Conclusion Educational attainment was independently associated with all-cause mortality and ischaemic stroke in patients with AF, but adverse clinical outcomes were not related to the types of health insurance in Thailand.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study explored the association between two sociodemographic factors (ie, educational attainment and health insurance plan) and the occurrences of adverse clinical outcomes in patients with atrial fibrillation.
- Data were derived from a large prospective and nationwide cohort.
- Causal relationships cannot be assumed from the outcomes of a cohort trial.
- Some patients were excluded because of missing information, which might have contributed to selection bias.

Trial registration number Thai Clinical Trial Registration; Study ID: TCTR20160113002.

INTRODUCTION

Atrial fibrillation (AF) is a common cardiovascular disease that increases the risks of death and stroke. Over the past two decades, there has been a twofold, global increase in the prevalence of AF, regardless of a country’s sociodemographic index. AF is a chronic, complex and multifaceted condition. Treatment of AF requires patients to change their lifestyle and adhere to chronic therapy. Education is an important factor for understanding one’s own illness. Indeed, education has been shown to be a major determinant of cardiovascular and cancer mortality. In the case of a complex and chronic disease such as AF, long-term commitments from patients are necessary to adhere to medications and
lifestyle adjustments. Patients with low educational attainment were shown to be associated with treatment non-compliance,\(^6\) worsened symptom severity\(^5\) and poorer prognosis.\(^6,8\)

The quality and accessibility of healthcare are crucial factors that affects clinical outcomes. Worldwide, achieving universal access to healthcare has been a goal. Accordingly, a health medical plan called universal coverage scheme (UCS) was implemented in Thailand.\(^9\)

UCS is a propoor and unremarkable medical scheme offered to all Thai citizens not eligible for other government based medical plans, namely Civil Servant Medical Benefit Scheme (CSMBS) and compulsory social security scheme (SSS). UCS is currently the most common health insurance plan across Thailand, covering more than 70% of the population.\(^10\)

After first being implemented in 2002, UCS is now globally regarded as a highly successful policy.\(^9,11\) By 2018, uninsured population numbers had been dramatically reduced from approximately 47 million (30% of the total population) to less 400,000 people (0.06% of the total population).\(^9,10\)

Life expectancy improved from 70.6 years in 2000 to 74.6 years in 2015.\(^3\) However, the path to achieve universal access to healthcare in Thailand is fraught with challenges. Similar to healthcare reform in many low-income and middle-income countries, UCS faces problems with financial sustainability and quality of services.\(^9,11\) The benefit package of UCS is less comprehensive than that of CSMBS because of budget limitation.\(^3\)

Previous studies have shown that the clinical outcomes of CSMBS beneficiaries are better than those of UCS beneficiaries.\(^12,13\) Over the last decade, UCS has responded by strengthening its primary healthcare system and expanding its benefit packages.\(^9\) However, the impact of these improvements has yet to be investigated. Both education and health care are among the major determinants of clinical outcomes. In a middle-income country such as Thailand, services provided by the government in both areas are still developing. In the present cohort trial, we prospectively analysed the AF patients enrolled in the national registry of Thailand. We aimed to explore whether the two sociodemographic factors (ie, educational attainment and insurance plan) were associated in adverse clinical outcomes of all-cause mortality, ischaemic stroke and major bleeding in these patients independent of other comorbidities. We believe that the results of this study can provide new insights into disparities of the education and insurance plan in Thailand as well as in other low and middle-income countries that implemented similar policies.

**METHODS**

**Participant selection**
Between 2014 and 2017, patients with AF across Thailand were consecutively enrolled in the cohort of antithrombotic use and optimal international normalised ratio (INR) level in patients with non-valvular atrial fibrillation in Thailand (COOL-AF) registry. Details of the COOL-AF study have been reported elsewhere.\(^14\) Briefly, patients age \(\geq\) 18 year with electrocardiography confirmed AF were eligible for the enrolment. The exclusion criteria\(^14\) were as follows: (1) ischaemic stroke within 3 months, (2) haematologic disorders that can increase the risk of bleeding, (3) mechanical prosthetic valve or valve repair, (4) rheumatic valve disease or severe valve disease, (5) AF associated with transient reversible cause, (6) current participation in a clinical trial, (7) life expectancy < 3 years, (8) pregnancy, (9) inability to attend follow-up visits and (10) refusal to participate in the study. Written informed consent was obtained from all enrolled patients.\(^14\)

This study included all patients enrolled in the registry, except those with missing information on educational attainment or insurance plan. Those who were excluded from the present study remained in the main registry until the end of follow-up (online supplemental appendix figure 1).

