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Performance of a Diagnostic Model for the Presence of Unruptured Intracranial Aneurysms in the General Population

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Keywords
Intracranial aneurysm · Diagnostic model · General population · Subarachnoid hemorrhage

Abstract

Introduction: The prevalence of unruptured intracranial aneurysms (UIAs) in the general population is 3%. Aneurysmal subarachnoid hemorrhage can be prevented by screening for UIAs followed by monitoring and, if needed, preventive neurosurgical or endovascular treatment of identified UIAs. Therefore, we developed a diagnostic model for the presence of UIAs in the general population to help identify persons at high risk of having UIAs. ***Methods:*** Between 2005 and 2015, participants from the population-based Rotterdam Study underwent brain magnetic resonance imaging at 1.5 T, on which the presence of incidental UIAs was evaluated. We developed a multivariable logistic regression model using candidate diagnostic markers that were selected based on the literature, including sex, age, hypertension, smoking, hypercholesterolemia, diabetes, alcohol, and their interactions. We corrected for overfitting using bootstrapping. Model performance was assessed with discrimination, calibration, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). ***Results:*** 5,835 persons were included (55.0% women, mean age 64.9 ± 10.9 years) with a 2.2% UIA prevalence. Sex, age, hypertension, smoking, diabetes, and interactions of sex with age, hypertension, and smoking were independent diagnostic markers. The resulting model had a c-statistic of 0.65 (95% confidence interval [CI]: 0.60–0.68) and 56% sensitivity, 52% specificity, 98% PPV, and 3% NPV for UIA presence at a cutoff value of 4%. Because of interactions with sex, additional models for men and women separately were developed. The model for men had a c-statistic of 0.70 (95% CI: 0.62–0.78) with age, hypertension, and smoking as diagnostic markers and comparable additional performance values as for the full model. The model for women had a

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c-statistic of 0.58 (95% CI: 0.52–0.63) with smoking as the only diagnostic marker. ***Conclusion:*** Our diagnostic model had insufficient performance to help identify persons at high risk of having UIAs in the general population. Rather, it provides insight in risk factors contributing to UIA risk and shows that these may be in part sex-specific.

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Plain Language Summary

A burst of a blood vessel in the brain, also known as a ruptured intracranial aneurysm, causes a severe and often fatal type of stroke (aneurysmal subarachnoid hemorrhage). When such an aneurysm has not ruptured yet, it is called an unruptured intracranial aneurysm (UIA). Approximately 3% of persons in the general population have a UIA. We developed models to help identify persons in the general population at high risk of having a UIA. These models show which person characteristics predict the risk of having a UIA. We developed a model for the whole general population and for men and women separately. We found that in the whole general population, female sex, higher age, high blood pressure, and smoking increased the risk of having a UIA, while diabetes decreased this risk. For men separately, only higher age, high blood pressure, and smoking increased the risk of having a UIA. For women separately, only smoking increased the risk of having a UIA. However, the models had insufficient performance to help identify persons at high risk of having a UIA from other persons in the general population. Rather, they provide insight into risk factors contributing to UIA risk and show that these may be in part sex-specific.

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Introduction

Around one-third of patients with aneurysmal subarachnoid hemorrhage (aSAH) die, and of those who survive, one half remains dependent on continuous care of others [1, 2]. Approximately 12% of patients with aSAH die before receiving medical attention and for those admitted to hospital, the early effects of aSAH are the principal cause of death [3, 4]. Thus, prevention of aSAH has high potential to prevent poor outcome from aSAH [5]. As unruptured intracranial aneurysms (UIAs) are usually asymptomatic before they rupture, screening is the only way to detect UIAs before rupture and to install preventive neurosurgical or endovascular treatment.

