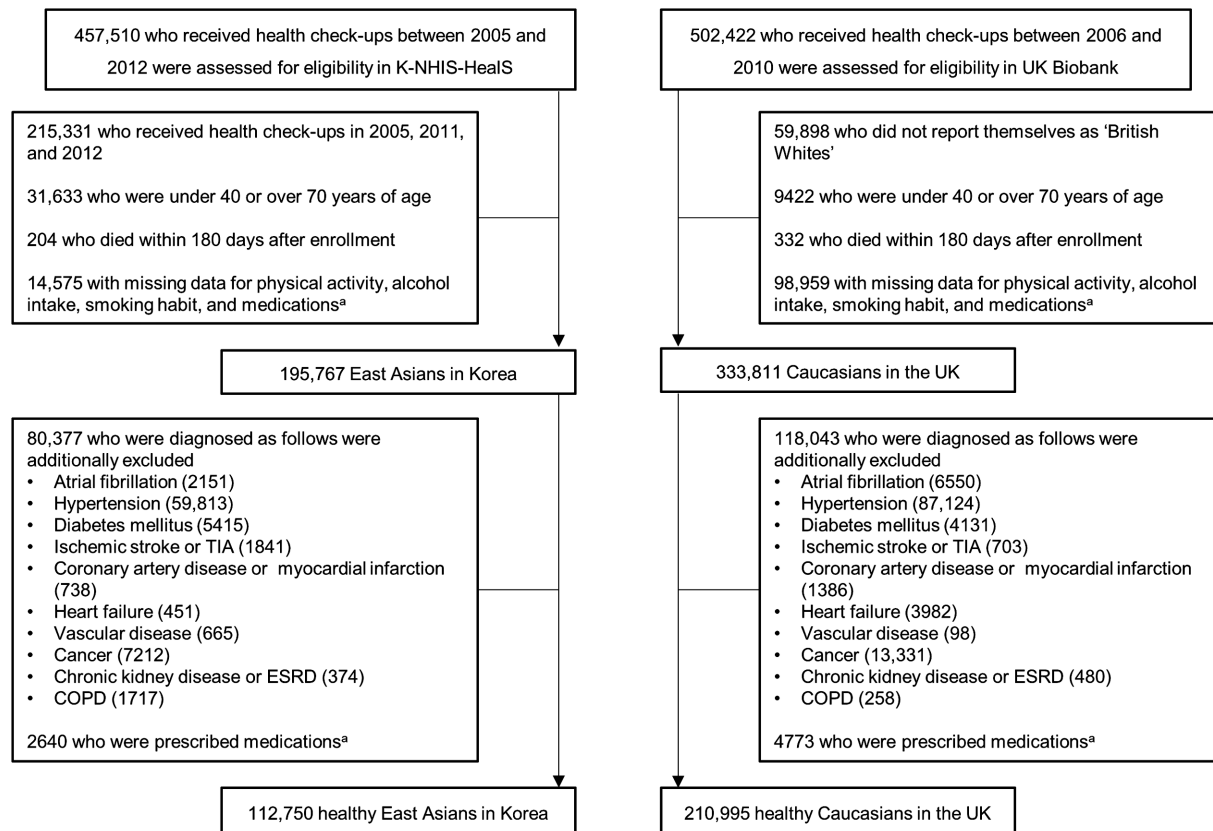


Fig. 1 Flow chart of enrollment and analysis of the participants. ^aMedications include oral anticoagulants, aspirin, P₂Y₁₂ inhibitors, statins, β blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, loop diuretics, and potassium-sparing diuretics. AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; K-NHIS-HealS, Korean National Health Insurance Service-Health Screening.

for 50.7% of East Asians in Korea and 45.5% of Caucasians in the United Kingdom. East Asians in Korea had a lower BMI (23.7 [2.8] vs. 26.4 [4.2] kg/m², $p < 0.001$) and a higher proportion of underweight participants (2.1% vs. 0.6%, $p < 0.001$) than Caucasians in the United Kingdom. In addition, East Asians in Korea tended to be physically inactive (4–7 days of moderate–vigorous physical activity/week; 9.8% vs. 67.1%, $p < 0.001$), consumed alcohol less frequently (≥ 3 times/week; 10.3% vs. 47.5%, $p < 0.001$), and were less likely to have ever smoked (nonsmokers; 71.8% vs. 57.7%, $p < 0.001$) than Caucasians in the United Kingdom.