**Data collection**
Baseline data including demographics, educational attainment level, insurance plan, medical history and administered medications taken were obtained from medical records and patient interviews at the enrolment. For educational attainment, data were self-report. Patient or their families completed the educational attainment questionnaire in the hospital registration form. The insurance plan information was centrally linked to the government database and available in the patients’ medical record. All patients were prospectively followed for the endpoints of death from any causes, ischaemic stroke or major bleeding. Data on adverse outcome events were collected from medical records and telephonic interviews every 6 months until the end of the 36-month follow-up period. All adverse outcome events were validated by an adjudication committee. Ischaemic stroke and major bleeding were defined according to the standard criteria.\(^15,16\)

**Data classifications**
The levels of educational attainment were defined as follows: no formal education, elementary education (grades 1–6), secondary education (grades 7–12) and higher education (ie, tertiary education or education beyond secondary education). The categories of the insurance plans were as follows: (1) SSS, a contributory and compulsory scheme for non-government employees; (2) CSMBS, a fringe benefit provided for government employees; (3) UCS, a non-contributory insurance scheme provided for all citizens of Thailand who were not covered by (1) or (2); and (4) non-government-based scheme (NGS), which included private insurance, opt-out of the plan and out-of-pocket payments.

According to standard guidelines,\(^2\) stroke and bleeding risks were assessed using congestive heart failure, hypertension, age \(\geq 75\) (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, and sex (female) (CHA\(_2\)DS\(_2\)-VASC) and hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition,
labile INR, elderly (>65 years), drugs/alcohol concomitantly (1 point each) (HASBLED) scores, respectively. In general, patients without clinical stroke risk factors do not typically require anticoagulation therapy, while patients with stroke risk factors (ie, CHA₂DS₂-VASc≥2) are likely to benefit from anticoagulant.² The HASBLED is a bleeding risk score. A higher HASBLED score is related to a higher risk of bleeding.²

The types of anticoagulants were grouped as follows: none, vitamin K antagonist (VKA) and direct oral anticoagulant (DOAC).

**Statistical analysis**

All analyses were performed using SAS software, V.9.4-M6 of the SAS OnDemand for Academics (SAS Institute). Categorical variables are expressed as numbers and percentages, and continuous variables are expressed as means and SDs. Chi-square and one-way analyses of variance were used to compare differences in baseline characteristics.

Event probabilities were assessed by restricted mean survival time (RMST) analyses using LIFETEST and RMSTREG procedures in the SAS/STAT software V.15.1. We initially chose to use a Cox proportional hazard model for the analyses. However, the proportionality hazard assumption of all three primary outcomes was violated (ie, p<0.05 based on the weighted Schoenfeld residual (online supplemental appendix table 1)). RMST analysis was selected as an alternative method. The RMST is equivalent to the area under the entire survival curve up to a fixed time point. It is widely advocated as an alternative to the Cox proportional hazard model, especially when proportionality is violated.¹⁷ ¹⁸