UIA prevalence is approximately three times higher in persons with a family history of aSAH (11% prevalence) compared to persons without a family history (3% prevalence) [6]. Repeated radiological screening for early detection of UIAs in persons with ≥2 affected first-degree relatives is cost-effective, with newly identified UIAs at first screening in 11% and in 8% at follow-up screening [7–9]. As a positive family history for aSAH accounts for 10% of aSAH cases, screening and preventive treatment of patients with familial preponderance of aSAH alone will cause a modest reduction of aSAH incidence at a population level [4]. Therefore, additional high-risk individuals within the general population in whom screening might also be effective, should be identified. As a first step in this identification, it is important to know who in the general population is at high risk of UIAs. Therefore, the aim of this study was to develop a diagnostic model for the detection of UIAs in the general population to help identify persons at high risk of having a UIA.

Methods

Study Design and Study Population

For this cross-sectional study, we used data from the Rotterdam Study, a general population-based prospective cohort study containing over 14,000 participants aged ≥45 years recruited in Ommoord, a neighborhood in Rotterdam, the Netherlands, for further details, please see online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000535471) [10]. For our study, we used data from the Rotterdam Scan Study, a random subset of participants of the Rotterdam Study who underwent brain magnetic resonance imaging (MRI) in 2005–2015 [11].

Assessment of UIAs

Our primary outcome measure was prevalent UIA on proton-density T2-weighted brain MRI scans for which a study-dedicated 1.5 T MRI scanner with an 8-channel head coil (General Electric Healthcare, Milwaukee, USA) was used [11]. The brain MRI scan protocol and details on the MRI scan assessment can be found in the online supplementary material. Only participants with saccular UIAs were included, as fusiform UIAs have a distinctly different etiology and lower risk of aSAH [12].

Assessment of Potential Diagnostic Markers

Prior examination of the literature guided the selection of candidate diagnostic markers and included sex, age, hypertension, smoking status, hypercholesterolemia, diabetes mellitus (DM), and alcohol consumption (please see online suppl. material for the definitions used) [13–15]. We included the interaction between smoking status and alcohol consumption since these were expected to influence their mutual effect sizes. We also included interactions with sex to study sex as a

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Table 1. Baseline characteristics of the study population

Characteristic	All participants (*n* = 5,835)	Men (*n* = 2,624)	Women (*n* = 3,211)
Prevalent UIA	130 (2.2)	41 (1.6)	89 (2.8)
Age			
<50 years	428 (7.3)	191 (7.3)	238 (7.4)
≥50 years	5,407 (92.7)	2,433 (92.7)	2,973 (92.6)
Mean±SD	64.9±10.9	64.7±10.7	65.1±11.0
Hypertension	3,715 (63.7)	1,740 (66.3)	1,973 (61.4)
Smoking status			
Never smoking	1,883 (32.3)	635 (24.2)	1,246 (38.8)
Former smoking	2,956 (50.7)	1,533 (58.4)	1,424 (44.3)
Current smoking	996 (17.1)	456 (17.4)	541 (16.8)
Hypercholesterolemia	2,406 (41.2)	1,045 (39.8)	1,362 (42.4)
DM	765 (13.1)	412 (15.7)	353 (11.0)
Alcohol consumption			
Never	474 (8.1)	154 (5.9)	320 (10.0)
<150 g per week	4,840 (82.9)	2,083 (79.4)	2,757 (85.9)
≥150 g per week	521 (8.9)	387 (14.7)	134 (4.2)

Data are *n* (%), unless otherwise indicated. UIA, unruptured intracranial aneurysm; SD, standard deviation; DM, diabetes mellitus.

potential effect modifier as UIAs have a female preponderance with two-thirds of patients being women, and there are suggested differential effects of risk factors according to sex [6, 12, 16].

Statistical Analysis

Data were missing for hypertension (0.5%), smoking status (0.6%), total cholesterol level (1.7%), cholesterol-lowering medication (0.6%), DM (1.2%), and alcohol consumption (5.7%). Missing data were imputed using the expectation maximization algorithm based on hypertension, smoking status, hypercholesterolemia, alcohol consumption, and UIA prevalence [13, 17].