Differences in 5-Year Incidence Rates for Primary and Secondary Outcomes

►Table 2 and ►Fig. 2 demonstrated the 5-year IRs for participants in both cohorts for the outcomes of interest. The mean duration of follow-up for East Asians in Korea and Caucasians in the United Kingdom was 6.5 (1.2) years and 11.8 (1.3) years, respectively. During the 5 years after the initiation of follow-up, 2,525 events of the primary outcome were reported for East Asians in Korea, whereas 6,532 events were reported for Caucasians in the United Kingdom (►Table 2). When adjusted for age and sex composition, East Asians in Korea were associated with a 38% lower incidence of the primary outcome than Caucasians in the United Kingdom (5-year IR of 3.88 events per 1,000 person-years in East Asians

in Korea vs. 6.29 in Caucasians in the United Kingdom; IRR: 0.62, 95% CI: 0.59–0.65).

Consistent with the primary outcome, East Asians in Korea also had a 14% lower incidence of major bleeding than Caucasians in the United Kingdom (5-year IR of 3.07 events per 1,000 person-years in East Asians in Korea versus 3.56 in Caucasians in the United Kingdom; IRR: 0.86, 95% CI: 0.81–0.91). This relative tendency for bleeding varied depending on the anatomical sites of the bleeding. Of the participants included in the analysis, 2,233 bleeding events were observed in 2,110 East Asians in Korea and 6,648 events were observed in 6,515 Caucasians in the United Kingdom; the proportions by anatomical site are shown in ►Fig. 3. In both cohorts, bleeding from the gastrointestinal system was the most common, followed by bleeding from the genitourinary and respiratory systems and ICH; however, ICH accounted for 13.8% of total bleeding events in East Asians in Korea, compared with only 2.8% in Caucasians in the United Kingdom. For ICH, East Asians in Korea had approximately three times more incidence than Caucasians in the United Kingdom (5-year IR of 0.56 events per 1,000 person-years in East Asians in Korea vs. 0.18 in Caucasians in the United Kingdom; IRR: 3.20, 95% CI: 2.67–3.84). For bleeding from the gastrointestinal system, the 5-year IR for East Asians in Korea was half that of Caucasians in the United Kingdom (5-year IR of 1.78 events per 1,000 person-years in East Asians in Korea vs. 3.39 in Caucasians in the United Kingdom; IRR 0.53, 95%

Table 1 Baseline characteristics of study participants according to race

Characteristics	East Asians in Korea (N = 112,750)	Caucasians in the UK (N = 210,995)	SMD
Age, y	52.6 (6.5)	55.0 (7.9)	0.33
40–45	6,346 (5.6)	26,092 (12.4)	
45–50	37,391 (33.2)	35,374 (16.8)	
50–55	32,114 (28.5)	36,920 (17.5)	
55–60	16,881 (15.0)	39,010 (18.5)	
60–65	13,456 (11.9)	45,195 (21.4)	
65–70	6,562 (5.8)	28,404 (13.5)	
Men	57,116 (50.7)	94,323 (44.7)	0.12
Enrollment year			1.98
2006	66,933 (59.4)	49 (0.0)	
2007	18,894 (16.8)	22,411 (10.6)	
2008	14,341 (12.7)	81,469 (38.6)	
2009	7,887 (7.0)	72,341 (34.3)	
2010	4,695 (4.2)	34,725 (16.5)	
Body mass index (kg/m ²)	23.7 (2.8)	26.4 (4.2)	0.78
<18.5	2,337 (2.1)	1,226 (0.6)	
18.5–23	44,817 (39.8)	40,330 (19.2)	
23–25	32,037 (28.4)	43,287 (20.6)	
25–30	31,478 (27.9)	89,909 (42.7)	
≥30	2057 (1.8)	35,651 (16.9)	
Frequency of moderate-to-vigorous physical activity			1.52
Not engaged	55,890 (49.6)	22,597 (10.7)	
1–3 days/week	45,856 (40.7)	46,804 (22.2)	
4–7 days/week	11,004 (9.8)	141,594 (67.1)	
Alcohol intake (frequency)			1.50
Non-	66,032 (58.6)	11,032 (5.2)	
1–3 times/month	17,100 (15.2)	42,295 (20.0)	
1–2 times/week	17,987 (16.0)	57,365 (27.2)	
≥3 times/week	11,631 (10.3)	100,303 (47.5)	
Smoking			0.63
Non-	80,955 (71.8)	121,842 (57.7)	
Ex-	9,825 (8.7)	67,826 (32.1)	
Current-	21,970 (19.5)	21,327 (10.1)	

Abbreviation: SMD, standardized mean difference.

Note: Data are presented as means (standard deviations) or No. (%).

