Risk factors for aneurysmal subarachnoid haemorrhage: pieces of the puzzle

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Risk factors for aneurysmal subarachnoid haemorrhage: pieces of the puzzle

Risicofactoren voor een aneurysmatische subarachnoïdale bloeding: stukjes van de puzzel

(met een samenvatting in het Nederlands)

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General introduction and outline of the thesis

GENERAL INTRODUCTION

Rupture of an intracranial aneurysm (IA) causes aneurysmal subarachnoid haemorrhage (aSAH). Since aSAH mostly affects relatively young people and has a high case fatality and morbidity, it is an important subtype of stroke.[1] The proportion of years of potential life lost from aSAH is comparable with that of ischaemic stroke and intracerebral haemorrhage,[2] and a recent calculation found a total economic burden of £510 million annually for aSAH in the United Kingdom.[3]

Non-invasive techniques for imaging of intracranial vessels have become increasingly available and used, which has resulted in an increased number of incidentally detected unruptured IAs. Reducing the development and rupture of IAs is an important method for reducing the incidence of aSAH, which has remained relatively stable over the last decades.[4]

Knowledge about risk factors for aSAH is necessary to better understand the pathophysiological mechanisms and to develop possible preventive measures. The risk of aSAH consists of three different components: 1) the development of IAs, 2) "chronic" risk factors for rupture, such as female sex, age and hypertension, and 3) "trigger" factors, which cause the actual rupture. In the present thesis we aimed to identify risk factors for the development of IAs and for aneurysmal rupture and trigger factors for aneurysmal rupture.

OUTLINE OF THE THESIS

Chapter 2 is a systematic review on the prevalence of unruptured IAs, with emphasis on sex, age, comorbidity, country and time period.

Patients who suffer from aSAH are often in a poor clinical condition and physicians often have to rely on proxies for information. In Chapter 3 we studied the completeness of the answers given by proxies on our questionnaire for risk factors and trigger factors for aSAH, and investigated the level of agreement between patient and proxies. Chapter 4 describes the case-crossover study we performed to identify trigger factors for the rupture of IAs and calculated the population attributable risk of each factor. In Chapter 5 we discuss these trigger factors in relation to patient and aneurysm characteristics.

In an effort to unravel the risk factors for aSAH into risk factors for developing an IA and for the rupture of an IA, we performed three case-control studies (patients with an unruptured IA vs. controls, patients with an aSAH vs. patients with an unruptured IA and patients with an aSAH vs. controls). The results of these studies are described in Chapters 6, 7 and 8. Based on the risk factors for aSAH we also developed a prognostic

model to calculate the life-time risk of aSAH based on the risk factors for aSAH, which is also presented in Chapter 8.

In Chapter 9 we critically reviewed the results as described in this thesis and discuss the implications of our findings. Also, future perspectives in the research on risk factors for aSAH are described.

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2

Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country and time period: a systematic review and meta-analysis

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ABSTRACT

Background: Unruptured intracranial aneurysms (UIAs) are increasingly detected and an important healthcare burden. We aimed to assess the prevalence of UIAs by family history, comorbidity, sex, age, country, and time period.

Methods: Through searches of PubMed and Embase, and Web of Science we updated our 1998 systematic review up to March 2011. We calculated prevalences and prevalence ratios (PR) with random-effects binomial meta-analysis. We assessed time trends with year of study as a continuous variable.

Results: We included 68 studies, which reported on 83 study populations and 1450 UIAs in 94912 patients from 21 countries. The overall prevalence was 3.2% (95% confidence interval [CI] 1.9-5.2) in a population without comorbidity, with a mean age of 50 years, and consisting of 50% men. Compared with populations without the comorbidity PRs were 6.9 (95% CI 3.5-14) for autosomal dominant polycystic kidney disease (ADPKD), 3.4 (95% CI 1.9-5.9) for a positive family history, 3.6 (95% CI 0.4-30) for brain tumour, 2.0 (95% CI 0.9-4.6) for pituitary adenoma, and 1.7 (95% CI 0.9-3.0) for atherosclerosis. The PR for women compared with men was 1.61 (95% CI 1.02-2.54), with a ratio of 2.2 (95% CI 1.3-3.6) in study populations with a mean age of 50 years. Compared with patients older than 80 years, we found no differences by age, except for patients younger than 30 years (PR 0.01, 95% CI 0.00-0.12). Compared with the USA, PRs were similar for other countries, including Japan (PR 0.8, 95% CI 0.4-1.7) and Finland (PR 1.0, 95% CI 0.4-2.4). There was no statistically significant time trend.

Conclusions: The prevalence of UIAs is higher in patients with ADPKD or a positive family history than in people without comorbidity. In Finland and Japan, the higher incidence of subarachnoid haemorrhage is not explained by a higher prevalence of UIAs, implicating higher risks of rupture.

INTRODUCTION

Rupture of an intracranial aneurysm causes subarachnoid haemorrhage. Because aneurysmal subarachnoid haemorrhage (aSAH) mostly affects relatively young people (i.e. younger than 65 years) and has a high case fatality and morbidity, it is an important subtype of stroke.[1] The proportion of years of potential life lost from aSAH is similar to that of ischaemic stroke and intracerebral haemorrhage, and a recent calculation found a total economic burden of £510 million annually for aSAH in the UK.[2,3]

The incidence of aSAH is higher in Finland and Japan than in other regions, increases with age, and is higher in women.[4] These regional, sex, and age differences and the slight decline in the incidence of aSAH between 1950 and 2005, might result from differences in the prevalence of aneurysms, differences in the risk of rupture, or both.[4]

In 1998, we published a systematic review on the prevalence of unruptured intracranial aneurysms (UIAs).[5] Since then, non-invasive techniques for imaging of intracranial vessels have become increasingly available and used, which has coincided with an increase in incidental detection of aneurysms and the publication of many new studies on the prevalence of UIAs.[6]

We aimed to incorporate the new data into the existing pooled data to provide more accurate estimates on the prevalence of UIAs in healthy populations and in groups of people undergoing brain imaging for a specific reason. We also aimed to increase the knowledge of prevalence in sex, age, and comorbidity subgroups, and to study regional differences and time trends in the extended data set.

METHODS

Search strategy and selection criteria

Our search methods were similar to those in our previous review.[5] We did a PubMed and Embase search to retrieve all studies on prevalence of UIAs published before March, 2011.

In brief, we used the keywords "aneurysm(s) AND (cerebral OR brain OR intracranial OR berry OR basilar OR saccular OR communicating) AND (unruptured OR incidental OR prevalence OR risk)" (see Supplemental Table S2.1). We also checked the Web of Science for articles citing our previous review and searched the personal database of one author (GJER) that has been prospectively built by daily search of PubMed over the past 15 years with terms related to aSAH and intracranial aneurysm. We searched the reference lists of all relevant publications for additional studies. We continued this method of cross-checking

until we could not identify any further studies. Finally, all papers used in our previous review were reassessed according to our present inclusion criteria.

Language other than English was not an exclusion criterion. We did not exclude any published work on the basis of language.[7] Our inclusion criteria were more strict than in our previous version of the review: cross-sectional or case-control design (in which cases are defined as people with a specific comorbidity and controls as people without that comorbidity); presentation of data that included crude numbers on number of patients with UIAs and on the population at risk, or that allowed recalculation of these crude numbers; UIAs reported separately from ruptured intracranial aneurysms; and investigation of ten or more patients. In family studies, the procedure for selection of families had to be specified, and the indication for imaging or autopsy had to be given. In studies of healthy volunteers, if screening for aneurysms was the main reason for imaging, the motivation for participation had to be clear. Imaging studies had to use CT angiography, MRI, magnetic resonance angiography, or intra-arterial digital subtraction angiography (IA-DSA). In MRI studies, the text had to specify that there was a specific search for intracranial aneurysms. In IA-DSA studies, the number of investigated vessels had to include at least both internal carotid arteries; in case-control studies, case and control participants had to be similar, without additional criteria for control participants. For cross-sectional studies in which more than 20% of the potential participants declined participation or did not undergo radiological examination, the reasons had to be specified.

MHMV did the literature search and screening of the titles for eligible studies. To assess further eligibility of the studies MHMV and RB independently assessed the abstracts according to the predefined inclusion criteria. If an abstract was judged by both authors to meet the requirements, the full article was read. Any disagreement was resolved by a third reviewer (GJER or AA).

Data extraction

After our initial assessment for eligibility, MHMV and RB independently completed a data extraction form. Any disagreement about the data was resolved by a third reviewer (GJER or AA). If possible, we calculated the prevalence after exclusion of other types of UIAs (e.g. traumatic, mycotic, or fusiform), since these types of aneurysms have a different pathophysiology. For each study we extracted data on mid-year of study, study design (cross-sectional or case-control), size of study population, number of patients with UIAs, number of UIAs, site and size of UIAs, demographic data of the study population and patients with UIAs, type of investigation (autopsy or method of imaging), and reason for

autopsy or imaging. If patients had UIAs that were additional to a ruptured aneurysm, these patients were excluded from our analysis.

We classified the studies as prospective or retrospective on the basis of how data were collected. We categorised imaging methods into IA-DSA, MRI, magnetic resonance angiography, and CT angiography. We classified IA-DSA studies as three vessel or four vessel (one or both vertebral and both carotid arteries) and two vessel (only both carotid arteries). We classified the site of the intracranial aneurysms as the internal carotid artery (including posterior communicating artery), anterior cerebral arteries (including the anterior cerebral artery, anterior communication artery, and pericallosal artery), middle cerebral artery, or posterior circulation (including the vertebral artery, basilar artery, cerebellar arteries, and posterior cerebral artery).

We categorised the sizes of intracranial aneurysms as less than 5 mm, 5-9 mm or 10 mm or greater. Some of the studies we identified used other categories; to include more studies in our analyses on size, we classed 5 mm or less as less than 5 mm and 6-9 mm as 5-9 mm.

On the basis of our previous review, we subdivided the studies according to the reason for brain imaging or autopsy: screening (including healthy volunteers and healthy control groups), a positive family history of UIAs or aSAH according to the paper being assessed, autosomal dominant polycystic kidney disease (ADPKD), atherosclerosis, pituitary adenoma, and other. We classed as screening any studies with cohorts of autopsied people and control series from case-control studies unless a different reason for autopsy or imaging was given. If there were two studies with the same reason for autopsy of imaging that did not fall into one of the predefined categories, we created a new category with that reason for investigation. If a study included more than one study population (e.g. ischaemic stroke patients and healthy controls) we classed them as two separate study populations; the patients with ischaemic stroke were included in the category of atherosclerosis and the healthy controls in the reference group without comorbidity.

Statistical analysis

We computed the crude prevalence for each study. We pooled the prevalences from multiple studies by means of a random-effects binomial meta-analysis, with the number of UIAs and the total number of included patients for each study population as variables.[8] Because of the heterogeneity in prevalence between studies, we used random-effects models to study possible causes of heterogeneity. When possible, we adjusted prevalences and PRs for the presence of comorbidity, for percentage of men in the study population, and mean age of the study population.

We first assessed whether all methods of imaging were similar in their detection of UIAs. We therefore compared magnetic resonance angiography, MRI, or CT angiography with IA-DSA, and two-vessel IA-DSA with three or more vessel IA-DSA. If a method was inferior to the others we would exclude studies with this method from further analyses. Then we compared autopsy studies with imaging studies.

Before assessing the effect of the different types of comorbidity, we tested an assumption made in our previous systematic review, that patients with a brain tumour have no increased prevalence of UIAs and can therefore be included into the reference group. Thus, we compared studies of people who had no comorbidity with studies of patients who had a brain tumour (other than a pituitary adenoma) before doing further analyses. If a brain tumour was associated with an increased prevalence of UIAs we would asses this factor separately; if not, then we would include this group into the reference group. We calculated PRs for presence of different comorbidities. We also calculated the prevalence for an average study population that was without comorbidity, consisting of 50% men, and had a mean age of 50 years. We calculated this prevalence as EXP ($\alpha+50\beta1+50\beta2$), where α, $\beta1$ en $\beta2$ were the regression coefficients of the random-effects model for, respectively, the intercept, age and sex.

For studies of people with a positive family history for aSAH or UIA, we did a subgroup analysis that compared studies of people who had two or more affected first-degree relatives with studies of patients who had only one affected first-degree relative. For ADPKD, we compared patients with ADPKD who had a family history of aSAH or UIA with those who had no such family history.

We assessed sex differences in three ways. First, we calculated the prevalence ratio for women with men as the reference. Second, we studied the influence of the percentage of men in a study population on the prevalence, because not all studies specified how many aneurysms were identified for each sex. The relation was expressed as the percentage change of the prevalence per increase in percentage of men. Third, we did a subgroup analysis to assess the PR of women compared with men in study populations with a mean age of 50 years or younger and older than 50 years. We did this because a previous study showed that the incidence of aSAH was substantially higher in men than in women before the age of 50 years, but after 50 years the incidence was substantially higher in women.[4]

We assessed age differences in two ways. First, we compared groups of different decade bands with people older than 80 years as a reference. Second, we compared groups of different ages with the mean age of each study population and calculated PRs dichotomising at 30 years, 40 years, and 50 years.

For our analysis by country, there had to be at least two studies from a country for it to be assessed separately. Most studies came from the USA and therefore we used this country as a reference. We assessed time trend with the mid-year of each study as an independent variable and expressed it as the percentage change of the crude prevalence rate per calendar year increase.

RESULTS

68 studies met our predefined inclusion criteria (Table 2.1 and Figure 2.1), 18 studies from our previous review and 50 new studies.[5,9-76] We included four case-control studies (of which one was an autopsy study),[33,50,60,61] 63 cross-sectional studies (16 autopsy studies)[9-32,34-49,51-58,62-76] and one combined cross-sectional and autopsy study.[59] Because our inclusion criteria were stricter than in the 1998 version of our review, four studies included in our previous review did not fulfil our new inclusion criteria.[77-80] The 68 studies included 83 study populations, 94912 patients, and 1450 UIAs. The mean overall prevalence of UIAs of all included studies was 2.8% (95% CI 2.0-3.9). The prevalence varied from 0% to 41.8% between studies (Figure 2.2).

With IA-DSA as the reference group,[10,13,18,19,25,27,35-38,63,67,69,75] we did not identify a significant difference in prevalence in studies with magnetic resonance angiography as the initial imaging method (PR 1.3, 95% CI 0.6-2.5),[14,15,21,26,30,31,33,39,40,47,48,50,54,55,57-59,61,64-66,70,73,74] but prevalence was lower in studies with MRI as the initial imaging method (PR 0.04, 95% CI 0.01-0.13).[9,41,68,71,72,76] The prevalence in studies using MRI as the initial method remained significantly lower after adjustment for sex and age (PR 0.10, 95% CI 0.01-0.35). The prevalence was also significantly lower in studies with MRI as the initial imaging method[9,68,76] if studies with magnetic resonance angiography as the initial imaging method were taken as the reference (PR 0.03, 95% CI 0.01-0.10).[15,21,26,30,33,39,40,47,48,50,54,55,61,64-66,70,73,74] No studies were done with CT angiography alone. The prevalences were not significantly lower in IA-DSA studies with both carotid arteries studied (PR 0.9, 95% CI 0.5-1.7)[25,27,36,38] compared with three-vessel or four-vessel IA-DSA studies.[13,19,35,63,67]

We excluded studies primarily done with MRI from all further analyses because they had a significantly lower prevalence; the overall prevalence was then 3.5% (95% CI 2.7-4.7) instead of 2.8%.