To study the association between candidate diagnostic markers and prevalent UIAs, we developed a multivariable logistic regression model. We used restricted cubic splines to evaluate whether the continuous variables could be analyzed as a linear variable. To assess whether candidate diagnostic markers contributed to the model, we performed backward selection based on Akaike Information Criterion (AIC) [18]. As models derived from multivariable regression can overestimate effect estimates when applied to a different population, we internally validated the model by applying a shrinkage factor to the regression coefficients, determined by bootstrapping procedures [18]. The estimated effect sizes of the independent diagnostic markers were expressed as odds ratios (OR) with 95% confidence intervals (CI). As the model assessing the whole study population included interactions between sex and other diagnostic markers, we also developed diagnostic models for men and women separately.

We assessed model performance by estimating discrimination, calibration, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) [19]. We aimed to use a cutoff value of 4% for UIA prevalence for estimating sensitivity, specificity, PPV, and NPV, meaning that persons with a predicted risk of UIA of 4% or higher were classified as having a positive result. We based this on the finding that screening for UIAs in persons with one first-degree relative who had an aSAH is likely to be cost-effective in case of a UIA prevalence of 4% [20]. If no individuals had a predicted UIA prevalence of 4%, we used a cutoff value of 1% instead. To calculate an individual person's absolute risk of having a UIA, we provided the original regression equation of the diagnostic models.

Results

Baseline Characteristics

After excluding participants with fusiform UIAs (*n* = 6), 5,835 participants were included in the current study (Table 1), of which 3,211 (55.0%) were women, and the mean age was 64.9 ± 10.9 years. A total of 130 (2.2%) participants had a saccular UIA, of whom 89 (68.5%) were women.

Diagnostic Model for Full Study Population

Restricted cubic splines showed that age could be analyzed as a continuous variable. Sex, age, hypertension, smoking status, DM, and the interactions of sex with age, hypertension, and smoking status were independent diagnostic markers of prevalent UIAs (Table 2). Following internal validation, the c-statistic was 0.65 (95% CI: 0.60–0.68). The model had 56% sensitivity, 52% specificity, 98% PPV, and 3% NPV for UIA detection at a

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Table 2. Univariable and multivariable logistic regression analysis of diagnostic markers of prevalent unruptured intracranial aneurysms (UIAs) in the full study population

Diagnostic marker	Univariable OR (95% CI)	Multivariable* OR (95% CI)
Female sex	1.80 (1.24–2.61)	14.43 (0.97–214.88)
Age per year	1.01 (0.99–1.02)	1.02 (0.99–1.06)
Hypertension	1.45 (0.98–2.12)	2.38 (0.95–5.99)
Smoking status		
Never smoking	Reference	
Former smoking	1.54 (0.96–2.46)	1.43 (0.46–4.39)
Current smoking	3.52 (2.14–5.77)	4.67 (1.51–14.39)
DM	0.67 (0.37–1.22)	0.70 (0.38–1.29)
Interactions		
Female sex*Age per year	0.97 (0.94–1.00)	0.98 (0.94–1.02)
Female sex*Hypertension	0.39 (0.15–1.04)	0.52 (0.18–1.47)
Female sex*Former smoking	0.87 (0.26–2.92)	1.07 (0.31–3.72)
Female sex*Current smoking	0.47 (0.14–1.63)	0.52 (0.15–1.87)

OR, odds ratio; CI, confidence interval; DM, diabetes mellitus. *The initial regression coefficients were corrected for overfitting with a shrinkage factor of 0.68.

cutoff value of 4%. The calibration plot of observed and predicted probabilities showed that this model slightly overestimated UIA risk (Fig. 1a).