CI: 0.49–0.56). In addition, East Asians in Korea had a 28% higher incidence of bleeding from respiratory system (5-year IR of 0.60 events per 1,000 person-years in East Asians in Korea vs. 0.47 in Caucasians in the United Kingdom; IRR: 1.28, 95% CI: 1.11–1.47) compared with Caucasians in the United Kingdom, and a 51% lower incidence of bleeding from genitourinary system (5-year IR of 1.13 events per 1,000 person-years in East Asians in Korea

vs. 2.33 in Caucasians in the United Kingdom; IRR: 0.49, 95% CI: 0.44–0.53).

Temporal Trends in the Incidence of Bleeding

The temporal trends in incidence of the primary outcome are shown in ►**Supplementary Table S3** (available in the online version). For East Asians in Korea, the 5-year IR for the

Table 2 Five-year incidence rates for primary and secondary outcomes according to race

	East Asians in Korea (N = 112,750)	Caucasians in the UK (N = 210,995)
Primary outcome		
Number of events	2,110	6,515
Person-years	544,336	1,035,171
Incidence rate (95% CI) ^a	3.88 (3.71–4.04)	6.29 (6.14–6.45)
Incidence rate ratio (95% CI)	0.62 (0.59–0.65)	1 [reference]
Secondary outcome		
Major bleeding		
Number of events	1,674	3,714
Person-years	545,220	1,042,056
Incidence rate (95% CI) ^a	3.07 (2.92–3.22)	3.56 (3.45–3.68)
Incidence rate ratio (95% CI)	0.86 (0.81–0.91)	1 [reference]
Intracranial hemorrhage		
Number of events	309	185
Person-years	548,159	1,050,374
Incidence rate (95% CI) ^a	0.56 (0.50–0.63)	0.18 (0.15–0.20)
Incidence rate ratio (95% CI)	3.20 (2.67–3.84)	1 [reference]
Bleeding from gastrointestinal system		
Number of events	975	3,532
Person-years	546,762	1,042,395
Incidence rate (95% CI) ^a	1.78 (1.67–1.90)	3.39 (3.28–3.50)
Incidence rate ratio (95% CI)	0.53 (0.49–0.56)	1 [reference]
Bleeding from respiratory system		
Number of events	329	493
Person-years	548,147	1,049,704
Incidence rate (95% CI) ^a	0.60 (0.54–0.67)	0.47 (0.43–0.51)
Incidence rate ratio (95% CI)	1.28 (1.11–1.47)	1 [reference]
Bleeding from genitourinary system		
Number of events	620	2,438
Person-years	547,452	1,044,648
Incidence rate (95% CI) ^a	1.13 (1.04–1.22)	2.33 (2.24–2.43)
Incidence rate ratio (95% CI)	0.49 (0.44–0.53)	1 [reference]

Abbreviation: CI, confidence interval.

^aIncidence rates were presented as per 1,000 person-years.

primary outcome was 4.41 for participants enrolled in 2006 and 4.51 for participants enrolled in 2010, with an overall stable temporal trend observed (p for trend = 0.51). In contrast, for Caucasians in the United Kingdom, the 5-year IR for the primary outcome was 7.04 for participants enrolled in 2007 and 5.76 for participants enrolled in 2010, with a significant decreasing temporal trend (p for trend < 0.001).

Sensitivity Analysis

The 1- and 3-year IRs for primary and secondary outcomes are presented in ► **Supplementary Tables S4** and **S5** (available

in the online version). The results were consistent with the main findings, suggesting that the differences in bleeding incidence between the two racial groups was evident from the early phase of the follow-up period. Through one-to-one PSM, differences in age, sex, and enrollment timing between the two cohorts were successfully adjusted, and 43,360 participants were selected in each group (► **Supplementary Table S6** [available in the online version]). Despite the PSM, East Asians in Korea still had a lower BMI, engaged in less physical activity, and had higher proportions of nondrinkers and nonsmokers than Caucasians in the United Kingdom.