| Table 1 Baseline characteristics by insurance plans (N=3026) |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                                | All (N=3026) | UHC (N=1333) | SSS (N=142) | NGS (N=154) | CSMBS (N=1397) | P value |
| Age, mean (SD), years          | 67.3 (11.3)  | 66.7 (11.2)  | 56.5 (10.5) | 65.4 (11.9) | 69.2 (10.6)  | <0.001  |
| Male, No. (%)                  | 1779 (58.8%) | 732 (54.9%)  | 37 (26.2%)  | 91 (59.1%)  | 856 (61.3%)  | <0.001  |
| CHA₂DS₂-VASc, mean (SD)       | 3.0 (1.7)    | 3.0 (1.6)    | 2.1 (1.7)   | 2.8 (1.7)   | 3.2 (1.7)    | <0.001  |
| HASBLED, mean (SD)            | 1.5 (1.0)    | 1.5 (1.0)    | 1.2 (1.1)   | 1.3 (1.0)   | 1.6 (1.0)    | <0.001  |
| CAD, No. (%)                   | 478 (15.8%)  | 198 (14.9%)  | 19 (13.4%)  | 21 (13.6%)  | 240 (17.2%)  | 0.255   |
| CHF, No. (%)                   | 829 (27.4%)  | 419 (31.4%)  | 33 (23.2%)  | 33 (21.4%)  | 344 (24.6%)  | <0.001  |
| Hypertension, No. (%)          | 2061 (68.1%) | 865 (64.9%)  | 81 (57.0%)  | 109 (70.8%) | 1006 (72.0%) | <0.001  |
| Dyslipidaemia, No. (%)         | 1703 (56.3%) | 616 (46.2%)  | 77 (54.2%)  | 102 (66.2%) | 908 (65.0%)  | <0.001  |
| Diabetes, No. (%)              | 730 (24.1%)  | 278 (20.9%)  | 36 (25.4%)  | 47 (30.5%)  | 369 (26.4%)  | 0.002   |
| Stroke/TIA, No. (%)            | 530 (17.5%)  | 237 (17.8%)  | 25 (17.6%)  | 20 (13.0%)  | 248 (17.8%)  | 0.512   |
| Vascular disease, No. (%)      | 510 (16.9%)  | 209 (15.7%)  | 24 (15.6%)  | 25 (17.4%)  | 257 (18.4%)  | 0.200   |
| Current smoker, No. (%)        | 98 (3.2%)    | 60 (4.5%)    | 8 (5.6%)    | 4 (2.6%)    | 28 (1.9%)    | <0.001  |
| Alcohol use, No. (%)           | 129 (4.3%)   | 53 (4.0%)    | 9 (6.3%)    | 10 (6.5%)   | 57 (4.1%)    | 0.289   |
| History of bleeding, No. (%)   | 304 (10.0%)  | 127 (9.5%)   | 19 (13.4%)  | 6 (3.9%)    | 152 (10.9%)  | 0.022   |
| Abnormal renal function, No. (%) | 90 (3.0%)   | 39 (2.9%)    | 6 (4.2%)    | 2 (1.3%)    | 43 (3.1%)    | 0.507   |
| Abnormal liver function, No. (%) | 67 (2.2%)   | 29 (2.2%)    | 2 (1.5%)    | 3 (1.9%)    | 29 (2.1%)    | 0.418   |
| Antiplatelets, No. (%)         | 802 (26.5%)  | 343 (25.7%)  | 39 (27.5%)  | 42 (27.3%)  | 378 (27.1%)  | 0.863   |
| Anticoagulants                 | <0.001       |              |              |              |              |         |
| VKA, No. (%)                   | 2075 (68.6%) | 995 (74.6%)  | 93 (65.5%)  | 107 (69.5%) | 880 (63.0%)  | <0.001  |
| DOAC, No. (%)                  | 182 (6.0%)   | 5 (0.4%)     | 1 (0.7%)    | 10 (6.5%)   | 166 (11.9%)  |         |
| None, No. (%)                  | 769 (25.4%)  | 333 (25.0%)  | 48 (33.8%)  | 37 (24.0%)  | 351 (25.1%)  |         |
| Educational attainment         | <0.001       |              |              |              |              |         |
| No formal education, No. (%)   | 788 (26.1%)  | 301 (22.6%)  | 18 (12.7%)  | 37 (23.9%)  | 346 (24.5%)  |         |
| Elementary, No. (%)            | 525 (17.4%)  | 215 (16.1%)  | 12 (8.5%)   | 15 (9.8%)   | 273 (19.6%)  |         |
| Secondary, No. (%)             | 613 (20.3%)  | 240 (18.1%)  | 25 (17.6%)  | 19 (12.4%)  | 221 (15.6%)  |         |
| Higher education, No. (%)      | 648 (21.4%)  | 275 (20.7%)  | 25 (17.6%)  | 23 (15.2%)  | 323 (23.1%)  |         |