Diagnostic Models for Women and Men Separately

Age, hypertension, and smoking status were independent diagnostic markers of prevalent UIAs in men (Table 3). The c-statistic was 0.70 (95% CI: 0.62–0.78). No men had a predicted UIA prevalence of 4%, so we used a cutoff value of 1%. The model had 62% sensitivity, 55% specificity, 99% PPV, and 2% NPV for UIA detection at this cutoff value. The calibration plot demonstrated fair agreement between observed and predicted probabilities of prevalent UIAs (Fig. 1b).

Smoking status was the only independent diagnostic marker of prevalent UIAs in women. The c-statistic of this model was 0.58 (95% CI: 0.52–0.63). As there was only one diagnostic marker in this model, we were unable to calculate additional performance measures for this model.

Individual Absolute Risks of Having a UIA

The regression equation of the diagnostic models is provided in Figures 2, 3. Based on the diagnostic model for the whole population, the risk of having a UIA ranged from 1.61% to 11.01% and in the model for men only from 0.39% to 1.86%.

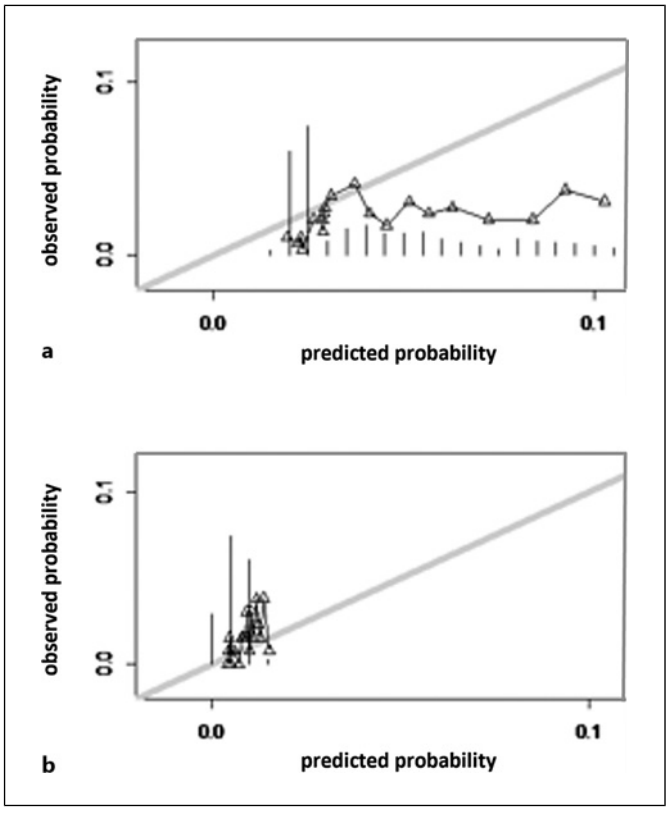

Fig. 1. Calibration plot of the diagnostic model for the full study population (**a**) and for men only (**b**).

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Table 3. Univariable and multivariable logistic regression analysis of diagnostic markers of prevalent unruptured intracranial aneurysms (UIAs) in men and women separately

	Univariable OR (95% CI)	Multivariable* OR (95% CI)
Diagnostic marker men		
Age per year	1.03 (1.00–1.06)	1.02 (1.00–1.04)
Hypertension	2.92 (1.22–6.97)	1.80 (1.07–3.03)
Smoking status		
Never smoking	Reference	
Former smoking	2.64 (0.78–8.97)	1.51 (0.75–3.05)
Current smoking	8.66 (2.53–29.57)	3.73 (1.84–7.55)
Diagnostic marker women		
Smoking status		
Never smoking	Reference	
Former smoking	1.82 (1.06–3.12)	1.38 (1.03–1.84)
Current smoking	3.22 (1.79–5.79)	1.87 (1.37–2.57)

OR, odds ratio; CI, confidence interval. *The initial regression coefficients were corrected for overfitting with a shrinkage factor of 0.57 in men and of 0.54 in women.