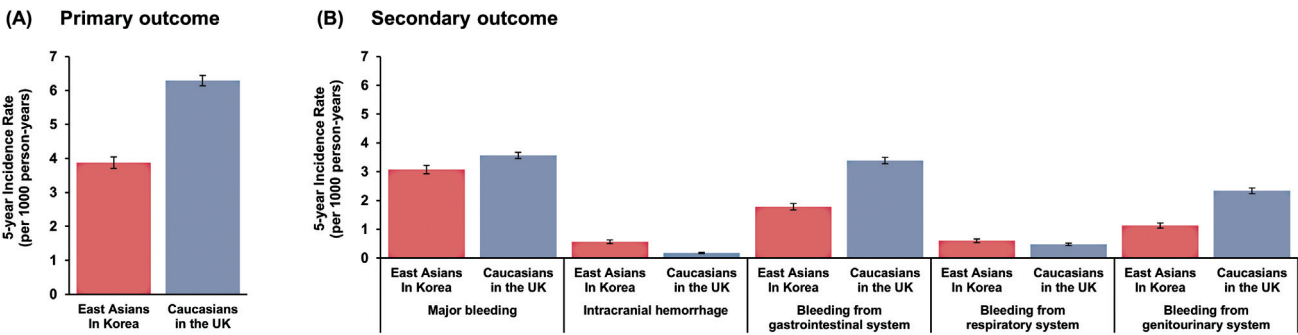


Fig. 2 Bar graph of 5-year incidence rates according to race. The incidence rates of the primary outcome are presented in panel (A), and the incidence rates of each component of the secondary outcome are presented in panel (B). Error bars indicate 95% confidence intervals for the incidence rates.

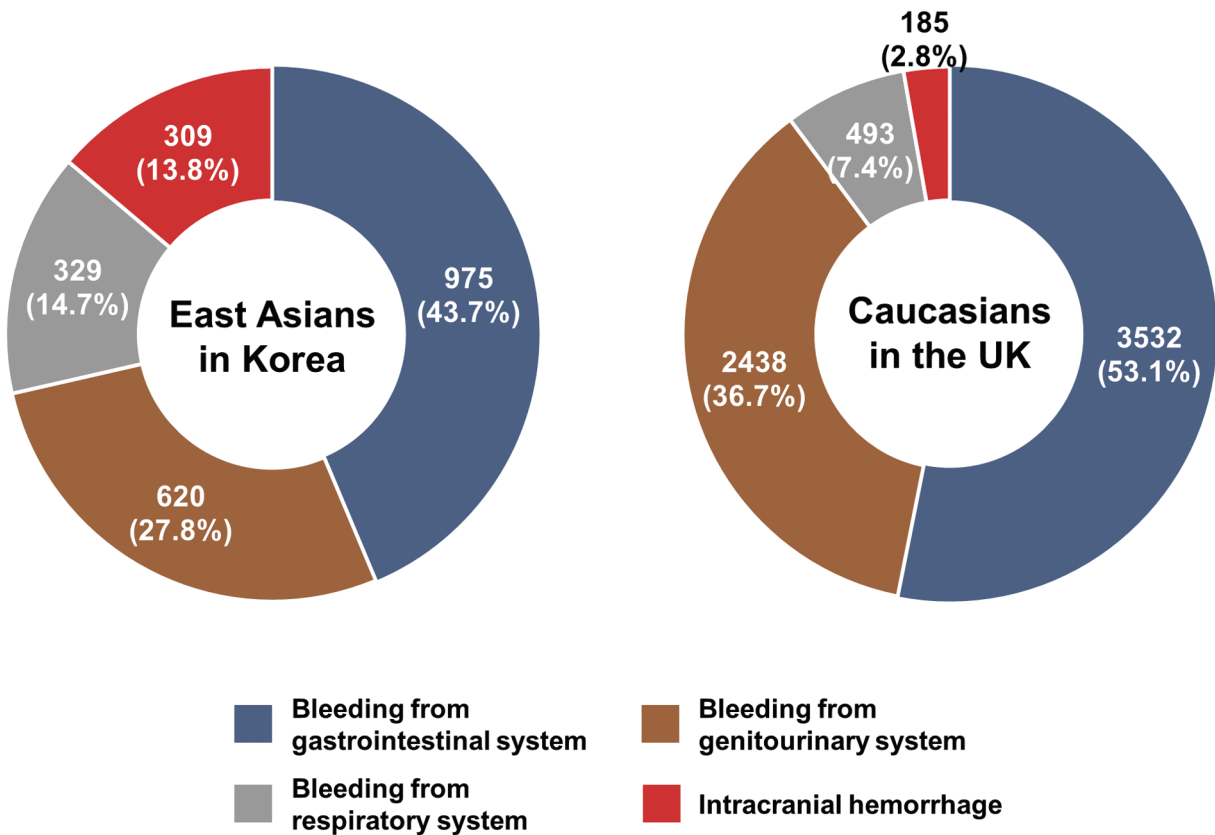


Fig. 3 Proportional distribution of components within the primary outcome. This figure illustrates the proportion, in No. (%), of each anatomical site of bleeding origin within the total bleeding events.