The prevalence of UIAs was higher in imaging studies than in autopsy studies (PR 3.5, 95% CI 2.1-6.1; 62 studies including 77 study populations).[10-40,42-67,69,70,74,75] After adjustment for sex, age, and comorbidity this difference disappeared (PR 1.1, 95% CI 0.3-3.6; 29 studies including 35 study populations).[10,13,15,21-23,26-28,31,33,36,39,43,47-52,57-59,65-67,69,70,73]

Table 2.1 Overview of the 83 included study populations from 68 studies

	Country	Mid-year of study	Number of people included	Number of patients with aneurysm	Design or method*	Reported on:						
						Sex	% men	Mean age (years)	Age categories	Reason for investigation†	Site	Size
Cohen, 1955[20]	Norway	1952	539	9	P,A	No	No	No	No	E	No	No
Chason, 1958[17]	USA	-	2749	80	R,A	No	No	No	Yes	E	No	No
Housepian, 1958[29]	USA	1934	8660	11	R,A	No	No	No	No	E	No	No
Berry, 1961[12]	USA	1950	3804	39	R,A	No	No	No	No	E	No	No
Du Boulay, 1965[25]	UK	1954	51	0	R,I	Yes	53	No	No	I	No	No
McCormick A, 1965[44]	USA	-	7523	26	R,A	No	No	No	No	E	No	No
McCormick B, 1965[44]	USA	-	197	12	R,A	No	No	No	No	E	No	No
Yanagawa, 1966[74]	Japan	-	203	1	P,I	No	No	40	Yes	E	No	No
McCormick, 1970[45]	USA	-	1619	82	P,A	No	No	No	Yes	E	No	No
Romy, 1973[56]	France	1962	11620	67	R,A	No	No	No	No	E	No	No
Stehbens, 1975,[62]	Australia	1931	979	43	P,A	No	No	No	No	E	No	No
Jakubowski A, 1978[36]	UK	1973	150	10	R,I	Yes	56	48.1	No	I	Yes	Yes
Jakubowski B, 1978[36]	UK	1982	33	1	R,I	Yes	39	43.0	No	I	Yes	Yes
Wakabayashi, 1983,[69]	Japan	1982	17	7	R,I	Yes	41	42	No	F	Yes	No
De la Monte, 1985[24]	USA	1971	12911	39	R,A	No	No	No	No	E	No	No
Atkinson, 1989[10]	USA	1983	278	3	R,I	Yes	55	53.0	Yes	I	Yes	Yes
Inagawa, 1990[32]	USA	1969	10259	84	R,A	No	No	No	Yes	E	Yes	Yes
Iwata, 1991[35]	Japan	1989	72	4	P,I	Yes	50	No	No	H	Yes	Yes
Ujiie A, 1991[67]	Japan	1989	616	16	R,I	Yes	51	40.1	No	H,I	No	No
Ujiie B, 1991[67]	Japan	1989	590	23	R,I	Yes	69	48.8	No	H,I	No	No

Schievink A, 1992[60]	USA	1969	72	3	R,A	No	No	No	No	E,F	No	No
Schievink B, 1992[60]	USA	1969	144	3	R,A	No	No	No	No	E,F	No	No
Chan, 1993[16]	China	1977	33	0	R,A	No	No	No	No	F	No	No
Huston A, 1993[30]	USA	1991	26	6	P,I	No	No	No	No	F	No	No
Huston B, 1993[30]	USA	1991	59	3	P,I	No	No	No	No	F	No	No
Sugai A, 1994[63]	Japan	1988	262	19	P,I	No	No	No	No	H,I	No	No
Sugai B, 1994[63]	Japan	1988	71	3	P,I	No	No	No	No	H,I	No	No
Leblanc, 1995[43]	Canada	-	41	1	P,I	Yes	32	41.2	No	G	No	No
Ronkainen, 1995[57]	Finland	1993	396	33	P,I	No	46	45.4	No	G	Yes	Yes
Griffiths, 1996[27]	UK	1993	100	9	P,I	No	52	62.0	No	H	Yes	Yes
Pappada, 1996[52]	Italy	-	389	10	R,I	Yes	75	67.0	No	H	Yes	Yes
Kann, 1997[37]	USA	-	209	10	R,I	No	No	No	No	H	Yes	Yes
Pant, 1997[51]	Japan	1985	465	23	R,I	Yes	36	41.0	No	I	Yes	Yes
Ronkainen A, 1997[58]	Finland	-	438	38	P,I	No	47	48.1	No	F,G	Yes	No
Ronkainen B, 1997[58]	Finland	-	22	2	P,I	No	No	No	No	F,G	Yes	No
Yue, 1997[76]	USA	-	3671	3	R,I	No	No	No	No	E	Yes	Yes
Cloft, 1998[18]	USA	1987	95	6	P,I	Yes	7	No	No	J	No	No
Iida, 1998[31]	Japan	1994	30	4	P,I	Yes	47	54.1	No	F	Yes	Yes
Kojima, 1998[39]	Japan	1994	380	40	P,I	Yes	40	54.8	No	G	Yes	Yes
Raaymakers, 1998[54]	Netherlands	1995	116	7	P,I	No	No	No	No	G	No	No
Ronkainen C, 1998[59]	Finland	1989	147	6	P,I	Yes	43	49.5	Yes	E,G	No	Yes
Ronkainen D, 1998[59]	Finland	1995	612	29	R,A	Yes	80	58.7	Yes	E,G	No	Yes
Brown A, 1999[14]	USA	1997	62	6	P,I	No	No	No	No	G	Yes	No
Brown B, 1999[14]	USA	1997	17	0	P,I	No	No	No	No	G	Yes	No
Cloft, 1999[19]	USA	1987	31	1	R,I	No	No	No	No	J	No	No
Conway, 1999[22]	USA	1965	25	1	R,A	Yes	68	39.0	No	J	Yes	Yes

Table 2.1 continues on next page

Table 2.1 *Continued*

	Country	Mid-year of study	Number of people included	Number of patients with aneurysm	Design or method*	Reported on:						
						Sex	% men	Mean age (years)	Age categories	Reason for investigation†	Site	Size
Iwamoto, 1999[34]	Japan	1976	1192	27	R,A	Yes	55	No	Yes	J	No	No
MARS, 1999[55]	Netherlands	1996	626	25	P,I	Yes	48	No	No	G	Yes	No
Nakagawa A, 1999[47]	Japan	1994	244	34	R,I	Yes	65	50.9	No	G	Yes	Yes
Nakagawa B, 1999[47]	Japan	1994	99	12	R,I	Yes	56	No	No	G	Yes	Yes
Nagakawa C, 1999[47]	Japan	1994	481	33	R,I	No	No	No	No	J	No	No
Kappelle, 2000[38]	USA	1989	2885	90	R,I	Yes	70	No	No	H	Yes	Yes
Nakajima, 2000,[48]	Japan	1995	15	3	R,I	Yes	27	57.9	Yes	F	Yes	Yes
Suyama, 2000[64]	Japan	1997	112	0	P,I	No	No	No	No	G	No	No
Yeung, 2000[75]	USA	1996	200	2	R,I	No	No	No	No	H	No	No
Conway, 2001[23]	USA	1948	25	0	R,A	No	60	30	No	J	No	No
Graf A, 2002[26]	Germany	-	32	3	P,I	No	47	46.8	No	F	No	No
Graf B, 2002[26]	Germany	-	11	3	P,I	No	55	42.5	No	F	No	No
Pittella, 2002[53]	Brazil	1988	237	2	R,A	No	62	No	No	J	No	No
Wang, 2002[70]	USA	-	96	4	P,I	Yes	36	39.0	No	G	Yes	No
Connolly, 2003[21]	USA	-	99	9	R,I	Yes	70	41.6	No	J	Yes	Yes
Nakatani A, 2003[50]	Japan	-	123	3	P,I	Yes	65	55.6	No	E	Yes	Yes
Nakatani B, 2003[50]	Japan	-	52	0	P,I	No	56	51.7	No	E	Yes	Yes
Weber, 2004[71]	Germany	2001	1813	0	P,I	Yes	98	20.5	No	E	No	No
Alphs, 2005[9]	USA	2002	589	5	P,I	Yes	100	60.1	No	J	No	No
Soljanlahti A, 2005[61]	Finland	-	39	1	P,I	No	No	30.0	No	E	No	No

Soljanlahti B, 2005[61]	Finland	-	25	0	P,I	No	No	30.6	No	E	No	No
Triantafyllidi, 2005[65]	Greece	-	10	1	P,I	No	No	51.0	No	H	Yes	No
Ballotta, 2006[11]	Italy	1995	474	11	P,I	No	No	No	No	H	Yes	Yes
Bourekas, 2006[13]	USA	-	78	8	R,I	Yes	51	47.8	No	I	No	Yes
Kumra, 2006[41]	USA	-	60	0	R,I	No	No	No	No	E	No	No
Uehara, 2006[66]	Japan	1994	84	6	R,I	Yes	69	61.1	No	H	No	No
Weber, 2006[72]	Germany	2002	2536	0	R,I	Yes	100	20.5	No	E	No	No
Vernooij, 2007[68]	Netherlands	2006	2000	35	P,I	Yes	48	63.3	No	E	No	Yes
Brown, 2008[15]	USA	-	303	58	P,I	Yes	40	51.0	No	G	Yes	No
Kumar, 2008[40]	Australia	-	478	1	P,I	No	53	No	No	E	No	No
Mostafazadeh, 2008[46]	Iran	2006	425	14	P,A	Yes	65	No	No	E	Yes	Yes
Oh, 2008[49]	South Korea	2007	258	17	P,I	Yes	62	66.1	No	H	Yes	Yes
Heman, 2009[28]	Netherlands	2005	194	8	R,I	Yes	68	70.0	No	H	Yes	Yes
Ishikawa A, 2010[33]	Japan	2007	7345	146	R,I	Yes	67	69.9	No	E	No	No
Ishikawa B , 2010[33]	Japan	2007	374	13	R,I	Yes	62	76.9	No	H	No	No
Kuzmik, 2010[42]	USA	2003	160	10	R,I	No	No	No	No	H	No	No
Xu, 2011[73]	China	2008	355	43	P,I	No	52	46.5	No	F	No	No

If several study populations are described in a paper, each study population has a different letter. Studies are listed according to publication date.
Sex= sex-specific subgroup data available; studies reporting on number of included men and women, and on number of men and women with aneurysms. % men= studies reporting on proportion of men and women in the study population. Age= studies reporting on number of patients, and number of patients with aneurysms for different age categories. Mean age= mean age of the study population.
* Design or method: R= retrospective, P= prospective, I= imaging, A= autopsy.
† Reason for investigation: E= screening, F= autosomal dominant polycystic kidney disease, G= family, H= atherosclerosis, I= brain tumour, J= other.

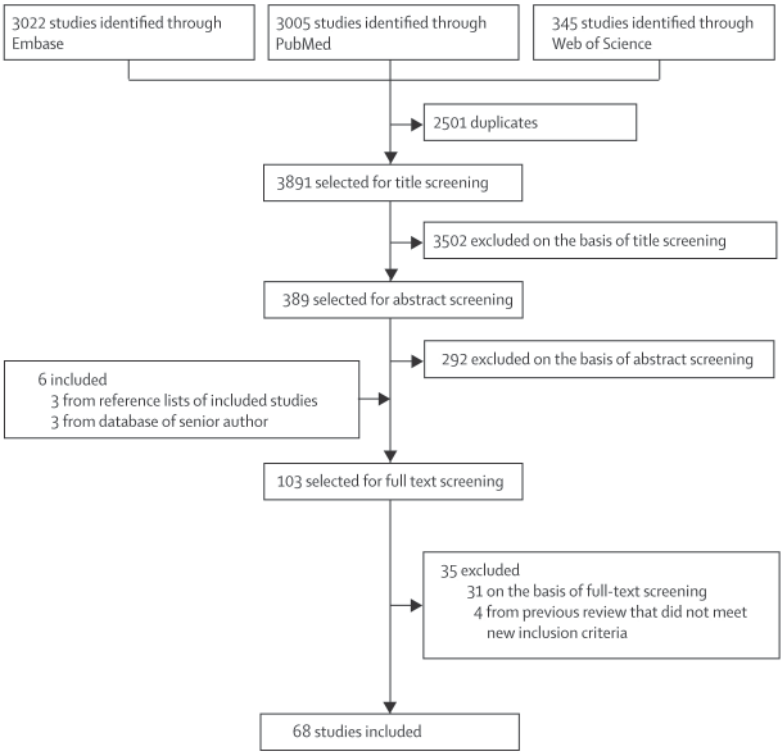

Figure 2.1 Selection of included studies.

We did not identify a statistically significant difference in prevalence for patients with a brain tumour compared with people without comorbidity when adjusted for age and sex (PR 3.6, 95% CI 0.4-30).[10,13,33,36,50,59,67] Therefore we included studies on patients with brain tumours in the reference group of studies on people without comorbidity. For the studies with data on sex and age, the crude prevalence of UIAs in the reference group was 2.9% (95% CI 1.9-4.5; 26 studies including 31 study populations). We estimated that the prevalence would be 3.2% (95% CI 1.9- 5.2) for a study population that consisted of 50% men and had a mean age of 50 years. Compared with patients who did not have the relevant comorbidity or risk factor, sex-adjusted, and age-adjusted PRs were significantly higher for patients with ADPKD[26,31,48,69] or a family history of aSAH or UIA,[15,39,43,47,57-59,70] but not for patients with atherosclerosis[27,28,49,52,65-67] or a pituitary adenoma (Table 2.2).[36,51]

The PR for patients with ADPKD and a family history of aSAH or UIA was 2.0 (95% CI 0.5-7.4) compared with patients with ADPKD but no family history of aSAH or UIA.[16,26,30,30,31,48,58,60,69,73] The PR was 2.2 (95% CI 1.5-3.3) for patients who had a positive

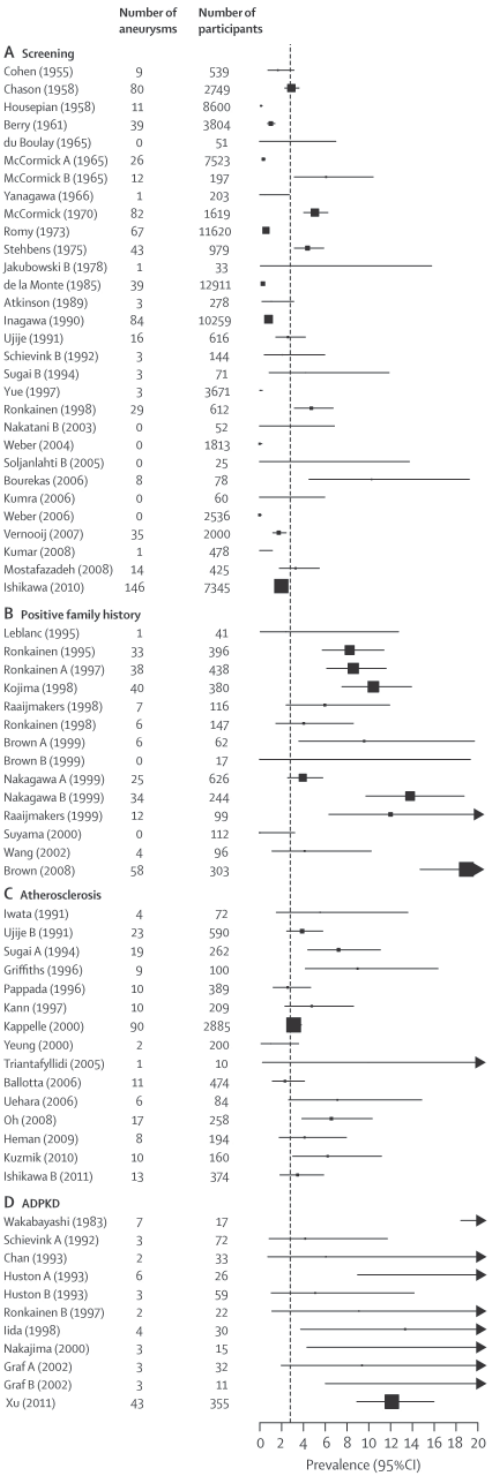

Figure 2.2 Prevalences of unruptured intracranial aneurysms in study populations without comorbidity (A), with a positive family history (B), with atherosclerosis (C), and with polycystic kidney disease (D). If several study populations are described in a paper, each study population has a different letter, as also indicated in Table 2.1. The dotted line is the overall prevalence of the 83 study populations. 13 study populations that did not fall into one of the four categories are not depicted. Sizes of the point estimates are proportional to the weight of the studies.