Discussion

We developed three diagnostic models for the presence of UIAs in the general population. The model for men showed the best performance with a c-statistic of 0.70 (95% CI: 0.62–0.78) with fair agreement between observed and predicted probabilities of prevalent UIAs. However, its additional performance values were suboptimal. Age, hypertension, and smoking status were independent diagnostic markers in men, and the risk of having a UIA ranged from 0.39% to 1.86%. The model for the whole population had a c-statistic of 0.65 (95% CI: 0.60–0.68) with comparable additional performance values. Next to sex, age, hypertension, smoking status, and DM, three interactions of sex with other diagnostic markers (age, hypertension, and smoking) were also independent diagnostic markers. Last, the model for women had a c-statistic of 0.58 (95% CI: 0.52–0.63), and with smoking status identified as the only independent diagnostic marker.

Since UIA rupture has devastating effects, false negative results for UIA detection should be low. Also, as in our study population, the UIAs were diagnosed on proton-density T2-weighted brain MRI scans; an additional MR angiography (or CT angiography) needs to be performed to confirm UIA presence. Therefore, specificity should also be high to reduce costs and patient burden. Consequently, a diagnostic model for UIA detection in the general population requires high sensitivity and specificity [19]. Although the model for men showed the best performance, its sensitivity of 62% and specificity of 55% were still limited. This may be explained by the relatively low prevalence of UIAs which contrasts with the relatively prevalent diagnostic markers [13–15]. Moreover, this model had an upper limit of UIA risk of 1.86%, while the overall prevalence of UIAs in the general population is approximately 3% [6]. Therefore, we believe that the performance measures of our models are insufficient to identify persons at high risk of having a UIA, as a first step in the development of screening for UIAs on a population level. Thus, our models in their current form are not suitable for use in clinical practice. Rather, our models provide insight into risk factors contributing to UIA and show evidence that not only risk factors for aSAH but also for UIAs may have sex-specific effects [16, 21].

UIAs are more prevalent in women than in men, especially after 50 years of age [6, 22]. It has been hypothesized that sex hormones play a role in UIA formation and rupture [23]. Also, differential effects of hypertension and smoking in men and women on the risk of developing aSAH have been shown [14, 15, 20]. Such effects have not been studied for UIAs yet. Because of these sex differences, we studied the interactions between sex and all other candidate diagnostic markers. The model for the whole population showed interactions of sex with hypertension and smoking. This result shows the importance of further research on the differential effect of these risk factors for UIAs.

Interestingly, in the model for women smoking status was identified as the only diagnostic marker, while the model for men showed more diagnostic markers. Given the relatively low sample size of our study, we cannot draw any definitive conclusions, but it could be that yet unknown female-specific risk factors additionally contribute to the risk of UIAs in women. This may be influenced by a potential gender bias, which may lead to potential female-specific risk factors being underrecognized [24].

An important strength of our study is the general population-based study design and sample size that enabled us to study a broad range of candidate diagnostic markers despite the relatively low UIA prevalence. Furthermore, the diagnostic markers in our models are all well-defined and easily ascertainable by general practitioners.

Our study also has limitations. First, the Rotterdam Study assessed the presence of UIAs on proton-density T2-weighted brain MRI scans, instead of on MR

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Linear predictor (LP)

-6.476 + 2.670 (if woman) + 0.023 (for age per year if man) - 0.022 (for age per year if woman) + 0.869 (if man and hypertension) - 0.653 (if woman and hypertension) + 0.354 (if man and former smoker) + 1.540 (if man and current smoker) + 0.069 (if woman and former smoker) - 0.644 (if woman and current smoker) - 0.363 (if DM)

Estimating individual persons' absolute risk of having an UIA is based on the following formula: 1/(1 + exp(-LP)), where LP is the linear predictor of the regression coefficients of the diagnostic model.

Based on this diagnostic model, the risk of having an UIA ranges from 1.61% to 11.01%. To illustrate how to obtain these risks using the formula, consider two men. The first man is 65 years old and has hypertension. The second man is 85 years old, has hypertension and is a current smoker.