The results remained consistent with the main findings when one-to-one PSM was applied (► **Supplementary Table S7** [available in the online version]), when baseline comorbidities in the UK Biobank cohort were defined solely by ICD-10 codes (► **Supplementary Table S8** [available in the online version]), and when participants prescribed antithrombotic agents were censored on the prescription date (► **Supplementary Table S9** [available in the online version]). Most subgroup analyses also showed consistent results; however, in the subgroup of participants who consumed alcohol ≥ 3 times/week, East Asians in Korea had higher incidences of the primary outcome (5-year IR

of 6.58 events per 1,000 person-years in East Asians in Korea vs. 5.85 in Caucasians in the United Kingdom; IRR: 1.12, 95% CI: 1.01–1.25), major bleeding (5-year IR of 5.48 events per 1,000 person-years in East Asians in Korea vs. 3.25 in Caucasians in the United Kingdom; IRR: 1.69, 95% CI: 1.49–1.91), and bleeding from the gastrointestinal system (5-year IR of 3.86 events per 1,000 person-years in East Asians in Korea vs. 3.08 in Caucasians in the United Kingdom; IRR: 1.26, 95% CI: 1.09–1.45) than Caucasians in the United Kingdom (► **Supplementary Figs. S1–S6** [available in the online version]).

Discussion

In this ecological epidemiological study utilizing patient-level data from South Korea and the United Kingdom, the principal findings are as follows: first, employing various statistical methods, East Asians in Korea exhibit a lower overall incidence of both primary outcome and major bleeding compared with Caucasians in the United Kingdom. Second, certain anatomical sites of bleeding, including ICH, were reported more frequently among East Asians in Korea than among Caucasians in the United Kingdom. Third, in contrast to Caucasians in the United Kingdom, the bleeding rates among East Asians in Korea remained relatively consistent regardless of the time of enrollment. Fourth, even among healthy participants from both cohorts, lifestyle differences were noted, whereby frequent alcohol intake (≥ 3 times/week) was associated with a higher bleeding incidence, particularly in East Asians in Korea.

Differences in Bleeding Tendency Based on Anatomical Sites

In a meta-analysis examining the incidence of ICH, the incidence was approximately twofold higher in Asian people compared with white people.¹⁶ A prior epidemiological study also noted that major bleeding events were more frequent in Chinese people than in European people, attributed to a heightened risk of ICH in the former.¹⁷ One hypothesis suggested that the increased susceptibility of East Asians to ICH is significantly influenced by the high prevalence of cardiovascular comorbidities, combined with a narrow therapeutic window for antithrombotic agents due to distinct pharmacokinetic and pharmacodynamic profiles.¹⁸ However, our study, focusing exclusively on “healthy” East Asians, revealed a persistent predisposition to ICH, even after excluding participants who received antithrombotic agents during the follow-up. This suggests that factors beyond medication use, such as racial differences in hemostatic states or vascular properties, could be contributing factors. Previous studies have indicated that the presence of microbleeds at baseline was correlated with an increased risk of subsequent ICH (odds ratio: 3.0), and the prevalence of microbleeds is notably higher in Asian patients with ICH compared with non-Asian patients (68.4% vs. 56.9%).¹⁹ The higher incidence of brain arteriovenous malformation reported in Asians compared with Western populations may also partly explain the vulnerability to ICH.^{20–22} Additionally, racial differences in salt sensitivity, as observed in experimental studies, may be relevant.²³ Asian populations tend to exhibit greater salt sensitivity and intake compared with Western populations, and a high salt intake is associated with a significantly increased risk of cardiovascular disease, thereby potentially augmenting the likelihood of ICH in East Asians.²⁴

In this study, over 40% of total bleeding events were bleeding from the gastrointestinal system, which emerged as a key factor largely determining the racial differences in primary outcome and major bleeding events. South Korea has a high IR of stomach cancer related to *Helicobacter pylori* infection, leading to biennial endoscopy for all individuals

over 40 years old.²⁵ The widespread implementation of eradication therapy for *H. pylori* infection, particularly the reduced infection rates in younger generations, has led to a decrease in the incidence of peptic ulcer disease over time.²⁶ Additionally, the exclusion of individuals taking medications that could promote bleeding from the gastrointestinal system, and the fact that major lower gastrointestinal bleed causes, such as diverticulosis, are more common in Western populations, may partially explain the lower incidence in East Asians.⁵

Studies reporting racial differences in bleeding rates at the anatomical site other than ICH and bleeding from the gastrointestinal system are limited. In a study evaluating the bleeding risk of dabigatran in patients with atrial fibrillation, a significant interaction between anatomical sites and bleeding risk was identified.²⁷ This suggests that the anatomical site of bleeding can be a major confounding factor in the analysis of bleeding-related outcomes. For example, the prevalence of tuberculosis, a cause of hemoptysis, is higher in East Asia, particularly in South Korea, while urogenital cancers, a common cause of hematuria, are more frequent in Western countries.^{28,29}