Table 2.2 Prevalences and prevalence ratios per reason for investigation, adjusted for sex and age

	Crude (57 studies, 69 study populations, 1353 UIA)	Age adjusted (28 studies, 33 study populations, 601 UIA)		Sex adjusted (34 studies, 39 study populations, 648 UIA)		Age and sex adjusted (26 studies, 31 study populations, 600 UIA)	
	PR	PR	Adjusted PR	PR	Adjusted PR	PR	Adjusted PR
ADPKD	8.8 (4.3-18)	8.1 (4.0-16)	8.3 (4.2-16)	9.4 (4.7-19)	8.9 (4.1-19)	6.2 (2.9-13)	6.9 (3.5-14)
Atherosclerosis	3.1 (1.7-5.5)	1.9 (1.1-3.6)	1.5 (0.7-3.1)	2.2 (1.2-3.7)	2.2 (1.3-3.8)	1.5 (0.7-3.0)	1.7 (0.9-3.0)
Family history*	4.8 (2.6-8.8)	3.9 (2.3-6.8)	4.0 (2.3-6.9)	4.0 (2.3-6.8)	3.7 (1.8-7.5)	2.9 (1.4-6.1)	3·4 (1.9-5.9)
Pituitary adenoma	4.1 (1.1-15)	2.7 (1.1-6.6)	2.6 (1.1-6.0)	2.7 (1.1-6.6)	2.6 (1.0-6.7)	1.9 (0.8-4.7)	2.0 (0.9-4.6)

Data are prevalence ratio (PR) or adjusted PR with 95% CI. The prevalence from studies with people without comorbidity or with patients with a brain tumour was used as the reference (brain tumour includes brain metastases). The calculated prevalence in a study population of people without comorbidity consisting of 50% men and with a mean age of 50 years is 3.2%, based on the model with 31 study populations.
UIA= unruptured intracranial aneurysms. ADPKD= autosomal dominant polycystic kidney disease.
* One or more affected relatives.

family history of aSAH or UIA with at least two affected first-degree relatives compared with those with only one affected first-degree relative.[43,47,54,55,57,58]

29 studies, including 34 study populations, reported on prevalences in men and women separately.[10,13,15,18,21,22,25,28,31,33-36,38,39,43,46-52,55,59,66,67,69,70] We identified a higher prevalence of UIAs in women (6.0%, 95% CI 4.5-8.0) compared with men (PR 1.57, 95% CI 1.04-2.37), which remained significant after adjustment for age and comorbidity (PR 1.61, 95% CI 1.02-2.54; 22 studies including 26 study populations).[10,13,15,21,22,28,31,33,36,39,43,47-52,59,66,67,69,70]

We also assessed the relation between the proportion of men in a study population and prevalence of UIAs (38 studies including 44 study populations) and identified a 2.1% relative decrease (95% CI 0.3-3.9) for each percentage point increase in percentage of men,[8,10,13,15,18,21-23,25-27,31,33-36,38-40,43,46-53,55,57-59,65-67,69,70,73] which remained statistically significant after adjustment for age (2.7% decrease, 95% CI 0.7-4.7; 29 studies including 35 study populations).[10,13,15,21-23,26-28,31,33,36,39,43,47-52,57-59,65-67,69,70,73] The PR for women compared with men was 1.1 (95% Cl 0.6-1.8) for study populations with a mean age of 50 years or younger (10 studies including 12 study populations),[13,21,22,36,43,51,59,67,69,70] but 2.2 (95% CI 1.3-3.6) for study populations with a mean age greater than 50 years (13 studies including 15 study populations).[10,15,28,31,33,39,47-50,52,59,66]

Eight studies, including nine study populations, provided data on prevalence of UIAs in one or more decade age groups.[10,17,32,34,45,48,59,74]

We adjusted for sex and comorbidity in these eight studies. Compared with patients aged 80 years or older (prevalence 3.0%, 95% CI 1.1-8.1),[17,32,34,45,48] prevalence was lower in patients younger than 30 years (PR 0.01, 95% CI 0.00-0.12),[10,17,32,34,45] but not in patients aged 30-39 years (PR 0.4, 95% CI 0.1-1.6),[17,32,34,45,48,59] 40-49 years (PR 0.4, 95% CI 0.1-1.3),[17,32,34,45,48,59,74] 50-59 years (PR 0.4, 95% CI 0.1-1.3),[17,32,34,45,48,59] 60-69 years (PR 1.0, 95% CI 0.3-3.3),[17,32,34,45,48,59] and 70-79 years (PR 0.6, 95% CI 0.2-2.1).[17,32,34,45,48]

31 studies, describing 38 study populations, provided information on mean age of the individuals involved. Prevalences were not significantly different between patients with a mean age less than 40 years (prevalence 2.1%, 95% CI 0.6-7.0) compared with those aged 40 years or older (PR 3.0, 95% CI 0.9-10.2). After adjustment for sex and comorbidity (35 studies including 29 study populations) we identified a PR of 2.8 (95% CI 0.1-10.0) for patients aged 40 years or older compared with patients younger than 40 years and a PR of 1.0 (0.6-1.7) for patients aged 50 years or older compared with patients younger than 50 years.[10,13,15,21-23,26-28,31,33,36,39,43,47-52,57-59,65-67,69,70,73] There were no studies left after adjustment for sex and comorbidity with a mean age less than 30 years, so we could not make a comparison with 30 years or older.

Table 2.3 Prevalences per country, adjusted for sex and age

	Crude (55 studies, 70 study populations, 1306 UIA)	Age adjusted (28 studies, 35 study populations, 596 UIA)		Sex adjusted (33 studies, 39 study populations, 747 UIA)		Age and sex adjusted (26 studies, 32 study populations, 594 UIA	
	PR	PR	Adjusted PR	PR	Adjusted PR	PR	Adjusted PR
Finland	1.8 (0.7-5.0)	0.9 (0.4-2.4)	0.8 (0.3-2.3)	1.2 (0.4-3.0)	0.8 (0.6-2.9)	1.1 (0.5-3.0)	1.0 (0.4-2.4)
Germany	6.4 (1.1-38)	3.0 (0.3-15)	3.0 (0.6-15)	3.1 (0.7-13)	3.1 (0.8-12)	2.9 (0.3-13)	2.5 (0.7-9.4)
Italy	0.9 (0.2-4.3)	0.4 (0.3-2.7)	0.3 (0.0-2.0)	0.5 (0.1-2.3)	0.9 (0.2-3.6)	0.4 (0.4-2.3)	0.6 (0.1-2.9)
Netherlands	1.7 (0.4-6.4)	0.7 (0.6-4.4)	0.4 (0.0-3.3)	0.7 (0.2-2.4)	0.9 (0.3-2.5)	0.7 (0.6-3.8)	0.7 (0.1-3.7)
UK	1.5 (0.4-5.4)	1.1 (0.1-3.9)	0.9 (0.3-3.5)	0.9 (0.3-2.4)	0.9 (0.4-2.3)	1.1 (0.1-3.6)	0.9 (0.3-2.5)
Japan	1.8 (1.0-3.6)	1.0 (0.4-2.2)	0.8 (0.3-2.0)	1.0 (0.5-2.0)	1.0 (0.6-1.9)	1.0 (0.5-2.3)	0.8 (0.4-1.7)
China	1.9 (0.3-12)	2.3 (1.0-13)	2.3 (0.4-13)	2.5 (0.5-11)	2.6 (0.7-9.5)	2.3 (1.0-11)	2.1 (0.6-7.5)

Data are prevalence ratio (PR) or adjusted PR with 95% CI. The prevalence in the USA was used as the reference. UIA= unruptured intracranial aneurysm.

Table 2.3 lists prevalence for the USA and the PRs for all other countries, adjusted for sex and age. With the USA as a reference,[10,13,15,21-23,70] we identified similar prevalences in Japan,[31,33,39,47,48,50,51,66,67,69] China,[73] and several European countries, including Finland,[57-59] Germany,[26] Italy,[52] the Netherlands[28] and the UK.[27,36]

46 studies, including 56 different study populations, provided information on mean year of data acquisition (range 1931-2008).[10-12,14,16,18-25,27-36,38,39,42,46-49,51,53-57,59,60,62-64,66,67,69,73,75]

Our regression analysis identified a 3.4% (95% CI 1.8-5.0) annual increase in prevalence. However, when we adjusted for sex, age, and comorbidity the increase of UIAs over time was no longer statistically significant (.0%; -2.3 to 4.3; 20 studies including 24 study populations, range 1948-2008).[10,21-23,27,28,31,33,36,39,47-49,51,57,59,66,67,69,73]

We collected data on intracranial aneurysm size from three autopsy studies[22,32,59] and 20 imaging studies.[10,11,21,27,28,31,35-38,47-52,57,58,69,70] 368 intracranial aneurysms were assessed for size (Table 2.4). Most aneurysms (241; 66%) were smaller than 5 mm. After correction for age, the number of aneurysms larger than 5 mm decreased by 4.9% (95% CI -8.3 to -1.5; 13 studies including 14 study populations) with each percentage point increase in percentage of men. This pattern remained significant after adjustment for comorbidity (5.7% decrease, -9.3 to -2.1). We did not identify a significant change in the prevalence of aneurysms larger than 10 mm (1.2% decrease, -6.9 to 10, with each percentage point increase in percentage of men). Compared with all other countries, the proportion of aneurysms of 5 mm or larger was not higher in Japan (PR 1.9, 95% CI 0.6-6.4) or Finland (0.5, 0.1-2.0).

We extracted data on site of UIAs from three autopsy studies[22,32,46] and 26 imaging studies.[10,11,14,15,21,27,28,31,33-39,47-52,55,57,58,65,69,70] 864 intracranial aneurysms were assessed for site (Table 2.4). The most common sites were the internal carotid artery (including posterior

Table 2.4 Proportions of aneurysms by size and site

	Total number of aneurysms (%)
Size of intracranial aneurysm	368 (100%)
<5 mm	241 (66%)
5-9 mm	101 (27%)
≥ 10 mm	26 (7%)
Site of intracranial aneurysm	864 (100%)
Anterior cerebral artery and branches	154 (18%)
Medial cerebral artery	303 (35%)
Internal carotid artery including posterior communicating artery	360 (42%)
Posterior communicating artery alone	85 (10%)
Vertebrobasilar arteries	47 (5%)

communicating artery) and the medial cerebral artery. In imaging studies the internal carotid artery was the largest category, but in autopsy studies the medial cerebral artery was the commonest site. The prevalence of aneurysms in the posterior circulation did not depend on the proportion of men (1.6% decrease with each percentage point increase in percentage of men; 95% CI -6.9 to 3.9). Compared with all other countries, the proportion of posterior circulation aneurysms was not higher in Japan (PR 1.2, 95% CI 0.4-3.5) and Finland (PR 2.0, 95% CI 0.4-8.8).

DISCUSSION

In our analysis, the prevalence of UIAs was influenced by the presence of polycystic disease, a positive family history, age, and sex, but not by region. The prevalence was significantly higher in patients aged 30 years or older compared with those who were younger than 30 years. Women had a higher prevalence of UIAs than men, mainly attributable to an excess in women older than 50 years. Patients with ADPKD and patients with a positive family history of intracranial aneurysm or subarachnoid haemorrhage both had a higher prevalence. We did not identify a higher prevalence in Finland and Japan. We identified a non-significant increase in the prevalence of UIAs per study year.

We calculated that in a population of people without comorbidity, consisting of 50% men and with a mean age of 50 years, the prevalence of UIAs is 3.2%. This is higher than the overall prevalence for people without comorbidity of 2.3% we identified in our previous review.[5] This difference can be explained by our correction for age and sex, inclusion of more recent studies with higher quality imaging techniques, and inclusion of fewer retrospective autopsy studies (which are uncorrected for age and sex and have a lower prevalence).[5] By contrast with our previous analysis we did not identify an increased prevalence in patients with atherosclerosis or a pituitary adenoma. Our present findings are probably more accurate, because we included three times as many studies as before and, more importantly, we were able to adjust PRs for sex and age.

Smoking and hypertension are major risk factors for aSAH, and patients who have survived an aSAH are at increased risk of cardiovascular diseases.[81] We identified a higher prevalence in study populations with atherosclerosis, but this increase in prevalence was not significant. Owing to a lack of data we could not separately assess the prevalence of UIAs in smokers and patients with hypertension. Patients who smoke and have high blood pressure were probably included in the reference group, which might explain the absence of a clear association between atherosclerosis and prevalence of aneurysms. This also means that the prevalence for people who do not smoke, do not have a high blood pressure, and

do not have other risk factors might be lower than 3.2%. The absence of data on smoking and hypertension is a limitation of our present analyses.

A previous review showed an overall higher incidence of aSAH in women compared with men, mainly caused by a higher incidence in women older than 55 years.[4] Our data suggest that the number of aneurysms larger than 5 mm is higher in study populations with more women, which might partly explain the higher incidence of aSAH in women, because larger aneurysms have a higher risk of rupture.[82] We think that the higher incidence in older women might in part also be explained by the age-dependent prevalence of UIAs in women, since we identified a higher prevalence in women compared with men in study populations older than 50 years, but not 50 years or younger, although the women-to-men PRs did not differ significantly between the two age-groups. Together with the increased risk of rupture of aneurysms in older patients, a higher prevalence might explain why the difference in incidence of aSAH between men and women increases with age.[82] Other investigators have postulated that decreases in oestrogen concentrations and oestrogen-receptor density contribute to an increased risk of intracranial aneurysm pathogenesis and an increased risk of aneurysm rupture in women during and after menopause.[83] This hypothesis is supported by the fact that hormone replacement therapy has shown to be a protective factor for aSAH.[84] Whether the risk of rupture is also higher in postmenopausal women still needs to be assessed.