In the first man, LP is filled in as follows:

-6.476 + 0.023*65 (for age) + 0.869 (for hypertension) = **-4.112**

1/(1 + exp(-LP))
LP = -4.112
1/(1 + exp(- -4.112)) = 1/(1 + exp(4.112)) = 1/(1 + 61.07) = 1/(62.07) = 0.0161 = 1.61%
He has a risk of having an UIA of 1.61%

In the second man, LP is filled in as follows:

-6.476 + 0.023*86 (for age) + 0.869 (for hypertension) + 1.540 (for current smoker) = **-2.089**

1/(1 + exp(-LP))
LP = -2.089
1/(1 + exp(- -2.089)) = 1/(1 + exp(2.089)) = 1/(1 + 8.08) = 1/(9.08) = 0.1101 = 11.01%
He has a risk of having an UIA of 11.01%

DM = diabetes mellitus.

Fig. 2. Original regression equation of the diagnostic model for the full study population to calculate the absolute risk of having an unruptured intracranial aneurysm (UIA).

angiography. Moreover, the proton-density T2-weighted brain MRI scans had a slice thickness of 1.6 mm, which means that smaller UIAs may have been missed because of a limited spatial resolution, thereby limiting the power of our study. In a systematic review from 2011, the overall UIA prevalence was estimated as 3.2% (95% CI: 1.9–5.2) [6]. Second, other potential diagnostic markers may have an association with prevalent UIAs that were unavailable in our study, such as family history of ASAH. Third, participants in the Rotterdam Scan Study were more likely to be white, middle-class persons. Because of this relatively homogenous study population, generalizability to other ethnic or socioeconomic populations is limited. Fourth, although we internally validated our models, our models have not been externally validated, a process recommended to improve generalizability and applicability [18]. However, as the performance measures of our models are insufficient for use in clinical practice, external

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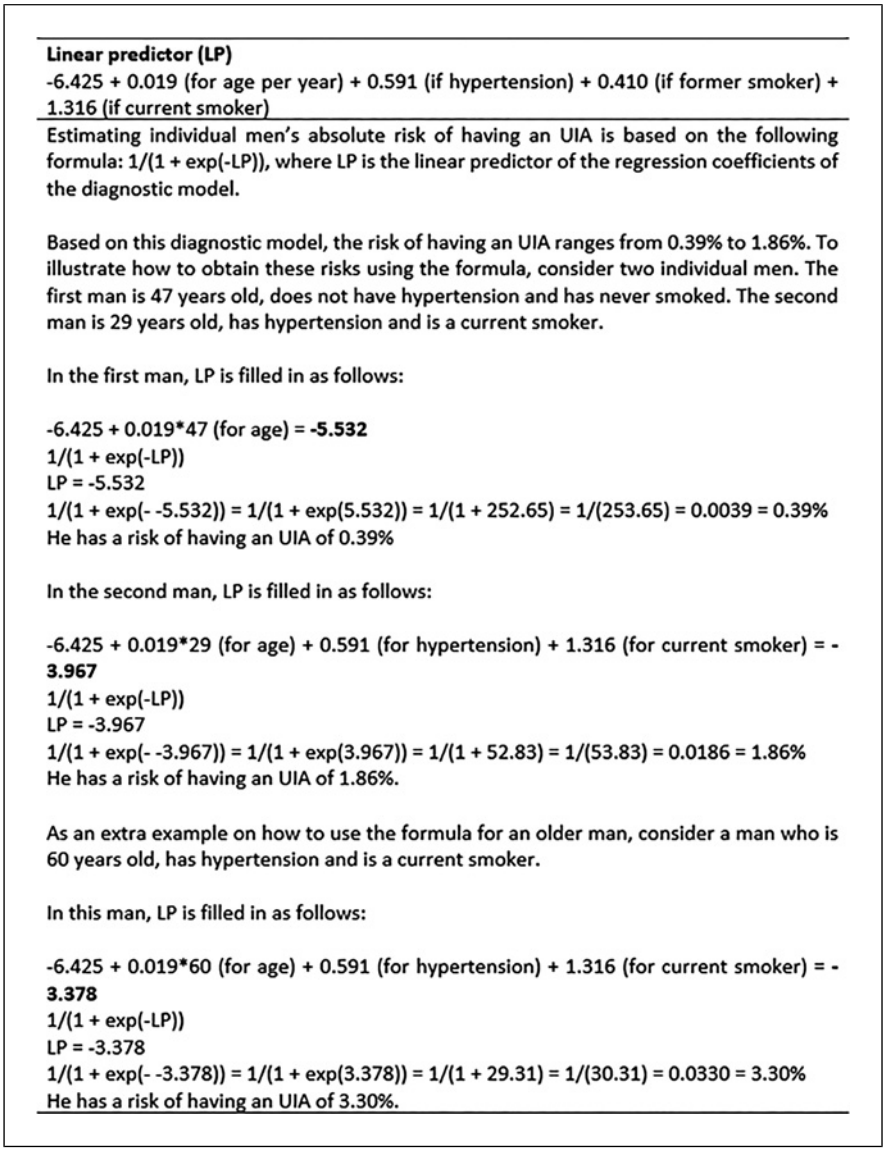