CAD, coronary artery disease; CHA₂DS₂-VASc, congestive heart failure, hypertension, age≥75 years, diabetes mellitus, stroke or transient ischaemic attack (TIA), vascular disease, age 65–74 years, sex category; CHF, congestive heart failure; CSMBS, civil servant medical benefit scheme; DOAC, direct oral anticoagulant; HASBLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs/alcohol concomitantly; NGS, non-government-based scheme; SSS, social-security scheme; UCS, universal coverage scheme; VKA, vitamin K antagonist.
Here, we computed RMST to the time horizon of 36 months using Kaplan-Meier method for survival probability estimation. We then adjusted RMST with multiple covariates using pseudovalue linear regression model.\(^{19}\)

The model consisted of age, sex, educational attainment, insurance plan, types of anticoagulant, CHA\(_2\)DS\(_2\)VASc and HASBLED scores. We also calculated adjusted RMST to ischaemic stroke and major bleeding among patients who were still alive at the end of the follow-up, to account for the competing risk of death.\(^{20}\) The results were presented as the differences of RMSTs and 95% CI for each covariate.

The RMST difference estimated months gain or loss of event-free time over a period of 36 months. P values were reported for all between-group comparisons. A p value<0.05 was considered significant.

## RESULTS

### Participants

The COOL-AF registry comprises of 3402 patients. Of these, 376 patients had incomplete data and were excluded from the study (online supplemental appendix figure 1 and table 2). Finally, data from 3026 patients were included in the analyses. None of the patients were lost to follow-up. The participant population (table 1) was approximately 67 years old and primarily male (N=1779, 58.8%). The most common comorbidity was hypertension (N=2061, 68.1%), followed by congestive heart failure (N=829, 27.4%) and diabetes (n=730, 24.1%). The mean CHA\(_2\)DS\(_2\)VASc and HASBLED scores were 3.0 (SD 1.7) and 1.5 (SD 1.0), respectively.

### Insurance plan

The participant population was predominantly insured by either CSMBS (N=1397, 46.2%) or UCS (N=1333, 44.1%). Patients insured by CSMBS were at greater risk of stroke and bleeding as assessed by CHA\(_2\)DS\(_2\)VASc (CMBS, 3.2; UCS, 3.0; NGS, 2.8; SSS, 2.1; p<0.001) and HASBLED (CMBS, 1.6; UCS, 1.5; NGS, 1.3; SSS, 1.2; p<0.001) scores.

### Educational attainment

More than one-third of the patients attained at least a secondary education level (N=1287, 42.5%). Among these patients, the male sex was predominant (N=948, 73.7%). Age, CHA\(_2\)DS\(_2\)VASc and HASBLED scores (online supplemental appendix table 3) were higher in those patients with no formal education (mean age, 74 years; CHA\(_2\)DS\(_2\)VASc, 3.9; HASBLED, 1.7) compared with those who attained an elementary (mean age, 69 years; CHA\(_2\)DS\(_2\)VASc, 3.3; HASBLED, 1.6), secondary (mean age, 64 years; CHA\(_2\)DS\(_2\)VASc, 2.7; HASBLED, 1.5) or higher level of education (mean age, 63 years; CHA\(_2\)DS\(_2\)VASc, 2.6; HASBLED, 1.4; p<0.001 for all comparisons).

### Adverse outcomes

During the 36 months follow-up, 248 patients died (8.2%), 95 had ischaemic stroke (3.1%) and 136 had major bleeding (4.5%). There were no significant differences in the rates of adverse events between those with missing information who were initially excluded and those patients whose data were included in the final analysis (online supplemental appendix table 2). Figure 1A,B shows the Kaplan-Meier survival curves of all-cause mortality with 95% confidence limits. (A) Kaplan-Meier curve for all-cause mortality by insurance plans. (B) Kaplan-Meier curve for all-cause mortality by educational attainment. CMBS, civil servant medical benefit scheme; NGS, non-government-based scheme; SSS, social-security scheme; UCS, universal coverage scheme.