We did not identify higher prevalences of UIAs in Finland and Japan. However, the incidence of aSAH is higher in these countries, suggesting a higher risk of rupture.[82] Investigators have also shown that UIAs larger than 5 mm or posterior circulation aneurysms have a higher risk of rupture.[82] We did not identify a higher proportion of aneurysms larger than 5 mm or posterior circulation aneurysms in Finnish and Japanese study populations compared with other study populations. Thus, the higher risk of rupture cannot be explained simply by higher proportions of larger or posterior circulation aneurysms in Finland and Japan. The reasons for higher risk of aneurysm rupture in these countries remain unknown.

The incidence of aSAH has declined slightly between 1950 en 2005.[4] In our analysis we did not identify a decrease in the prevalence of UIAs. Therefore, the decrease in incidence is probably the result of an overall decreased risk of aneurysm rupture, related to factors such as a change in smoking habits or an increased use of preventive treatment.

The large number of studies, the large number of included patients, the use of very strict inclusion criteria, and the adjustment for sex, age, and reason for investigation, all add to the reliability of our data. Accurate estimates are of great importance, since they are used in cost-effectiveness analyses to develop screening strategies. Our subgroup analyses by age,

sex, family history, comorbidity, country, and time period were based on smaller numbers of studies and should be interpreted with caution, especially in those subgroups where point estimates had wide Cls. Nevertheless, most of our confidence limits were narrow, even after adjustment for sex, age, and comorbidity. A limitation of our study is that the prevalence might be influenced by our search strategy; theoretically, negative studies on incidental findings might be less likely to use "aneurysm" as a key word than studies on intracranial aneurysms. This might have caused an underrepresentation of studies that did not show a relation between a presumed risk factor and prevalence of UIAs.

Our finding that older women might have a higher prevalence is possibly an important clue for how aneurysms are formed and future well designed studies should focus on the role of oestrogen in the pathogenesis of UIAs. Our findings also show that the prevalence of UIAs in Japan and Finland is not higher, nor do they have a higher prevalence of aneurysms larger than 5 mm or posterior circulation aneurysms to explain the higher incidence of aSAH. Research on aSAH in Finnish and Japanese populations should therefore be aimed at finding other risk factors for rupture of intracranial aneurysms.

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Supplemental Table S2.1 Search strings

Pubmed search string ('aneurysm'[tiab] OR 'aneurysms'[tiab]) AND ('cerebral'[tiab] OR 'brain'[tiab] OR 'intracranial'[tiab] OR 'berry'[tiab] OR 'saccular'[tiab]) AND ('unruptured'[tiab] OR 'incidental'[tiab] OR 'prevalence'[tiab] OR 'risk'[tiab]) limit: only human studies
Embase search string ('Aneurysm':ti,ab OR 'aneurysms':ti,ab) AND ('Cerebral':ti,ab or 'brain':ti,ab or 'intracranial':ti,ab or 'berry':ti,ab or 'saccular':ti,ab) AND ('unruptured':ti,ab OR 'incidental':ti,ab OR 'prevalence':ti,ab OR 'risk':ti,ab) limit: only human studies

3

Comparison of patient and proxy responses on risk factors for stroke

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ABSTRACT

Background: For studies on chronic risk factors and trigger (i.e. acute risk) factors, stroke researchers often have to rely on proxies. The reliability of proxy responses regarding trigger factors for stroke is unknown.

Methods: Thirty patients with stroke and their proxies were interviewed about chronic risk factors and trigger factors. We assessed the completeness of proxy-derived data by calculating the level of non-response and the level of agreement using Cohen kappa statistics.

Results: For most chronic risk factors and trigger factors, the response rate to whether or not exposure had taken place in the past year was 87% or higher. If couples agreed on exposure, patient and proxy could also provide a comparable estimate of the average frequency of exposure. Although the non-response on last time of exposure was higher, proxies who could answer provided a reasonably good estimate for most trigger factors.

Conclusions: Proxies provide reliable information on exposure to chronic risk factors and trigger factors for stroke. For exposure and average frequency of exposure, non-response is low and the level of agreement is high for most chronic risk factors; for last time of exposure non-response is higher, but proxies who could respond provided reliable estimates of last time of exposure to most trigger factors.

INTRODUCTION

Risk factor assessment is important in clinical practice and in stroke research. When a stroke patient presents with aphasia or a depressed level of consciousness, physicians and researchers have to rely on information given by proxies. Studies on proxy reliability in various groups of patients have demonstrated different levels of agreement and completeness.[1-8] In most studies, data from proxies were reliable on factors such as presence or absence of smoking and alcohol consumption, but response rates and reliability decreased on more detailed questions such as frequency of exposure.[1-8] The mode of interviewing (open or categorised vs. dichotomised questions) and the relation of the proxy to the patient are also important determinants for the agreement between patient and proxy respondents.[5,9] Only three previous studies have investigated proxy reliability in patients with stroke; two on patients with aneurysmal subarachnoid haemorrhage and one on patients with ischaemic stroke and their proxies.[4,7,8] They all reported an excellent reliability of proxy-derived data on cigarette and alcohol use, although both over- and underestimation by proxies of cigarette and alcohol use was reported.[4,8]

Risk factors for stroke can be divided into chronic risk factors and trigger factors (i.e. acute risk factors). In recent years, research on triggers of cardio- and cerebrovascular diseases has gained interest and investigators often need to use proxy-derived information.[10-13] However, agreement between patients and proxy respondents regarding exposure to trigger factors is unknown. The aim of our study was to investigate the degree of completeness of information from proxies and the level of agreement between patients and proxies on chronic risk factors and trigger factors for stroke.

PATIENTS AND METHODS

During a six-week period (29 March 2006 to 9 May 2006) approximately 70 patients with a possible stroke were admitted to the stroke unit or visited the TIA-clinic. Thirty patients and their proxies were included in this study. Patients were eligible if they were admitted to the hospital or visited the TIA-clinic because of a suspected stroke, were 18 years or older, spoke Dutch, were alert, oriented, had no obvious cognitive deficits or disabling aphasia and had a proxy available. Proxies were eligible when they were able to provide information about chronic risk factors, trigger factors and the daily life of the patient according to the patient, were 18 years or older, spoke Dutch and had no obvious cognitive deficits or disabling aphasia. Patients were identified by review of admission records of the stroke unit and TIA-clinic of our service. Nineteen patients were interviewed at the medium care unit. This is a high care facility within the stroke unit with six beds where

Table 3.1 Agreement between patients and proxies on medical history, family history, exposure in the past year and frequency of exposure to 24 chronic risk factors

	N1	N2	Kappa		N3	Mean	Median difference (P25-P75)**
			All	Spouses			
Medical history							
Ischaemic stroke	30	7	0.9	0.9			
High cholesterol	27	4	0.8	1.0			
Diabetes	30	4	1.0	1.0			
Cardiac problems	30	4	1.0	1.0			
Extracranial aneurysms	30	0	1.0	1.0			
Hypertension	28	7	0.9	0.8			
Family history							
Subarachnoid haemorrhage	23	0	0	0.1			
Ischaemic stroke	25	1	0.6	1.0			
Cerebral haemorrhage	23	1	0.3	0.4			
Heart attack	26	1	0.2	0.6			
Risk factors							
Caffeine	30	30	1.0	1.0			
Coffee	30	28	0.9*	1.0	28	4.1	0 (-0.1 – 1.8)
Tea	30	16	0.8	0.7	16	1.8	-0.1 (-1.9 – 0.8)
Cola	30	8	0.7	0.7	6	1.6	0 (-0.7 – 0.4)
Alcohol	30	26	1.0	1.0			
Beer	30	16	0.9	0.9	16	0.4	0 (-0.3 – 0)
Wine	30	15	0.9	0.8	14	1.1	0 (-0.1 – 0.3)
Liquor	30	12	0.7	0.6	11	0.7	0 (-0.8 – 0.3)
Smoking	30	10	0.9	0.8			
Cigarette	30	10	0.9	0.8	9	13.1	0 (-4.7 – 2.1)

Drugs	30	2	0.8	0.8	NC		
Sauna	30	4	1.0	1.0	4	0.1	0 (0-0)
Flu/cold	30	12	0.5	0.5	11	0	0 (0-0)
Fever	28	3	0.3	0.5	2	0	0 (0-0)
Valsalva							
Strain for defecation	26	8	0	0	4	0.5	-0.2 (-0.8 – 0.4)
Lifting 12.5-25 kg	28	15	0.4	0.4	10	1.6	0 (0 – 1.4)
Lifting 25-50 kg	26	7	0.7	0.8	6	0.2	0.7 (0.1 – 5.0)
Lifting > 50 kg	26	1	0.3	0.4	1	0	0
Sneezing	30	29	1.0*	0.9*	15	1.7	0.1 (-0.9 – 3.4)
Coughing	30	20	0.3	0.4	7	2.3	0.3 (0 – 1.0)
Nose-blowing	30	28	0.7	0.6	15	1.4	0 (-0.7 – 0.4)
Sex							
Sexual intercourse	26	17	0.9	0.8	13	0.1	0 (-0.2 – 0)
Masturbation	18	4	0.9	0.8	1	0	0
Emotions							
Startle	27	6	0.1	0.2	3	0	0 (0)
Anger	30	8	0.5	0.5	7	0.2	0 (0)
Activity							
Vigorous exercise	29	21	0.7	0.7	21	1.3	0 (-0.3 - 0.4)
Heavy to extreme exercise	29	8	0.4	0.5	8	0.4	0 (-0.2 - 0)

N1= Number of couples of which both patient and proxy answered 'yes' or 'no' to the question "Has the patient been exposed in the past year?" All pairs of which either patient or proxy gave no response (i.e. 'I do not know' or 'I decline to answer') were considered a non-response for that particular chronic risk factor; N2= Number of couples of which both patient and proxy responded that the patient had been exposed in the past year; N3= Number of N2 couples of which both patient and proxy gave an estimate of the frequency of exposure; NC= no couples; Mean= mean frequency according to the patients; Median difference= median difference between patients and proxies with P25 and P75 representing the interquartile (25-75%) range.

* Because of almost perfect agreement the kappa could not be calculated. Therefore we provide the agreement not adjusted for chance;

** Median scores less than zero indicate that proxies tended to overestimate the frequency of exposure, median scores above zero indicate that proxies underestimated these variables.

patients are under continuous observation. At this medium care unit, all patients are monitored for at least 24 h after admittance and patients with aneurysmal subarachnoid haemorrhage at least until occlusion of the aneurysm. All other patients and all proxies were interviewed in a separate room. Only one proxy per patient was interviewed. If no close relative (i.e. spouse, child or parent) was available as a proxy, we asked the patient which person could give the best information about the daily life of the patient. For all ambulant patients who were enrolled through the TIA-clinic, we interviewed the proxy who accompanied the patient to the hospital, which was always a relative (most often the spouse).

This study is a pilot study for a larger research project on trigger factors for aneurysmal subarachnoid haemorrhage. We translated the structured questionnaire that was previously used in the Stroke Onset Pilot Study into Dutch with the forward-backward translation method and added the following potential trigger factors for aneurysmal subarachnoid haemorrhage: consumption of Redbull® (energy drink), use of sildenafil, masturbation and activities leading to a Valsalva manoeuvre (i.e. sneezing, coughing, playing a wind instrument and nose-blowing).[13,14] Patients and proxies were first asked for demographics, medical and family history and exposure to 24 risk factors. Some factors are established chronic risk factors (e.g. smoking) or trigger factors for stroke (e.g. physical exercise), but most factors we investigated are only potential risk factors for stroke, especially subarachnoid haemorrhage. We assessed all risk factors as if they were a chronic risk factor (Table 3.1) as well as a trigger factor (Table 3.2). Therefore, for each factor, patients and proxies were asked about exposure in the past year and average frequency of exposure in the past year (for assessment as a chronic risk factor) and about last time of exposure (for assessment as a trigger factor).

The physical activity rating scale, which was previously used in the Determinants of Myocardial Infarction Onset Study and the Stroke Onset Pilot Study, was used for questions on physical activity.[12,13] Two categories were defined: vigorous exertion (metabolic equivalent of task [MET] level 6) and heavy to extreme exertion (MET levels 7 and 8).

The study protocol was approved by the medico-ethical review committee of the University Medical Center Utrecht and all participants gave their written informed consent.

Analysis

The completeness of proxy-derived data was assessed by calculating the proportion of non-response. When the patient or proxy responded a question with 'I do not know' or declined to answer ('no answer'), these responses were considered a non-response.

As described earlier, patients and proxies were asked whether there had been exposure in the past year (dichotomous answers). When a patient or his proxy gave 'no answer', the couple was included in the non-response calculation for that particular factor. To calculate

Table 3.2 Agreement between patients and proxies on last time of exposure to 24 trigger factors for stroke

Trigger factors	N2	N4	Mean time before stroke	Median difference (P25-P75)*
Caffeine				
Coffee	28	25	18.4 (hours)	0 (-2.5 – 0.8)
Tea	16	15	12.4 (hours)	0 (-6.8 – 7.0)
Cola	8	3	10.3 (hours)	-1.0 (-4.0 – 0)
Alcohol				
Beer	16	11	1.5 (days)	0 (-1.0 – 0)
Wine	15	12	2.7 (days)	-1.5 (-7.0 – 0.8)
Liquor	12	9	8.7 (days)	0 (-10.6 – 0)
Smoking				
Cigarette	10	6	3.7 (hours)	0.2 (-7.2 – 5.6)
Drugs	2	0	NC	
Sauna	4	4	17.5 (days)	0.5 (0 – 6.3)
Flu/cold	12	9	1.6 (months)	0 (-2.6 – 0)
Fever	3	3	2.3 (months)	0 (-1.8 – 0)
Valsalva				
Strain for defecation	8	0	NC	
Lifting 12.5-25 kg	15	8	10.1 (days)	0 (0 – 4.5)
Lifting 25-50 kg	7	4	2.0 (days)	1.0 (0 – 4.9)
Lifting > 50 kg	1	1	0.3 (days)	0
Sneezing	29	0	NC	
Coughing	20	4	0.7 (months)	-1.5 (-3.7 – 0)
Nose-blowing	28	4	17.5 (hours)	4.5 (-12.8 – 20.3)
Sex				
Sexual intercourse	17	8	24.7 (days)	0 (-5.3 – 0)
Masturbation	18	1	0 (days)	0
Emotions				
Startle	6	3	2.7 (weeks)	-4.0 (16.0 – 0)
Anger	8	6	2.2 (weeks)	0.4 (-1.6 – 2.6)
Activity				
Vigorous exercise	21	20	7.8 (days)	0 (-3.7 – 0)
Heavy to extreme exercise	8	8	8.1 (days)	0 (-8.9 – 0)

N2= Number of couples of which both patient and proxy responded that the patient had been exposed in the past year; N4= Number of N2 couples of which both patient and proxy gave an estimate of the last time of exposure; Mean time before stroke= mean time before stroke according to the patients; NC= no couples; Median difference= median difference between patients and proxies with P25 and P75 representing the interquartile (25-75%) range.
* Median scores less than zero indicated that proxies tended to overestimate the time lapse between exposure to the trigger factor and stroke onset; median scores above zero indicated that proxies underestimated these variables.

the level of agreement on exposure in the past year for those couples that did provide an answer (N2 in Figure 3.1), we used Cohen kappa statistics.[15] Kappa values between 0 and 1 were categorised after Landis;[16] 0 is no agreement, 0-0.2 is slight agreement, 0.2-0.4 is fair agreement, 0.4-0.6 is moderate agreement, 0.6-0.8 is substantial agreement, 0.8-1.0 is almost perfect agreement, 1 is excellent agreement. A kappa value above 0.6 was considered satisfactory.