Fig. 3. Original regression equation of the diagnostic model for men to calculate the absolute risk of having an unruptured intracranial aneurysm (UIA) for individual men.

validation currently has no added value. Fifth, although we judge the performance measures of our models as insufficient, we do not know what the performance of a diagnostic model should exactly be to achieve a cost-effective screening program. This should be assessed in a cost-effectiveness study. Lastly, other population cohorts to further assess the consistency of our findings are currently not available. Only smaller populations exist, with 19 persons with UIAs identified in 1,006 participants of the Nord-Trøndelag Health (HUNT) Study and 122 persons with UIAs identified in 1,862 participants of the Tromsø Study [25, 26].

We found that the diagnostic model for men had the best performance. Despite this, the sensitivity and specificity of the model were limited, and the model could not identify men with a UIA prevalence above the UIA prevalence in the general population. Larger population cohorts are needed to assess the consistency of our findings. Future research should also further assess sex-differential effects of risk factors.

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Statement of Ethics

This study was performed in compliance with the Declaration of Helsinki. The Rotterdam Study has obtained approval from the Medical Research Ethics Committee (MREC) of the Erasmus MC University Medical Center Rotterdam (approval number MEC 02.1015) and from the Review Board of the Dutch Ministry of Health, Welfare and Sports (Population Screening Act WBO, approval number 10712172-159521-PG), and this approval is renewed every 5 years. All participants provided written informed consent.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Vita M. Klieverik: data analysis, data interpretation, drafting the manuscript, and final approval of the manuscript;

Bob Roozenbeek: conception and design of the study, data acquisition, data interpretation, reviewing the manuscript, and final approval of the manuscript;

Tim Y. Cras: data acquisition, data analysis, reviewing the manuscript, and final approval of the manuscript;

Meike W. Vernooij: data acquisition, data interpretation, reviewing the manuscript, and final approval of the manuscript;

Mirjam I. Geerlings: data interpretation, reviewing the manuscript, and final approval of the manuscript;

Daniel Bos: conception and design of the study, data acquisition, data analysis, data interpretation, and reviewing the manuscript; and

Ynte M. Ruigrok: conception and design of the study, data interpretation, drafting and reviewing the manuscript, and final approval of the manuscript.

Data Availability Statement

Access to the dataset by qualified researchers trained in human subject confidentiality protocols is considered upon request. Data are not publicly available due to ethical reasons. Further inquiries can be directed to the corresponding author.

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