**Figure 1** Kaplan-Meier curve for all-cause mortality with 95% confidence limits. (A) Kaplan-Meier curve for all-cause mortality by insurance plans. (B) Kaplan-Meier curve for all-cause mortality by educational attainment. CMBS, civil servant medical benefit scheme; NGS, non-government-based scheme; SSS, social-security scheme; UCS, universal coverage scheme.
mortality by insurance plan and educational attainment, respectively. Patients with higher levels of educational attainment survived longer than those with lower levels (RMST for higher education vs secondary vs elementary vs no formal education, 35.02 vs 34.29 vs 33.70 vs 31.98 months; p<0.001). They also experienced longer event-free time to ischaemic stroke (RMST for higher education vs secondary vs elementary vs no formal education, 35.58 vs 35.46 vs 35.11 vs 34.15 months; p=0.004) and major bleeding (RMST for higher education vs secondary vs elementary vs no formal education, 35.31 vs 34.72 vs 37.82 vs 34.18 months; p=0.03) than those with lower educational attainment (online supplemental appendix table 4). The RMSTs of all three adverse outcomes did not differ among patients with different insurance plans (online supplemental appendix table 5).

In the multivariate analyses, educational attainment was associated with all-cause mortality and ischaemic stroke, independently of comorbidities (figures 2 and 3). After adjusting for death as a competing risk of ischaemic stroke, educational attainment remained independently associated with ischaemic stroke (online supplemental appendix table 6). Over the 36-month follow-up, patients with AF and no formal education lost 1.78 months before they died (RMST difference −1.78; 95% CI, −3.25 to −0.30; p=0.02) and 1.04 months before they developed ischaemic stroke (RMST difference −1.04; 95% CI, −2.03 to −0.04; p=0.04) compared with those attained a level of higher education.

Older age and higher CHA2DS2-VASc score also shortened the survival time to all-cause mortality. Survival time was lost by 0.45 months for every 10-year increase in age (RMST difference, −0.45; 95% CI, −0.8 to −0.1; p=0.01), and 0.35 months for every single point increase in CHA2DS2-VASc score (RMST difference, −0.35; 95% CI, −0.6 to −0.1; p=0.01). Time to major bleeding (figure 4) was lost in patients with older age (RMST difference per 10 years, −0.35; 95% CI, −0.59 to −0.11; p=0.003), those of male sex (RMST difference, −0.68; 95% CI, −1.11 to −0.25; p=0.002) and with the use of VKA (RMST difference,
−0.65; 95% CI, −1.04 to −0.26; p=0.001). For all three major outcomes, the type of insurance plan was not associated with a gain or loss in survival times (figures 2–4), even after adjusting for the competing risk of death (online supplemental appendices tables 6 and 7).

**DISCUSSION**

In the COOL-AF registry of patients with AF across Thailand, educational attainment was associated with all-cause mortality and ischaemic stroke, independently of age, sex, stroke and bleeding risks, anticoagulant use, and types of insurance. Over the 36-month follow-up period, those with no formal education died approximately 1.8 months sooner and suffered stroke 1 month sooner than those attained the level of higher education. UCS, the propoor medical scheme, was not linked to elevated risks of all-cause mortality, ischaemic stroke or major bleeding.

The significant impact of education on cardiovascular outcome has been demonstrated globally. Among Asian population, data from the Asia Pacific Cohort Studies Collaboration reported that Asians attained the lowest level of education had a 54% higher risk of stroke and 78% higher risk of cardiovascular mortality than those with a tertiary education. Among patients with AF, a large-scale study in Norway reported an educational gradient in mortality between patients who attained higher education level and those who attained a high school education or less. Findings from a patient survey showed that higher levels of educational attainment were associated with a better understanding of anticoagulant therapy and lower incidence of bleeding. In this prospective cohort study, we explored the association between educational attainment and three adverse outcomes, namely all-cause mortality, ischaemic stroke and major bleeding. We reported educational disparities in all-cause mortality and ischaemic stroke but not major bleeding. Disparities were detected between the educational attainment level of no formal education and higher education, independently
of age, sex, bleeding and stroke risk, type of insurance plan, and anticoagulant use. Patients with no formal education are more likely to have a reduced health literacy, which subsequently lead to poorer outcomes especially for chronic disease such as AF.