A flowchart of reporting on the completeness of data and agreement between patients and proxies on exposure is given in Figure 3.1. When patient and proxy responded that exposure to a chronic risk factor or trigger factor had taken place (N2 in Figure 3.1) in the past year, both persons were asked to estimate the average frequency of exposure and the time lapse between last exposure and the onset of symptoms. Only if both patient and proxy provided an estimate the couple was included for further analysis (N3 and N4 in Figure 3.1); all other couples were excluded for that particular risk factor. To evaluate the level of agreement between patients and proxies on frequency of exposure, we first subtracted the estimate of the proxy from that of the patient. Then we calculated the median differences for all patient-proxy pairs for that particular factor. Median scores less than zero indicated that proxies tended to overestimate the frequency of exposure, median scores above zero indicated that proxies underestimated these items. Time lapse between last exposure and the onset of stroke was analysed similarly.

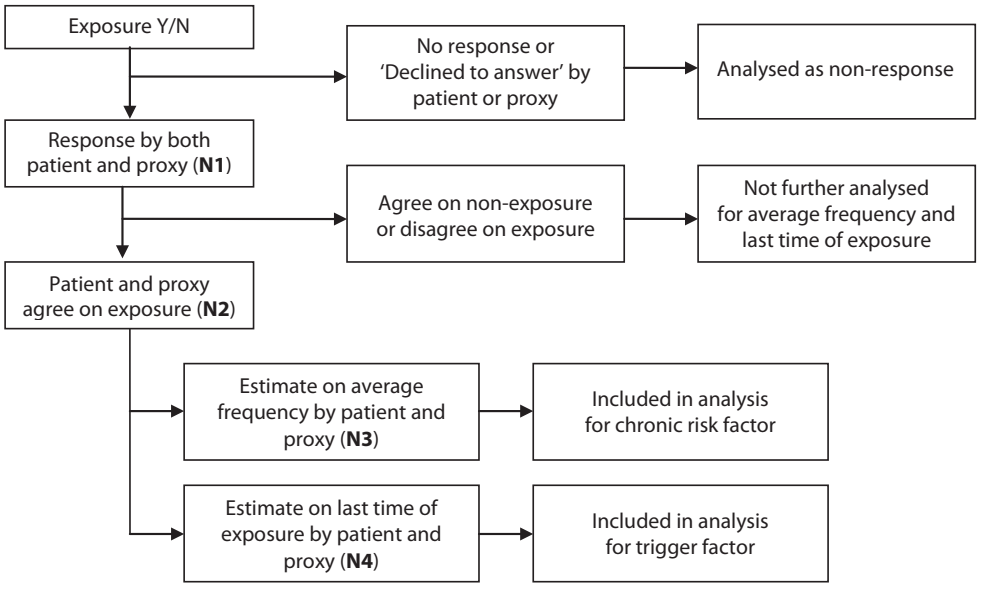

Figure 3.1 Flowchart of reporting on completeness and agreement between patients and proxies on exposure to a chronic risk factor or trigger factor.

RESULTS

The patients from the 30 included patient-proxy couples were evaluated for a TIA (eleven patients), ischaemic stroke (seven patients), spontaneous subarachnoid haemorrhage (nine patients), haemorrhage from an arteriovenous malformation (one patient) and idiopathic thunderclap headache (two patients). Most patients were men (80%), while most proxies were women (77%). The mean age was 58 for patients (range 18-88) and 55 for proxies (range 26-87). Of the proxies who were interviewed, 19 were spouses (63%), three children (20%), six parents (10%) and others: one ex-wife and one close neighbour (7%). All spouses and one parent lived with the patient, all others did not, but had regular contact with the patient. Patients with stroke were interviewed at a mean of 3.2 days after the stroke. Patients and proxies were interviewed with a maximum of 4 days apart. Patients with a TIA and their proxies were interviewed at a mean of 6.4 days after the first symptoms.

Response rate

The response rate was high on medical and family history (Table 3.1). The proportion of response (N2 divided by N1 in Table 3.1) on whether or not exposure to a chronic risk factor had taken place was 87% or higher for all factors except for masturbation. Most of the couples who agreed that exposure had taken place in the past year (N2 in Table 3.1) could also provide an estimate of the average frequency of exposure in the past year (N3 in Table 3.1). For chronic risk factors such as caffeine and alcohol consumption, smoking, sauna use and physical exercise, the response rate was higher than 75%. However, on some chronic risk factors, such as sneezing, coughing, blowing one's nose, masturbation, straining for defecation and startling, the response on the frequency of exposure in the past year was between 25 and 54%. This high proportion of non-response was mainly attributable to the high proportion of proxies who could not estimate the frequency (30-50%). However, with most of these chronic risk factors, up to 30% of the patients also were not able to provide an estimate of the average frequency (data not shown).

More than 60% of the couples who agreed that the patient had been exposed in the past year could also provide an estimate of the time lapse between last exposure and onset of stroke (N2 and N4 in Table 3.2) on most trigger factors. However, on trigger factors such as sexual activities, defecation, sneezing, coughing and blowing one's nose, the response was 50% or less for both patients and proxies.

Level of agreement

The level of agreement between patients and proxies was almost perfect (kappa > 0.8) on items concerning the medical history of the patient, while there was no more than moderate agreement on family history (kappa 0.4-0.6) (Table 3.1). The level of agreement on whether the patient had been exposed in the past year was substantial to almost perfect (kappa > 0.6) for most chronic risk factors, except for the flu or a cold, lifting, coughing, emotions and heavy lifting. The kappa for these chronic risk factors with less than substantial agreement did not improve when the analyses were restricted to spouses as proxies.

Table 3.1 shows the mean frequency of exposure in the last year according to the patients and the median difference between the estimated frequency of the patient and proxy for each factor. The median difference on frequency of exposure was small for all chronic risk factors except for lifting 25-50 kg, which was underestimated by most proxies.

Data on mean time of the last exposure according to the patients and median difference between patients and proxies for each trigger factor are presented in Table 3.2. The median difference on mean time of the last exposure was very small for all trigger factors, except for blowing one's nose, which was underestimated, and for startling, coughing and wine consumption, which was overestimated by proxies.

DISCUSSION

We found a high proportion of response for patients and proxies and a high level of agreement between patients and proxies on exposure to chronic risk factors for stroke. Response rates were good on exposure to all chronic risk factors except for masturbation. Rates were lower when asked for detailed questions about average frequency of exposure, especially for chronic risk factors such as straining for defecation, sneezing and masturbation. The high response rates for proxies we found in our study can probably be explained by the high proportion of spouses and first-degree relatives amongst proxies.

Other studies on response to questions about exposure to and quantity of smoking and alcohol consumption also showed a lower level of response on average frequency than on exposure status.[1,4,5,17] In our study, the proportion of proxy responses was lowest when asked to estimate the time lapse between last exposure to trigger factors and stroke onset. A first explanation for this lower proportion of responses is that often proxies were not present at the time of stroke onset. Another explanation for the lower response rate on average frequency and last time of exposure for activities such as coughing, sneezing and blowing one's nose is probably that these often go unnoticed by the patient and especially

by the proxy. Also, activities such as straining for defecation and masturbation are most often not performed in proximity of a proxy. Because most patients were interviewed at the medium care unit and all proxies were interviewed in a separate room, questions on private subjects may also explain the lower levels of response by patients because they were surrounded by other patients.

Besides response rates, we also studied agreement between patients and proxies. We found an excellent agreement on medical history, but agreement on family history was much lower, which is consistent with other studies.[5,8] The latter might be explained by the high proportion of spouses we included as proxies, because several studies have shown that siblings, and probably also parents, are better informed about the subjects concerning family history, while spouses and children are more able to describe events that occurred during adult life, such as medical history and exposure to trigger factors.[4,5]

The level of agreement between patients and proxies on whether a patient has been exposed to a chronic risk factor in the past year was almost perfect for most factors. The high level of agreement on exposure in our study may in part be explained by the dichotomised answers to these questions, because agreement between individuals rises when fewer categories are used.[9] Other studies also concluded that surrogate respondents are useful in correctly identifying the user status for cigarette smoking and consumption of coffee and alcohol.[1-3,6-8]

We found a lower proportion of response on detailed questions, such as average frequency of exposure and last time of exposure, but proxies who could answer these questions provided a good estimate. This confirms an earlier study that found higher levels of non-response on average frequency and time since last use for cigarette smoking and alcohol consumption, but also a high level of agreement.[4] The median difference on average frequency of exposure to alcohol, caffeine and smoking in our study was small between patients and proxies. This is in agreement with previous studies on patients with stroke and Alzheimer, which also showed a high level of agreement for average consumption of coffee, alcohol and cigarettes between patients and their proxies.[3,4,6-8] In contrast to other studies, the proxies in our study did not over- or underestimate the use of cigarettes or alcohol.[4,8] This might be explained by the high level of spouses in our study, because the relationship to the patient influences proxy reliability.[3]

This study was designed to investigate the completeness and level of agreement between patients and proxies, not to investigate the accuracy of the answers given. As the reliability of both patient and proxy responses decreases with increasing time since onset, one of the advantages of our study is the small delay between the event and the interview.[3] Also, because habits change after surviving an acute event, the time lapse between the acute

event and the interview may influence the memory of previous behaviour and thus the levels of agreement.[18,19] We did not formally assess cognition of patients and proxies before the interview, so subtle cognitive deficits may have been undetected. However, if cognitive problems of the patient or proxy would have gone undetected, we would have expected the level of agreement between patients and proxies to be lower. Recall bias may have occurred as patients and proxies could both have underestimated alcohol, drugs or cigarette use because of shame or guilt. However, the influence of recall bias is probably low, because one would not expect the bias of both patient and proxy to be in the same direction and to the same extent.

This study supports the view that proxies can very well be used to evaluate exposure to risk factors for stroke. We found that this is true not only for chronic risk factors, but also for trigger factors. The results of our study can thus be used in future investigations into stroke, but can also be applied to everyday clinical practice when patients are unable to give information and proxies are available.

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4

Trigger factors and their attributable risk for rupture of intracranial aneurysms: a case-crossover study

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ABSTRACT

Background: Little is known about activities that trigger rupture of an intracranial aneurysm. Knowledge on what triggers aneurysmal rupture increases insight in the pathophysiology and facilitates development of prevention strategies. We therefore aimed to identify and quantify trigger factors for aneurysmal rupture and to gain insight into the pathophysiology.

Methods: During a 3-year period, 250 patients with aneurysmal subarachnoid haemorrhage completed a structured questionnaire regarding exposure to 30 potential trigger factors in the period soon before subarachnoid haemorrhage (hazard period) and for usual frequency and intensity of exposure. We assessed relative risks (RR) of rupture after exposure to triggers with the case-crossover design comparing exposure in the hazard period with the usual frequency of exposure. Additionally, we calculated population-attributable risks.

Results: Eight triggers increased the risk for subarachnoid haemorrhage: coffee consumption (RR 1.7, 95% confidence interval [CI] 1.2-2.4), cola consumption (RR 3.4, 95% CI 1.5-7.9), anger (RR 6.3, 95% CI 4.6-25), startling (RR 23.3, 95% CI 4.2-128), straining for defecation (RR 7.3, 95% CI 2.9-19), sexual intercourse (RR 11.2, 95% CI 5.3-24), nose-blowing (RR 2.4, 95% CI 1.3-4.5), and vigorous physical exercise (RR 2.4, 95% CI 1.2-4.2). The highest population-attributable risks were found for coffee consumption (10.6%) and vigorous physical exercise (7.9%).

Conclusions: We identified and quantified eight trigger factors for aneurysmal rupture. All triggers induce a sudden and short increase in blood pressure, which seems a possible common cause for aneurysmal rupture. Some triggers are modifiable, and further studies should assess whether reduction of exposure to these factors or measures preventing sudden increase in blood pressure decrease the risk of rupture in patients known to have an intracranial aneurysm.

INTRODUCTION

Approximately 2% of the population has an intracranial aneurysm (IA), but only few IAs rupture.[1,2] With the increasing use of neuroimaging techniques, more incidental aneurysms are being detected.[3]

The risk of rupture of an IA is composed of "chronic" risk factors, such as being female, age, and hypertension, and "trigger" factors, which cause the actual rupture.[4] Activities such as physical exercise, sexual activity, alcohol use, smoking, emotional stress, or a Valsalva manoeuver often precede rupture, but the triggering potential of most factors has not been quantified.[5-8] Only physical exercise has been associated with an elevated risk for aneurysmal rupture.[5,9]

The case-crossover design enables studying the effect of transient exposure to potential trigger factors on the risk of an acute event, such as aneurysmal subarachnoid haemorrhage (aSAH), by comparing exposure in a period soon before the event with the patient's usual frequency of exposure.[10] Insight into trigger factors and into the pathophysiology of aneurysmal rupture helps to develop strategies to reduce the risk of rupture. We therefore aimed to identify and quantify trigger factors for rupture of IAs and to determine their attributable risks.

METHODS

Design and study population

We performed a case-crossover study among patients with aSAH admitted in the Utrecht Stroke Center and who were 18 years of age or older. Informed consent was given by either patient or proxy. aSAH was defined as an abrupt onset of severe headache or loss of consciousness with or without focal neurological signs with subarachnoid blood proven by CT or lumbar puncture and radiologically proven IA. The study protocol was approved by our medico-ethical review committee.

Few proxies of seriously ill or deceased patients consented to participate and completed the questionnaire. Based on these initial experiences, we decided to only include patients who could complete the questionnaire themselves or with the help of a proxy. We compared medical record notes for activities at the time of onset of aSAH (e.g. sexual activity, toilet use, sleep, exercise) of patients included in our study and those with aSAH who were not included.

Procedures

A structured questionnaire that was used previously in the Stroke Onset Pilot Study was translated into Dutch and adapted for aSAH.[11,12] The time of onset of aSAH was defined as the time of the symptoms that led to referral. Data were obtained on the activities at onset, demographics, medical and family history, and site of the ruptured aneurysm. For all potential trigger factors, patients were asked about exposure in the past year, usual frequency of exposure, and presence of exposure in the 'hazard period'. The hazard periods were predefined according to the estimated duration of effect of each potential trigger factor: 1 hour for coffee or cola consumption, smoking, Valsalva manoeuver, heavy lifting, emotions, sexual activity, temperature change (e.g. sauna use or a cold shower), and vigorous to extreme physical exercise (metabolic equivalent of task (MET) ≥6);[13] 4 hours for cocaine, marijuana, and sildenafil use; and 24 hours for fever, a flu-like disease, and alcohol use. Patients were asked about exposure in the hazard period and about the last time of exposure before onset of aSAH to check the consistency of answers about exposure in the hazard period. If answers were inconsistent, then the data of that patient were not used in the main analysis of that particular factor.