Lifestyle Habits and Bleeding Risks

Lifestyle habits such as smoking and alcohol intake have been associated with the bleeding occurrence in previous studies. A study in the Danish general population reported that current smokers had a higher risk of bleeding in all anatomical sites, including the brain and gastrointestinal system, compared with never smokers.³⁰ Similarly, another study among Danes found that individuals consuming alcohol ≥ 420 g/week had over twice the risk of ICH and bleeding from the gastrointestinal system compared with those consuming 12 to 72 g.³¹ The specific mechanisms behind this increased risk of bleeding are complex, with various hypotheses proposed. For smoking, its inclusion of several thousand chemicals can generate free radicals and decrease the production of nitric oxide in the endothelium. This can increase arterial rigidity and lead to a leaky endothelium allowing various cells and proteins to pass through.³² For alcohol, it can damage the processes of blood coagulation and thrombolysis, reduce platelet aggregation, and dose-dependently decrease the number and function of blood cell precursors in the bone marrow.^{31,33} Moreover, bleeding from the gastrointestinal system is associated with alcohol causing severe gastric epithelial damage and necrosis of deeper layers of the mucosa, increasing permeability.³¹

In our study, East Asians in Korea who drank ≥ 3 times/week showed particularly poorer outcomes compared with their Caucasian counterparts. The mechanism explaining this racial-driven heterogeneity is unclear, but factors including lower BMI of East Asians and genetic variations related to alcohol metabolism may contribute. Generally, leaner individuals can exhibit higher blood alcohol concentrations when consuming the same amount of alcohol, and various statistical methods have consistently shown that East Asians have a lower BMI compared with Caucasians, potentially making them more vulnerable to alcohol.³⁴ Moreover, over 90% of alcohol is detoxified in the liver

through first-pass metabolism, a process in which the mitochondrial enzyme ALDH2 plays a crucial role. However, variants like the *ALDH2*2* allele, which reduces enzyme activity by over 60%, are observed much more frequently in East Asians than in Caucasians.³⁵ This leads to increased exposure to acetaldehyde following alcohol consumption, resulting in poor prognosis for alcohol-related adverse outcomes.³⁶

Implications of Health Screening across the General Population, Including High-Risk Cohorts

This study, based on health check-ups, emphasizes the need for race-specific holistic approaches to risk stratify, prevent, and treat bleeding.^{3,37} Although participants who are over 70 years old or those with underlying comorbidities (i.e., atrial fibrillation, multimorbidity, polypharmacy, and frailty are common, with major implications for outcomes, including bleeding) were not included in this study, the likelihood of such populations experiencing more bleeding events suggests that interventions tailored to the race-specific bleeding predictors and prevalent bleeding sites identified could have a significant impact. Conducting health check-ups across the general population, including high-risk cohorts, would enable a more effective allocation of medical resources.^{38–40} It would also facilitate holistic approaches that reflect the characteristics of different populations, as recommended in guidelines, and ultimately lead to better outcomes.^{41,42}

Limitations

Some limitations still exist in our study. First, as an observational ecological study, there are concerns regarding residual confounding factors, and we cannot determine the causality of the observed differences. Second, because the diagnosis was dependent on the ICD-10 codes, a misdiagnosis due to a coding error cannot be excluded. In addition, as medication use is based on self-reported information, measurement errors may exist. Third, while K-NHIS-HealS data are considered to be representative of the general population because 10% of all Koreans are randomly selected, the UK Biobank participants are volunteer participants who are relatively healthy compared with the general population, and are likely to be from high socioeconomic areas and women.⁴³ Fourth, because participants over the age of 70 or under the age of 40 were not included in this study, we cannot extrapolate our findings to this population. Fifth, changes in anthropometric and comorbidity variables over time were not accounted for in the statistical analysis. Sixth, because the East Asians we studied were all from South Korea, our findings cannot be applied to Asians from other regions.

Conclusion

This ecological epidemiological study highlighted that East Asians in Korea tended to have fewer bleeding events overall compared with Caucasians in the United Kingdom, but the relative incidence of bleeding between the two racial groups varied depending on the anatomical sites of the bleeding and lifestyle habits. Of note, the IRs of ICH and bleeding from the

respiratory system were higher in East Asians. Tailored approaches in bleeding management based on race may be needed.

Funding

This research was supported by a grant of Patient-Centered Clinical Research Coordinating Center (PACEN) funded by the Ministry of Health & Welfare, Republic of Korea (HC19C0130).

Conflict of Interest

B.J. has served as a speaker for Bayer, BMS/Pfizer, Medtronic, and Daiichi-Sankyo and received research funds from Medtronic and Abbott. No fees have been received directly or personally. G.Y.H.L. has been a consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, and Anthos. No fees are received personally. He is co-principal investigator of the AFFIRMO project on multimorbidity in AF, which has received funding from the European Union's Horizon 2020 Research and Innovation Program under grant agreement number 899871. The remaining authors have nothing to declare.