Low-education and low-income statuses often coincide. Low income could lead to a lack or poor choice of health insurance. In Thailand, these consequences have been ameliorated with the implementation of UCS. The UCS provides healthcare coverage to the unemployed, who primarily are in the low-income group. According to the 2004 national health insurance data, half of UCS beneficiaries were from the two poorest quintiles while half of CSMBS insurers were in the richest quintile. Unlike other insurance plans for the poor, UCS provides extensive and comprehensive benefit packages. Unlike other insurance plans for the poor, UCS provides extensive and comprehensive benefit packages. High-cost services, such as percutaneous cardiac intervention, heart transplantation or catheter ablation, are currently covered by UCS. A remaining discrepancy between the UCS and CSMBS packages is the drug plan. UCS restricts access to medications outside the National List of Essential Medicines, notably DOAC. In contrast, CSMBS covers the use of DOACs for some conditions. In this cohort of patients with AF, discrepancies in the coverages provided by different types of insurance plans did not result in outcome disparities. UCS beneficiaries had RMSTs for all-cause mortality, ischaemic stroke and major bleeding similar to beneficiaries of other plans.

However, outcome disparities between UCS and CSMBS have been previously reported. In a retrospective analysis from 2010 National Insurance Database, 5-year mortality after AF admission was higher in UCS beneficiaries than in CSMBS beneficiaries. In contrast to previous studies, patients in our cohort were prospectively enrolled and subjected to structured follow up. The enrolment process took place after the third strategic plan of the UCS began in 2012. With the implementation of the plan, the benefits were expanded to seasonal influenza vaccination, screening of complications from diabetes and hypertension, and long-term care for dependent elderly.

Figure 4 Differences in adjusted restricted median survival time to major bleeding over a period of 36 months. The model was adjusted for age, sex, educational attainment, insurance plan, types of anticoagulant, CHA2DS2-VASc, and HASBLED scores. CAD, coronary artery disease; CHA2DS2-VASc, congestive heart failure, hypertension, age≥75 years, diabetes mellitus, stroke or transient ischaemic attack (TIA), vascular disease, age 65–74 years, sex category; CHF, congestive heart failure; CSMBS, civil servant medical benefit scheme; DOAC, direct oral anticoagulant; HASBLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs/alcohol concomitantly; NGS, non-government-based scheme; SSS, social-security scheme; UCS, universal coverage scheme; VKA, vitamin K antagonist.
The differences in trial designs and timing of enrolment periods could explain the discrepancies between our results and those of previous trials focusing on outcome disparities between UCS and CSMBS beneficiaries.

In this study, we reported the effect size of educational disparities using months loss. The reported value may appear small, but they indicate a time loss over a fixed period of 36 months. For those patients with no formal education, losing 1.8 months of survival time equates to losing 5% of their lifetime during follow-up. In the health production function analyses conducted in 35 members of Organisation for Economic Co-operation and Development countries, a 10% increase in education of the population was associated with a gain of 3.2 months in life expectancy and a 100% increase in education of the population was associated with a gain of 23.8 months.

Our results provide some insights to the national health insurance policy in Thailand. We have shown that in a moderate-to-high income country such as Thailand, the disparity in insurance coverage could be reduced or even removed by a well maintained, propoor health insurance, such as the UCS. Our findings also emphasise the utmost importance of national education level. Education can keep people healthier. For a chronic condition such as AF, adherence to the therapy requires some understanding towards the disease, which entails education.

In our cohort, the educational attainment level of higher education was associated with better clinical outcomes, but this level is only attained in a minority of Thai population. Education remains. Owing to the non-binary nature of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility for the accuracy or otherwise of the information contained in this article. This work is protected by copyright. Persons may reproduce, display or distribute this article for non-commercial purposes if: (i) the right is not withheld in reply to a request for permission; (ii) the reproduction, display or distribution is not made for gain; and (iii) the reproduction, display or distribution does not take place for profit or other pecuniary advantage. All material published in BMJ Journals is protected by copyright. TheBMJhas a policy of free online access to research articles as part of its mission to disseminate medical knowledge for the benefit of patients. This does not affect the copyright status of material prior to January 2004, nor does it apply to non-article content, book reviews, or other material.BMJJournalsare openaccess. Some content is protected by copyright. Permission to reproduce may be required. Further information available atBMJOpenBMJOpen: first published as 10.1136/bmjopen-2021-053166 on 10 August 2022. Downloaded fromhttp://bmjopen.bmj.com/ on September 18, 2023 by guest. Protected by copyright. http://bmjopen.bmj.com/ BMJ Open: first published as 10.1136/bmjopen-2021-053166 on 10 August 2022. Downloaded from http://bmjopen.bmj.com/ on September 18, 2023 by guest. Protected by copyright.
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