If patients were unable to complete the questionnaire during the hospitalisation period, then they were asked to bring the completed questionnaire to their first check-up. If patients forgot to bring it, then they received a copy and were asked to return it by postal mail.

Data analysis

The ratio of the observed exposure frequency in the hazard period (before the onset of aSAH) and the expected frequency was used to calculate relative risks (RR) with corresponding 95% CI.[14,15] Expected frequencies were calculated with the usual annual frequency of exposure.

We calculated that assuming a type 1 error of 5%, 80% power, and an exposure in the hazard period of 10% of the population, a sample size of 200 patients would be large enough to calculate a RR of 2.2 with sufficient precision.

To check the consistency of the results from our main analysis we performed 4 sensitivity analyses. First, an analysis (sensitivity analysis [SENS] 1) was performed using only the yes-or-no question on exposure in the hazard period and disregarding the question about last time of exposure. Patients who were excluded from the main analysis because of inconsistent answers on exposure in hazard period and last time of exposure were now included. In a second sensitivity analysis, patients with inconsistent data were first assumed to be exposed in the hazard period (SENS 2A), and then assumed not to be exposed (SENS 2B). Assuming 6 hours of sleep and less exposure to most triggers, an analysis was performed

maximising the number of exposed hours to 18 hours per day, excluding patients whose aSAH occurred between midnight and 6.00 AM (SENS 3).

Assuming a hazard period of 24 hours for alcohol, patients who drink ≥1 glass of alcohol per day are considered to be always exposed. Considering their usual frequency, these patients will often also report exposure in the hazard period. In the case-crossover design, patients who report exposure in the hazard period and are considered always exposed do not contribute to the RR.[16] Therefore, we changed the hazard period for alcohol to 6 hours (SENS 4A) and two hours (SENS 4B). Now, only patients who drink ≥4 glasses of alcohol per day (SENS 4A) or ≥12 glasses of alcohol per day (SENS 4B) are considered always exposed and more patients contribute to the RR.

The fraction of patients with aSAH that can be attributed to a particular trigger factor, the population-attributable risk, is calculated as follows: population-attributable risk= prevalence of exposure (RR – 1)/[prevalence of exposure (RR – 1) + 1].[17] The prevalence of exposure for each factor was calculated as the mean number of exposures per year and divided by the annual number of hazard episodes.

RESULTS

The characteristics of the 250 included patients (Figure 4.1) are given in Table 4.1. The activities reported in the medical records were similar for patients who were included in

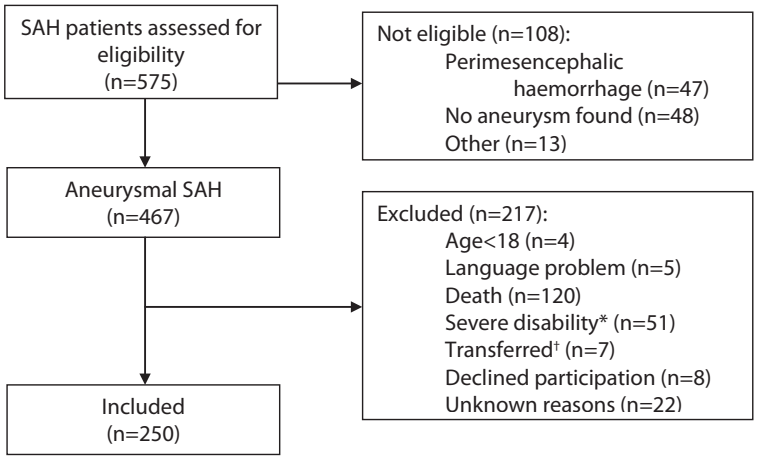

Figure 4.1 Flowchart of patient inclusion.
SAH= aneurysmal subarachnoid haemorrhage. * Critically ill without sufficient recovery for participation. † Transferred to another hospital before being asked to participate.

Table 4.1 Baseline characteristics of the 250 patients

Characteristic	Patients (n=250)
Men, n (%)	62 (24.8)
Mean age, years	54.7
Time from aSAH to survey, n (%)	
<2 weeks	80 (32.0)
2-6 weeks	68 (27.2)
≥6 weeks	102 (40.8)
Site symptomatic aneurysm, n (%)	
Anterior circulation*	224 (89.6)
Posterior circulation	26 (10.4)
Cigarette smoking, n (%)	
Never	53 (20.8)
Past	42 (16.8)
Current <20 cigarettes/day	85 (33.6)
Current ≥20 cigarettes/day	70 (28.0)
Alcohol, n (%)†	
0 units/week	52 (21.6)
1-12 units/week	143 (59.3)
≥12 units/week	46 (19.1)
Vigorous physical exercise, n (%)‡	
≥3 times/week	51 (23.2)
<3 times/week	72 (32.7)
Never	97 (44.1)
Medical history, n (%)	
SAH	5 (2.0)
Hypertension†	66 (26.6)
Heart disease†	15 (6.0)
Diabetes†	6 (2.4)
Positive family history, n (%)	
aSAH†§	12 (4.8)
ADPKD	1 (0.4)

aSAH= aneurysmal subarachnoid haemorrhage; ADPKD= autosomal-dominant polycystic kidney disease.
* including anterior cerebral artery, anterior communicating artery and pericallosal artery.
† <5% missing data.
‡ Vigorous physical exercise was defined as metabolic equivalent of task ≥6; 12% missing data.
§ At least one first-degree relative with aSAH.

our study and those who were not (data not shown). Fifty percent of the surveys were completed within three weeks (range, 1 day - 34 weeks).

Table 4.2 summarises the exposures and RR for all potential trigger factors. Coffee consumption is used as an example to explain the data presentation in detail; the analysis for all factors was performed in a similar way. For coffee consumption, data were used from 197 patients. Fifty-three patients gave incomplete answers (either on average exposure or

Table 4.2 Relative risks for potential trigger factors for rupture of intracranial aneurysms

Risk factors*	Included in analysis (always exposed, exposed in hazard period)	Not exposed in past year	No or inconsistent data	RR (95% CI)
Caffeine				
Coffee	169 (0, 48)	28	53	1.7 (1.2-2.4)
Tea	100 (0, 6)	116	34	0.7 (0.3-1.5)
Cola	92 (0, 8)	135	23	3.4 (1.5-7.9)
Alcohol				
All types	128 (78, 64)	52	70	0.2 (0.1-0.2)
Beer	88 (23, 22)	143	19	0.2 (0.1-0.4)
Wine	139 (62, 51)	86	25	0.1 (0.1-0.2)
Liquor	76 (14, 15)	154	20	0.3 (0.1-0.5)
Smoking				
Cigarettes	119 (24, 80)	103	28	1.1 (0.8-1.6)
Cigar	13 (0, 2)	230	7	1.0 (0.2-5.6)
Drugs				
Marijuana	6 (0, 2)	241	3	1.4 (0.4-5.4)
Temperature				
Temperature change	38 (0, 2)	199	13	2.9 (0.6-14)
Flu-like illness	79 (0, 1)	134	37	2.4 (0.3-16)
Valsalva manoeuvre				
Sneezing	116 (0, 3)	34	100	0.5 (0.2-1.3)
Coughing	88 (0, 7)	55	107	1.4 (0.6-3.3)
Nose-blowing	113 (0, 12)	49	88	2.4 (1.3-4.5)
Straining for defecation	87 (0, 5)	117	46	7.3 (2.9-19)
Lifting >50kg	23 (0, 0)	209	18	-
Lifting >25kg	69 (0, 2)	150	43	0.8 (0.2-2.9)
Lifting >12,5kg	150 (2, 7)	65	56	0.7 (0.4-1.4)
Emotions				
Startling	55 (0, 2)	148	47	23.3 (4.2-128)
Anger	66 (0, 2)	149	35	6.3 (1.6-25)
Sexual activity				
Intercourse	113 (0, 8)	85	52	11.2 (5.3-24)
Masturbation	40 (0, 8)	155	55	5.9 (0.8-42)
Physical exercise				
MET ≥6	115 (0, 11)	88	47	2.4 (1.4-4.2)
MET ≥7	30 (0, 1)	177	43	3.5 (0.5-25)

RR= relative risk; CI= confidence interval; MET= metabolic equivalent of task.
* No RR could be calculated for cocaine use, sildenafil use, consumption of Red Bull® (Red Bull GmbH, Santa Monica, CA), and fever, because no patients were exposed in the hazard period.

the hazard period) or inconsistent data. Of the 197 patients who provided consistent data, 169 patients had consumed coffee in the past year and 28 had not. Using the assumption of a one-hour exposure period of coffee, none of the 169 patients were all-day drinkers

(i.e. ≥24 cups/day). The risk of rupture of an IA was 1.7-times (95% CI 1.2-2.4) higher in the hour after drinking a cup of coffee compared with no coffee.

Similarly, we found elevated RRs for drinking cola, nose-blowing, straining for defecation, startling, anger, sexual intercourse, and vigorous to extreme physical exercise (metabolic equivalent of task ≥6). In contrast, we found a decreased RR for all types of alcohol. The RR essentially did not change when comparing patients who completed the questionnaire before and after six weeks (data not shown).

Sensitivity analyses are given in Table 4.3 and Supplemental Table S4.1. In the sensitivity analysis limited to the yes-or-no question on exposure in the hazard period (SENS 1), the RR increased for all triggers. In the sensitivity analyses, in which patients with inconsistent data were considered exposed (SENS 2A) or not exposed (SENS 2B) in the hazard period, all factors that were statistically significant in the original analysis remained significant (Supplemental Table S4.1). When reducing the maximum number of exposed hours per day to 18 hours (SENS 3), the RRs remained statistically significant, except for liquor consumption and nose-blowing (Supplemental Table S4.1).

The RRs of beer, wine, liquor, and all types of alcohol consumption remained <1 when the hazard period was six hours (SENS 4A), but not when it was two hours (SENS 4B; Table 4.3).

Table 4.3 Relative risks for potential trigger factors for rupture of intracranial aneurysms

	Alcohol hazard period		
Risk factor	24-hours	6-hours	2-hours
All types	0.2 (0.1-0.2)	0.2 (0.1-0.4)	0.9 (0.5-1.6)
Beer	0.2 (0.1-0.4)	0.1 (0.0-0.6)	0.1 (0.0-1.3)
Wine	0.1 (0.1-0.2)	0.4 (0.2-0.6)	1.1 (0.6-2.1)
Liquor	0.3 (0.1-0.5)	0.3 (0.1-0.9)	1.3 (0.4-4.5)

Values are relative risks and corresponding 95% confidence intervals.

Population-attributable risk

The population-attributable risks associated with trigger factors for aSAH are shown in Table 4.4. Trigger factors that contributed most to ruptures of IAs were drinking coffee (10.6%) and physical exercise (7.9%).

Table 4.4 Relative risks, prevalences, and population-attributable risks associated with trigger factors for rupture of intracranial aneurysms

Risk factor	RR (95% CI)	% of population exposed	Prevalence (%)*	PAR (%)
Coffee	1.7 (1.2-2.4)	88.1	17.5	10.6
Cola	3.4 (1.5-7.9)	42.8	1.5	3.5
Nose-blowing	2.4 (1.3-4.5)	73.7	4.1	5.4
Strain	7.3 (2.9-19)	47.3	0.6	3.6
Startling	23.3 (4.2-128)	29.2	0.1	2.7
Anger	6.3 (1.6-25)	33.5	0.2	1.3
Sexual intercourse	11.2 (5.3-24)	59.1	0.4	4.3
Physical exercise†	2.4 (1.4-4.2)	58.1	6.1	7.9

RR= relative risk; CI= confidence interval; PAR= population-attributable risk.
* Percent of the population that is exposed in any given hour.
† Metabolic equivalent of task ≥6.

DISCUSSION

Our study shows that drinking coffee or cola, nose-blowing, straining for defecation, startling, anger, sexual intercourse and vigorous to extreme physical exercise were all associated with the triggering of aneurysmal rupture. For drinking coffee, the population-attributable risk was >10%; for all other triggers it was less.

Previously, a case-crossover study on trigger factors for aSAH showed a 2.7-fold increase in the risk of aneurysmal rupture in the two hours after moderate to extreme physical exercise (metabolic equivalent of task ≥5), which is comparable with the RR of 2.4 we found.[9] However, another case-crossover study showed a 15-fold increase of aSAH in the minutes after vigorous to extreme exercise (metabolic equivalent of task ≥6).[5] The risk of rupture is possibly the highest in the first 15 minutes and subsides in time thereafter.

A case-control study found an increased risk for aSAH in the initial 3 hours after cigarette smoking (odds ratio 7.0, 95% CI 3.7-13.1).[6] We found no triggering effect of cigarette use, and neither did another case-crossover study.[9] These contradicting results are probably explained by the difference in design. First, the case-control study used control subjects from the general population, of which only 2% harbor IA and are at risk for aSAH.[2] Second, patients with aSAH have a different risk factor profile than the general population. There were twice as many subjects who smoke heavily in the aSAH population than in the control population. The higher proportion of subjects who smoke in the aSAH population three hours before aSAH compared with the control group may reflect the difference in smoking

habits between the two populations. In the case-crossover design there is no bias regarding smoking status because it compares the exposure to smoking in the hazard period with that in a control period for the same patient.

Immediately after the aSAH, patients are seriously ill and a considerable proportion never recovers. Inevitably, this has led to some limitations in our study. First, it has resulted in an interval between the aSAH and completion of the questionnaire of >2 weeks for two-thirds of the patients. The retrospective assessment, the time lapse between aSAH and completion of the questionnaire, and specifically asking for exposure in a prespecified period may have led to recall bias. Second, the inclusion of patients in a relatively good clinical condition could have led to survival bias if certain triggers affect prognosis after aSAH. However, we found no significant difference between activities from the medical records of patients who were included in our study and those who were not. Also, a previous study interviewing proxies for patients with poor outcome found no difference in risks after exposure to physical exercise or proxy-derived data.[9] For other trigger factors, this has not been investigated. A third limitation is the assumption of a 24-hour hazard period for alcohol. Many patients who reported exposure in the hazard period had a daily intake of ≥1 glass per day and therefore did not contribute to the RR in the main analysis. We analysed the effect of these patients on our primary results by using different hazard periods and found that the risks of alcohol change according to the presumed exposure time. Risks are higher soon after alcohol ingestion and decrease thereafter. A previous case-crossover study also found a decreased risk of aneurysmal rupture during the initial two hours after alcohol consumption, although this decrease was not statistically significant.[9] The effects of dosage and time lapse since alcohol intake on acute risk of aSAH remain unclear and should be further investigated.

The strengths of our study are the use of the case-crossover design (no control selection bias), the inclusion of patients with a proven aSAH (no misclassification bias), and the inclusion of patient-derived data (increasing reliability and completeness of data). The large number of included patients and consistency of the results in the sensitivity analyses support the robustness of our results.

Because blood pressure and intra-arterial pressure are directly related, an increase in blood pressure increases the transmural pressure, which is a risk factor for aneurysmal rupture.[18] Several of the factors we investigated are known to cause a short-lasting and sudden increase in blood pressure.[19-24] Our data support the view that a sudden and short-lasting increase in blood pressure caused by daily activities is a relevant pathophysiological pathway for aneurysmal rupture. Many of the trigger factors we found concern lifestyle, which may have implications for patients with an unruptured IA or aSAH patients awaiting treatment.