Acknowledgment

We would like to thank the National Health Insurance Service of Korea for their cooperation.

References

- 1 Roberts SE, Button LA, Williams JG. Prognosis following upper gastrointestinal bleeding. *PLoS One* 2012;7(12):e49507
- 2 Poon MT, Fonville AF, Al-Shahi Salman R. Long-term prognosis after intracerebral haemorrhage: systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2014;85(06):660–667
- 3 Kim HK, Tantry US, Smith SC Jr, et al. The East Asian Paradox: an updated position statement on the challenges to the current antithrombotic strategy in patients with cardiovascular disease. *Thromb Haemost* 2021;121(04):422–432
- 4 Ono K, Iwasaki YK, Akao M, et al; Japanese Circulation Society and Japanese Heart Rhythm Society Joint Working Group. JCS/JHRS 2020 guideline on pharmacotherapy of cardiac arrhythmias. *Circ J* 2022;86(11):1790–1924
- 5 Wang FW, Chuang HY, Tu MS, et al. Prevalence and risk factors of asymptomatic colorectal diverticulosis in Taiwan. *BMC Gastroenterol* 2015;15:40
- 6 Morgan E, Arnold M, Gini A, et al. Global burden of colorectal cancer in 2020 and 2040: incidence and mortality estimates from GLOBOCAN. *Gut* 2023;72(02):338–344
- 7 Norby FL, Benjamin EJ, Alonso A, Chugh SS. Racial and ethnic considerations in patients with atrial fibrillation: JACC focus seminar 5/9. *J Am Coll Cardiol* 2021;78(25):2563–2572
- 8 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(03):e1001779
- 9 Lee SS, Ae Kong K, Kim D, et al. Clinical implication of an impaired fasting glucose and prehypertension related to new onset atrial fibrillation in a healthy Asian population without underlying disease: a nationwide cohort study in Korea. *Eur Heart J* 2017; 38(34):2599–2607
- 10 Elliott AD, Linz D, Mishima R, et al. Association between physical activity and risk of incident arrhythmias in 402 406 individuals: evidence from the UK Biobank cohort. *Eur Heart J* 2020;41(15): 1479–1486