Reducing caffeine consumption or treating constipated patients with unruptured IAs with laxatives may lower the risk of aSAH. Although physical exercise has a triggering potential, we do not advice refraining from physical exercise because it is also an important factor in lowering the risk of other cardiovascular diseases.[25] Whether prescribing antihypertensive drugs to patients with unruptured IAs is beneficial in terms of preventing aneurysmal rupture and other cardiovascular diseases should be studied in randomised trials.

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Supplemental Table S4.1 Sensitivity analyses for relative risks associated with trigger factors for rupture of intracranial aneurysms

Risk factor	Original analysis	SENS 1	SENS 2A	SENS 2B	SENS 3
		Only y/n question on hazard period	Inconsistent data→ exposed	Inconsistent data→ not exposed	Exposed time max 18 hours
Caffeine					
Coffee	1.7 (1.2-2.4)	2.5 (1.8-3.3)	2.5 (1.9-3.4)	1.4 (1.0-2.0)	1.7 (1.2-3.1)
Cola	3.4 (1.5-7.9)	4.8 (2.3-9.9)	4.8 (2.3-9.9)	3.2 (1.4-7.4)	3.4 (1.5-7.9)
Alcohol					
All types	0.2 (0.1-0.2)	0.1 (0.1-0.2)	0.1 (0.1-0.2)	1.1 (0.9-1.4)	0.6 (0.5-0.9)
Beer	0.2 (0.1-0.4)	0.2 (0.1-0.4)	0.2 (0.1-0.4)	0.2 (0.1-0.3)	0.5 (0.3-0.8)
Wine	0.1 (0.1-0.2)	0.2 (0.1-0.3)	0.2 (0.2-0.4)	0.1 (0.1-0.2)	0.6 (0.4-0.9)
Liquor	0.3 (0.1-0.5)	0.4 (0.2-0.7)	0.4 (0.2-0.7)	0.2 (0.1-0.5)	0.5 (0.2-1.0)
Valsalva manoeuver					
Nose-blowing	2.4 (1.3-4.5)	3.4 (2.0-5.9)	3.4 (2.0-5.9)	2.3 (1.2-4.2)	1.3 (0.5-3.3)
Straining for defecation	7.3 (2.9-19)	12.3 (5.7-26)	14.5 (6.9-31)	5.7 (2.3-14)	9.5 (3.2-28)
Emotions					
Startling	23.3 (4.2-128)	35.2 (8.8-141)	35.2 (8.8-141)	23.3 (4.2-127)	14.2 (1.1-176)
Anger	6.3 (1.6-25)	18.6 (7.5-46)	18.6 (7.5-46)	4.8 (1.2-19)	8.6 (2.2-34)
Sexual intercourse	11.2 (5.3-24)	15.4 (8.1-29)	15.4 (8.1-29)	10.8 (5.2-22)	13.4 (6.0-30)
Physical exercise*	2.4 (1.4-4.2)	3.7 (2.4-5.8)	4.2 (2.8-6.4)	2.4 (1.4-4.2)	2.4 (1.4-4.2)

Values are relative risks and corresponding 95% confidence intervals.
SENS= sensitivity analysis; RR= relative risk; SENS 1: Only the yes/no question on exposure in the hazard period was used, the detailed question on last time of exposure was disregarded; SENS 2A= In case of inconsistent data on exposure in the hazard period, patients were taken to be exposed in the hazard period; SENS 2B= Identical to analysis 2A, but now inconsistent patients were taken not to be exposed in the hazard period; SENS 3= Maximum exposure time 18 hours, assuming 6 hours of sleep for each patient.
* Metabolic equivalent of task ≥6.

5

Trigger factors for rupture of intracranial aneurysms in relation to patient and aneurysm characteristics

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ABSTRACT

Background: Female gender, age above 60 years, and an aneurysm larger than 5mm or location on the posterior circulation are associated with a higher rupture risk of intracranial aneurysms. We hypothesized that this association is explained by a higher susceptibility to (one of) the eight trigger factors that were recently identified.

Methods: We included 250 patients with aneurysmal subarachnoid haemorrhage. We calculated relative risks (RR) with 95% confidence intervals (CI) of aneurysmal rupture for trigger factors according to sex, age, site and size of the aneurysms by means of the case-crossover design.

Results: None of the triggers except for physical exercise differed according to patient and aneurysm characteristics. In the hour after exposure to physical exercise: (1) patients over the age of 60 have a six-times higher risk of rupture (RR 13, 95% CI 6.3-26) than those of 60 years of age and under (RR 2.3, 95% CI 1.3-4.1); (2) aneurysms at the internal carotid artery have a higher risk than those at other locations (RR 17, 95% CI 7.8-37), but this was only statistically significant when compared to anterior communicating artery aneurysms (RR 3.2, 95% CI 1.6-6.1); (3) aneurysms ≤5 mm had a higher risk of rupture (RR 9.5, 95% CI 4.6-19) than larger aneurysms (RR 2.4, 95% CI 1.3-4.3); and (4) women and men had similar risks.

Conclusions: A higher susceptibility to exercise might explain part of the higher risk of rupture in older patients. Why women and patients with aneurysms >5 mm or posterior circulation aneurysms have a higher risk of rupture remains to be settled.

INTRODUCTION

Three percent of the general population harbours an intracranial aneurysm and the number of incidentally discovered unruptured intracranial aneurysms is rising with the increasing quality and availability of non-invasive imaging techniques.[1,2] Only a minority of aneurysms rupture, but when it happens, it is still usually a disabling or fatal occurrence.[3]

The precise pathophysiological mechanism of aneurysmal rupture is not completely understood. It is important to identify risk factors for aneurysmal rupture in order to tailor treament of intracranial aneurysms. Female gender and an age above 60 years are factors associated with an increased risk of rupture, as are an aneurysm size of more than 5 mm and location of the aneurysm on the posterior circulation.[4] However, the reason why the risk of rupture is higher in females, patients over 60 years of age, and patients with a large aneurysm or one located at the posterior circulation, is still poorly understood.[4]

We recently identified eight trigger factors for aneurysmal rupture, namely coffee and cola consumption, physical exercise, nose-blowing, straining for defecation, sexual intercourse, anger, and startling.[5] We hypothesized that a different susceptibility to trigger factors could explain the difference in risk of rupture between patients of different sex and age and between aneurysms of different sites and sizes. We therefore assessed the risk of aneurysmal rupture by eight confirmed trigger factors according to sex and age of the patients and according to site and size of the aneurysm.

METHODS

Design and study population

The design of this study is described elsewhere.[5] In short, we performed a case-crossover study among patients who had been admitted to the Utrecht Stroke Center for aneurysmal subarachnoid haemorrhage (aSAH). aSAH was defined as an abrupt onset of severe headache or loss of consciousness, with or without focal neurological signs, with subarachnoid blood proven by neuro-imaging or lumbar puncture, and a radiologically proven aneurysm. The study protocol was approved by the medico-ethical review committee of our hospital.

Procedures

The case-crossover design enables studying the effect of transient exposure to potential trigger factors on the risk of an acute event, such as aSAH, by comparing exposure in a

period shortly before the event with the patient's usual frequency of exposure.[6] In the present study we included as determinants only those factors that were found to be trigger factors in our previous case-crossover study.[5] For these triggers, we had collected information on exposure in the past year, the usual frequency of exposure, and the presence of exposure in the 'hazard period', which we defined as the hour before SAH, according to the estimated duration of effect of each trigger.

For each patient, we collected data on sex and age, as well as on site and size of the ruptured aneurysm. Age was categorised as 60 years or younger or as above 60 years, because in a previous review risk of rupture increased above this age limit.[4] Site was categorised as follows: anterior cerebral artery, anterior communicating artery, and pericallosal artery combined (ACA), internal carotid artery, posterior communicating artery, ophthalmic artery and anterior choroidal artery combined (ICA), middle cerebral artery (MCA), and vertebrobasilar arteries (VBA). In addition, we also combined the ACA, ICA, and MCA into an anterior circulation (ANT) group. Sizes were categorised as ≤5 mm, 5.1-10 mm and >10 mm based on the largest diameter of the aneurysm.

Data analysis

With the case-crossover design, exposure to potential trigger factors in the hour before onset of SAH (hazard period) was compared with the usual frequency over the year before the SAH and was expressed as relative risk (RR) with corresponding 95% confidence intervals (CI).[7]

This analysis was done for men and women, patients over 60 years and those of 60 years of age and under, and also for each site and size category. RRs with 95% CIs of different age, gender, site, and size categories were compared between categories to assess whether they overlapped. We also performed analyses with site and size categories combined.

RESULTS

We included 250 patients (62 men and 188 women) with aSAH. The mean age was 54.7 years (55.7 years for men, 54.3 years for women). Nineteen men and 63 women were over 60 years old.

Of the 250 ruptured aneurysms 150 (60.0%) were >5 mm and 24 (9.6%) were >10 mm. Aneurysms were located in the ACA in 41.6%, MCA 20.0%, ICA 28.0% and in the VBA in 10.4% (Table 5.1).

Table 5.1 Site and size of 250 ruptured aneurysms in 250 included patients

	Size	
Location	≤5 mm (n=100)	>5 mm (n=150)
ACA	52	52
ICA	26	44
MCA	17	33
VBA	5	21

ACA= anterior communicating artery, anterior cerebral artery, and pericallosal artery combined; ICA= internal carotid artery, posterior communicating artery, ophthalmic artery, and anterior choroidal artery combined; MCA= middle cerebral artery; VBA= vertebrobasilar arteries.

Sex

Data on trigger factors according to sex are given in Table 5.2. We found no statistically significant difference between men and women for any of the trigger factors.

Age

Data on trigger factors according to age are given in Table 5.2. Patients above 60 years have a significantly higher risk of rupture after physical exercise than patients of 60 years

Table 5.2 Relative risks for eight trigger factors according to sex and age

	Sex		Age	
Trigger factor	Men (n=62)	Women (n=188)	≤60 years (n=168)	>60 years (n=82)
Coffee	2.2 (1.3-3.8)	2.7 (1.9-3.9)	2.5 (1.7-3.6)	2.6 (1.5-4.5)
Cola	3.6 (0.9-13.9)	5.5 (2.3-13)	4.7 (2.2-10)	6.0 (0.9-40)
Nose-blowing	2.1 (0.6-7.1)	4.1 (2.3-7.5)	3.4 (1.8-6.4)	3.5 (1.3-9.7)
Straining for defecation	7.4 (1.8-30)	15.3 (6.1-39)	8.9 (3.3-24)	23 (6.7-79)
Startling	NP	40 (10-165)	41 (6.1-276)	28 (3.9-194)
Anger	14 (3.5-56)	22 (6.6-76)	20 (7.2-56)	13 (1.8-103)
Sexual intercourse	28 (11-71)	10 (3.9-25)	17 (8.7-34)	7.7 (1.03-56)
Physical exercise	1.9 (0.9-4.2)	6.2 (3.6-11)	2.3 (1.3-4.1)	13 (6.3-26)

Values are relative risks and corresponding 95% confidence intervals.
NP= No patients in this category; therefore no RR could be calculated; Exercise= vigorous to extreme physical exercise (MET >6).

or younger. A similar pattern was observed after stratification for usual frequency of exercise into <3 vs. ≥3 times per week. For all other trigger factors, there was no statistically significant difference.

Site

For all trigger factors, the RR was not statistically different between site categories, except for physical exercise (Table 5.3). The risk of rupture after exposure to physical exercise was higher for aneurysms located on the ICA compared to those on the ACA, but not for those on the MCA. None of the ruptures of ICA aneurysms were triggered by startling and none of the VBA aneurysms were triggered by physical exercise or anger. When relative risks of ANT aneurysms were compared to the VBA aneurysms 95% CI overlapped for all trigger factors.

Size

Initially, sizes were categorised as ≤5 mm, 5.1-10 mm, and >10 mm, based on the largest diameter of the aneurysm. However, due to the small number of aneurysms >10 mm in

Table 5.3 Relative risks for trigger factors according to aneurysm site

Trigger factor	Site ruptured aneurysm				
	ACA (n=104)	ICA (n=70)	MCA (n=50)	ANT (n=224)	VBA (n=26)
Coffee	2.7 (1.7-4.2)	3.9 (2.0-7.6)	1.7(0.9-3.3)	2.6 (1.9-3.6)	1.9 (0.8-4.5)
Cola	19 (4.9-72)	2.1 (0.3-14)	3.5 (0.9-14)	5.7 (2.6-12.6)	2.0 (0.3-13.2)
Nose-blowing	2.3 (0.9-5.8)	6.6 (2.2-18)	6.2 (2.2-18)	3.8 (2.2-6.9)	1.9 (0.4-8.5)
Straining for defecation	13 (4.6-39)	6.5 (0.8-54)	8.6 (0.9-87)	11 (4.5-26)	23 (5.3-98)
Startling	40 (1.5-1098)	NP	46 (6.3-339)	29 (5.0-173)	57 (8.1-406)
Anger	20 (4.8-88)	38 (7.2-196)	7.9 (1.2-53)	20 (7.8-48)	NP
Sexual intercourse	20 (7.5-52)	11 (2.5-48)	4.7 (0.7-34)	12 (5.9-25)	47 (11-203)
Exercise	3.2 (1.6-6.1)	17 (7.8-37)	3.2 (0.8-12.8)	5.1 (3.3-8.1)	NP

Values are relative risks and corresponding 95% confidence intervals.
ACA= anterior communicating artery, anterior cerebral artery, and pericallosal artery combined, ICA= internal carotid artery, posterior communicating artery, ophthalmic artery, and anterior choroidal artery combined, MCA= middle cerebral artery, ANT= anterior circulation (combining ACA, MCA and ICA), VBA= vertebrobasilar arteries, NP= No patients in this category; therefore no RR could be calculated, Exercise vigorous to extreme physical exercise (MET >6).

our study, the 95% CI overlapped with the other categories (data not shown). Therefore, we dichotomised size as ≤5 mm and >5 mm.

The risk of rupture in the hour after physical exercise was higher for aneurysms ≤5 mm compared to aneurysms >5 mm. For all other trigger factors, the risk of rupture did not statistically significantly differ between size categories (Table 5.4). We did an additional analysis for ACA aneurysms of ≤5 mm and >5 mm, since ACA was the most common site of aneurysms. The RR of ACA aneurysms ≤5 mm was 17 (7.2-39), but 0.5 (0.1-2.9) for ACA aneurysms >5 mm.

Table 5.4 Relative risks for trigger factors according to aneurysm size

Trigger factor	Aneurysm size	
	≤5 mm (n=100)	>5 mm (n=150)
Coffee	2.2 (1.3-3.9)	2.7 (1.9-4.0)
Cola	9.8 (2.4-41)	3.7 (1.6-8.8)
Nose-blowing	3.6 (1.4-9.0)	3.4 (1.8-6.5)
Straining for defecation	20 (7.5-52)	5.4 (1.3-22)
Startling	59 (7.3-479)	20 (2.8-139)
Anger	9.0 (1.3-63)	23.8 (8.3-69)
Sexual	15 (5.0-45)	15.7 (7.1-35)
Exercise	9.5 (4.6-19)	2.4 (1.3-4.3)

Values are relative risks and corresponding 95% confidence intervals.
Exercise= vigorous to extreme physical exercise (MET >6).