- 11 Kim D, Yang PS, You SC, et al. Treatment timing and the effects of rhythm control strategy in patients with atrial fibrillation: nationwide cohort study. *BMJ* 2021;373(991):n991
- 12 Chadalavada S, Jensen MT, Aung N, et al. Women with diabetes are at increased relative risk of heart failure compared to men: insights from UK Biobank. *Front Cardiovasc Med* 2021; 8:658726
- 13 Khurshid S, Weng LC, Al-Alusi MA, et al. Accelerometer-derived physical activity and risk of atrial fibrillation. *Eur Heart J* 2021;42 (25):2472–2483
- 14 Chun MY. Validity and reliability of Korean version of international physical activity questionnaire short form in the elderly. *Korean J Fam Med* 2012;33(03):144–151
- 15 Chao TF, Liu CJ, Tuan TC, et al. Lifetime risks, projected numbers, and adverse outcomes in Asian patients with atrial fibrillation: a report from the Taiwan Nationwide AF Cohort Study. *Chest* 2018; 153(02):453–466
- 16 van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. *Lancet Neurol* 2010;9(02): 167–176
- 17 Tse WC, Grey C, Harwood M, et al. Risk of major bleeding by ethnicity and socioeconomic deprivation among 488,107 people in primary care: a cohort study. *BMC Cardiovasc Disord* 2021;21 (01):206
- 18 Singleton MJ, Imtiaz-Ahmad M, Kamel H, et al. Association of atrial fibrillation without cardiovascular comorbidities and stroke risk: from the REGARDS study. *J Am Heart Assoc* 2020;9(12): e016380
- 19 Lovelock CE, Cordonnier C, Naka H, et al. Antithrombotic drug use, cerebral microbleeds, and intracerebral hemorrhage: a systematic review of published and unpublished studies. *Stroke* 2010;41 (06):1222–1228
- 20 Ryu JY, Chang YJ, Lee JS, et al. A nationwide cohort study on incidence and mortality associated with extracranial vascular malformations. *Sci Rep* 2023;13(01):13950
- 21 Kim T, Kwon OK, Bang JS, et al. Epidemiology of ruptured brain arteriovenous malformation: a National Cohort Study in Korea. *J Neurosurg* 2018;130(06):1965–1970
- 22 Lawton MT, Rutledge WC, Kim H, et al. Brain arteriovenous malformations. *Nat Rev Dis Primers* 2015;1:15008
- 23 Brothers RM, Fadel PJ, Keller DM. Racial disparities in cardiovascular disease risk: mechanisms of vascular dysfunction. *Am J Physiol Heart Circ Physiol* 2019;317(04):H777–H789
- 24 Strazzullo P, D'Elia L, Kandala NB, Cappuccio FP. Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. *BMJ* 2009;339:b4567
- 25 Cha JM, Moon JS, Chung IK, et al. National endoscopy quality improvement program remains suboptimal in Korea. *Gut Liver* 2016;10(05):699–705
- 26 Chung IS, Kim BW. Peptic ulcer diseases in Korea. *Korean J Helicobacter Up Gastrointest Res* 2012;12(01):19–22
- 27 Hernandez I, Baik SH, Piñera A, Zhang Y. Risk of bleeding with dabigatran in atrial fibrillation. *JAMA Intern Med* 2015;175(01): 18–24
- 28 Song W, Jeon HG. Incidence of kidney, bladder, and prostate cancers in Korea: an update. *Korean J Urol* 2015;56(06):422–428
- 29 GBD Tuberculosis Collaborators. Global, regional, and national burden of tuberculosis, 1990–2016: results from the Global Burden of Diseases, Injuries, and Risk Factors 2016 Study. *Lancet Infect Dis* 2018;18(12):1329–1349
- 30 Langsted A, Nordestgaard BG. Smoking is associated with increased risk of major bleeding: a prospective cohort study. *Thromb Haemost* 2019;119(01):39–47
- 31 Askgaard G, Christensen AI, Nordestgaard B, Grønbaek M, Tolstrup JS. Alcohol and risk of non-traumatic bleeding events requiring hospital care in the general population: a prospective cohort study. *Alcohol* 2020;87:73–78
- 32 Powell JT. Vascular damage from smoking: disease mechanisms at the arterial wall. *Vasc Med* 1998;3(01):21–28
- 33 Ballard HS. The hematological complications of alcoholism. *Alcohol Health Res World* 1997;21(01):42–52
- 34 Jung MH, Shin ES, Ihm SH, Jung JG, Lee HY, Kim CH. The effect of alcohol dose on the development of hypertension in Asian and Western men: systematic review and meta-analysis. *Korean J Intern Med (Korean Assoc Intern Med)* 2020;35(04):906–916
- 35 Chang JS, Hsiao JR, Chen CH. ALDH2 polymorphism and alcohol-related cancers in Asians: a public health perspective. *J Biomed Sci* 2017;24(01):19
- 36 Liangpunsakul S, Haber P, McCaughan GW. Alcoholic liver disease in Asia, Europe, and North America. *Gastroenterology* 2016;150 (08):1786–1797
- 37 Gorog DA, Gue YX, Chao TF, et al. Assessment and mitigation of bleeding risk in atrial fibrillation and venous thromboembolism: executive summary of a European and Asia-Pacific Expert Consensus Paper. *Thromb Haemost* 2022;122(10):1625–1652
- 38 Lip GYH, Genaidy A, Tran G, Marroquin P, Estes C, Sloop S. Improving stroke risk prediction in the general population: a comparative assessment of common clinical rules, a new multimorbidity index, and machine-learning-based algorithms. *Thromb Haemost* 2022;122(01):142–150
- 39 Zheng Y, Li S, Liu X, Lip GYH, Guo L, Zhu W. Effect of oral anticoagulants in atrial fibrillation patients with polypharmacy: a meta-analysis. *Thromb Haemost* 2023 (e-pub ahead of print). Doi: 10.1055/s-0043-1770724
- 40 Treewaree S, Lip GYH, Kittayaphong R. Non-vitamin K antagonist oral anticoagulant, warfarin, and ABC pathway adherence on hierarchical outcomes: win ratio analysis of the COOL-AF registry. *Thromb Haemost* 2024;124(01):69–79
- 41 Chao TF, Joung B, Takahashi Y, et al. 2021 Focused update consensus guidelines of the Asia Pacific Heart Rhythm Society on Stroke Prevention in Atrial Fibrillation: executive summary. *Thromb Haemost* 2022;122(01):20–47
- 42 Romiti GF, Pastori D, Rivera-Caravaca JM, et al. Adherence to the 'Atrial Fibrillation Better Care' pathway in patients with atrial fibrillation: impact on clinical outcomes—a systematic review and meta-analysis of 285,000 patients. *Thromb Haemost* 2022;122(03):406–414
- 43 Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. *Am J Epidemiol* 2017; 186(09):1026–1034