DISCUSSION

We found that patients over the age of 60 have a higher risk of aneurysmal rupture in the hour after exposure to physical exercise than patients under the age of 60. No difference in trigger factors was found between women and men. We also did not find an increased susceptibility for trigger factors for aneurysms located at the posterior circulation or for aneurysms >5 mm in size. In contrast, our results suggest a higher risk of rupture for aneurysms ≤5 mm after exposure to physical exercise, in particular when located at the ACA.

A review on risk factors for rupture of intracranial aneurysms showed a higher risk for women and patients above the age of 60.[4] We found a higher risk of rupture after physical

exercise for patients above 60, which may partly explain the higher rupture rate in older patients. When interpreting the risk increase of exercise among the elderly, one should realise nevertheless that they exercise less frequently than younger persons. There are few studies on cerebrovascular response to exercise in elderly people.[8-10] One of these studies reported a delay in cerebral autoregulation in older persons compared to younger persons.[9,10] Since exercise causes a rise in systemic blood pressure, a delayed cerebral autoregulation may lead to an initial short-lasting increase in mean cerebral blood flow velocity. However, not all studies agree on differences in cerebral autoregulation between younger and older persons, therefore our hypothesis remains a speculative one.[8,9]

The risk of rupture of ICA aneurysms after exposure to vigorous physical exercise seems higher compared to that of ACA aneurysms. Possibly, the arterial blood pressure is transmitted more directly to the most proximal cerebral vessels, such as the ICA and BA, which in turn may lead to a higher rupture rate for aneurysms at the ICA and BA. However, no data are available comparing blood flow in different cerebral vessels during exercise.

We found a higher risk of rupture after exposure to physical exercise for aneurysms sized ≤5 mm compared to aneurysms >5 mm, which was mainly due to a very high risk for small ACA aneurysms. Others have already suggested that ACA aneurysms might be unstable and rupture at a small size, while those that reach a larger size are a selection of more stable aneurysms.[11,12] Our findings support this theory and may partly explain the high number of small ACA aneurysms in SAH studies, while ACA aneurysms are less prevalent in studies on unruptured aneurysms.[4] However, since our analysis on size and site combined was an additional analysis on a smaller group of aneurysms, this may also be a chance finding. Only two earlier reports have been published on trigger factors for SAH, but they did not differentiate according to site and size.[13,14] Hence, we cannot further compare our results with those in the literature.

The present study includes information on trigger factors from 250 patients, which may be considered as a strong point given the severity of the illness. The use of the case-crossover design (no control selection bias) and the inclusion of patient-derived data only (increasing reliability and completeness of data) are other strengths of our study. However, the present study also has some limitations. Of the 250 included patients, only 10% had an aneurysm in the VBA, which makes it difficult (and for anger and physical exercise even impossible) to compare rupture risks to other sites. Another limitation is that multiple testing and subgroup analyses on smaller numbers of aneurysms may have led to chance findings.

If our data on higher susceptibility to physical exercise as a trigger factor for older patients and patients with small ACA aneurysms are confirmed by others, the next step would be to

further study the haemodynamics in intracranial vessels after exercise in these subgroups. Furthermore, trigger factors should be studied in Finnish and Japanese patients, since aneurysms in these populations have a higher risk of rupture.[4] This might reveal a different susceptibility to trigger factors per site and size and could even yield new trigger factors. The higher rupture rates in women and the predisposition for rupture of aneurysms >5 mm and aneurysms located at the posterior circulation can so far not be explained by a difference in susceptibility to trigger factors and remain to be unravelled.

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6

Independent risk factors for intracranial aneurysms and their joint effect: a case-control study

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ABSTRACT

Background: Three percent of the population has an unruptured intracranial aneurysm (UIA). We aimed to identify independent risk factors from life style and medical history for the presence of UIAs and to investigate the combined effect of well-established risk factors.

Methods: We studied 206 patients with an UIA who never suffered a subarachnoid haemorrhage and 574 controls who were randomly retrieved from GP files. All participants filled in a questionnaire on potential risk factors for UIAs. With logistic regression analysis we identified independent risk factors for UIA and assessed their combined effect.

Results: Independent risk factors were current smoking (odds ratio [OR] 3.0, 95% confidence interval [CI] 2.0-4.5), hypertension (OR 2.9, 95% CI 1.9-4.6), family history of stroke other than SAH (OR 1.6, 95% CI 1.0-2.5), hypercholesterolaemia (OR 0.5, 95% CI 0.3-0.9) and regular physical exercise (OR 0.6, 95% CI 0.3-0.9). The joint risk of smoking and hypertension was higher (OR 8.3, 95% CI 4.5-15.2) than the sum of the risks independently.

Conclusions: Current smoking, hypertension and family history of stroke increase the risk of UIA, with smoking and hypertension having an additive effect, whereas hypercholesterolaemia and regular physical exercise decrease this risk. A healthy life style probably reduces the risk of UIA and thereby possibly also that of aneurysmal subarachnoid haemorrhage (aSAH). Whether smoking and hypertension increase the risk of aSAH only through an increased risk of aneurysm formation or also through an increased risk of rupture remains to be established.

INTRODUCTION

Three percent of the general population harbours an unruptured intracranial aneurysm (UIA).[1] Reducing the risk of developing UIAs is an important method for reducing the incidence of aneurysmal subarachnoid haemorrhage (aSAH), which has remained relatively stable over the last decades.[2]

Female sex, a positive family history for aSAH or UIA, and polycystic kidney disease are non-modifiable risk factors for UIAs.[1] Hypertension and smoking are well established modifiable risk factors. Data on other modifiable risk factors such as hypercholesterolaemia, ischaemic heart disease, diabetes, low body mass index and excessive alcohol use as independent risk factors are limited and sometimes conflicting.[3-5] Also, the joint effect of these risk factors is unknown.

The aim of the current study was to identify risk factors for UIAs from life style and medical history data in a Caucasian population and to study the joint effect of well-established risk factors.

METHODS

Study population

Between September 2006 and September 2009, we included 206 patients who were known at the Utrecht Stroke Center of the University Medical Center Utrecht for having an UIA. Eligible were patients who had an UIA, who never had an aSAH, were 18 years or older and spoke Dutch. The UIA had to be confirmed by CT angiography, MR angiography or conventional angiography. The study protocol was approved by the medico-ethical review committee of our hospital. Between January 2009 and January 2010, 574 controls were recruited from 5 different general practices in the catchment area of the Utrecht Stroke Center.[6]

Data collection

All patients and controls were asked to fill in a structured questionnaire. We collected data on demographics (age, sex), height, weight, smoking, use of alcohol, physical exercise, medical history (diabetes mellitus, heart disease, hypertension, hypercholesterolaemia, migraine) and family history of stroke (aSAH or other).[6] Obesity was defined as a body mass index (BMI) ≥30 according to the World Health Organization classification.[7] Smoking was defined as smoking at time of diagnosis of the UIA (patients) or at time of

the interview (controls). Excessive alcohol use was defined as ≥18 units (i.e. ≥150 grams) per week.[8] Regular physical activity was defined as vigorous physical exercise (metabolic equivalent of task ≥6) >3 times a week.[9] For history of heart disease we included those persons who had had a myocardial infarction, angina pectoris, coronary artery bypass grafting and percutaneous transluminal coronary arterioplasty. In UIA patients diagnoses of diabetes, hypertension, heart disease and hypercholesterolaemia were checked against medical records to confirm that the diagnosis was made prior to discovery of the UIA. Family history was based on the information from the questionnaire. In cases, we collected data on the indication for imaging from the medical records of the UIA patients and predefined 5 categories: 1) atherosclerotic disease (including TIA and stroke, but not aSAH), 2) positive family history for UIA or aSAH, 3) headache, 4) screening without obvious medical indication, and 5) other.

Statistical analysis

All variables listed in Table 6.1 were assessed as possible risk factors. The controls we used for the current study had also served as controls in a previous case-control study for which they had been matched for sex and age with a cohort of aSAH patients.[10] Because the age and sex distribution of patients with aSAH and patients with UIAs did not differ to a large extent, the controls were approximately matched for sex and age with the group of UIA patients as well. For this reason, we were unable to study age and sex as risk factors for UIAs. Because a family history of aSAH or UIA or a history of (transient) cerebral ischaemia was often the reason for detecting the aneurysm we also decided not to study these factors because of the high likelihood of selection bias.

Univariable analyses were performed to calculate crude odds ratios (OR) with 95% confidence intervals (CI). Subsequently, we performed a multivariable backward stepwise logistic regression analysis to identify independent risk factors. Risk factors with p-value under 0.05 were considered statistically significant.

Because many patients with an UIA had imaging because of atherosclerotic disease we did two sensitivity analyses to investigate the role of selection bias. First we did an analysis excluding UIA patients who were investigated for atherosclerotic disease. Second, we did an analysis excluding all UIA patients and controls with a history of stroke.

In an additional logistic regression analysis, we assessed the joint effect of smoking and hypertension, which are the most established risk factors of UIAs.

Table 6.1 Characteristics of the 206 patients with UIA and 574 population based controls

Characteristic	Patients with UIA (n=206)	Controls (n=574)
Men, n (%)	68 (33.0)	177 (30.8)
Mean age, years	54.6	54.8
Alcohol use, n (%)	173 (84.0)*	475 (83.2)*
Alcohol ≥18 units/week, n (%)	26 (12.6)*	67 (11.7)*
Smoking, n (%)	96 (46.8)*	138 (24.1)*
Body mass index ≥30, n (%)	32 (15.8)*	72 (12.9)*
Vigorous exercise ≥3 times/week, n (%)	35 (17.2)*	147 (25.7)*
Medical history, n (%)		
Hypertension	77 (38.1)	104 (19.0)*
Hypercholesterolaemia	26 (14.4)‡	76 (14.9)‡
Diabetes	9 (4.4)*	26 (4.6)*
Atrial fibrillation	5 (2.6)*	10 (1.8)*
Heart disease	12 (6.0)*	37(6.7)*
Migraine	14 (7.0)*	62 (11.1)*
Family history		
Stroke, n (%)§	62 (32.5)	127 (22.7)*
Myocardial infarction, n (%)	22 (11.4)†	40 (7.2)*

* <5% missing data.
† 5-10% missing data.
‡ 10-15% missing data.
§ Including ischaemic and haemorrhagic stroke, but excluding subarachnoid haemorrhage.

RESULTS

Study population

The baseline demographic data and risk factor data of cases and controls are summarised in Table 6.1. Reasons for imaging in UIA patients were atherosclerotic disease (23%), positive family history for UIA or aSAH (18%), headache (8%), screening without obvious medical indication (3%), and other (46%).

Risk factors for UIAs

Current smoking, hypertension and family history of stroke all independently increased the risk of UIAs; hypercholesterolaemia and regular physical exercise independently decreased the risk of UIAs (Table 6.2).

Current smoking and history of hypertension were the strongest independent risk factors (Table 6.2). In the sensitivity analysis excluding UIA patients who were investigated for atherosclerotic disease and in the sensitivity analysis excluding all UIA patients and controls with a history of stroke, we found that point estimates for smoking, a history of hypertension or hypercholesterolaemia remained essentially the same, although the OR for hypercholesterolaemia was no longer statistically significant because of wider confidence intervals attributable to the smaller sample size (Supplemental Table S6.1).

The joint risk of smoking and hypertension (OR 8.3, 95% CI 4.5-15.2) was higher than the sum of the individual risks for smoking (OR 3.0, 95% CI 2.0-4.4) and hypertension (OR 2.9, 95% CI 1.9-4.6) (Table 6.3).

Table 6.2 Risk factors for intracranial aneurysms

	Univariable analysis (n=780)	Multivariable analysis (n=615)
Alcohol ≥18 units/week, n(%)	1.1 (0.7-1.8)	-
Smoking	2.8 (2.0-3.9)	3.0 (2.0-4.5)
Body mass index ≥30	1.3 (0.8-2.0)	-
Vigorous exercise ≥3 times/week	0.6 (0.4-0.9)	0.6 (0.3-0.9)
Medical history		
Hypertension	2.6 (1.8-3.7)	2.9 (1.9-4.6)
Hypercholesterolaemia	1.0 (0.6-1.6)	0.5 (0.3-0.9)
Diabetes	0.9 (0.4-2.1)	-
Atrial fibrillation	1.4 (0.5-4.2)	-
Heart disease	0.9 (0.5-1.7)	-
Migraine	0.6 (0.3-1.1)	-
Family history		
Stroke*	1.6 (1.1-2.4)	1.6 (1.0-2.5)
Myocardial infarction	1.7 (1.0-2.9)	-

Values are odds ratios with corresponding 95% confidence intervals. - = not statistically significant in multivariable analysis

Table 6.3 Interaction between smoking and hypertension for the risk of intracranial aneurysms

	Patients with UIA (n=206)	Controls (n=574)	OR (95% CI)
No smoking, no hypertension	65	353	Ref
Smoking, no hypertension	64	117	3.0 (2.0-4.4)
Hypertension, no smoking	45	83	2.9 (1.9-4.6)
Smoking and hypertension	32	21	8.3 (4.5-15.2)

DISCUSSION

Current smoking, hypertension and family history of stroke other than aSAH, increase the risk of UIA, whereas hypercholesterolaemia and regular physical exercise decrease this risk. Smoking and hypertension combined yielded a higher risk increase than expected on basis of the individual components.

Other studies also found smoking and hypertension to be strong and independent risk factors for UIAs[3-5,11,12] The novel finding that smoking and hypertension have an additive effect suggests a synergism between these two prominent risk factors in the development of UIAs.

A family history of aSAH or UIA was the primary reason for imaging in one-fifth of the UIA patients; therefore, we could not study this factor. Although we found that a family history of stroke other than aSAH also increases the risk for UIAs, these data should be interpreted with caution. Family members are known to have difficulty differentiating between ischaemic stroke, intracerebral haemorrhage and aSAH; therefore, the association with family history of stroke might be due to misclassification.[13] We could not compare our findings on family history of stroke with other studies, because we did not find reports on this issue.

Our data on hypercholesterolaemia are somewhat in contrast to previous data. Japanese investigators reported that hypercholesterolaemia increases the risk of UIAs, whereas a Chinese study found no effect.[3,4] Our data show that hypercholesterolaemia decreases the risk of UIAs, which is more plausible, because it also decreases the risk of aSAH, at least in our European population.[8,10] The differences in findings between our study and previous studies may be explained by the difference in populations (Caucasians versus Asians), the difference in controls (randomly retrieved from the general population in our study versus hospital-based controls in others), and the different methods used for data acquisition (questionnaire combined with medical records in our study versus review of medical records only in others). Our results on hypercholesterolaemia may also be explained by the use of statins, since a recent animal study has shown an association between statins and reduction of UIA formation.[14] However, a recent study in humans found no significant beneficial effect on UIA development.[5] Due to the small number of cases and controls using statins we were not able to study the role of statins in our population.

Physical exercise decreased the risk of UIAs in our study. We could not find other studies reporting on physical exercise as an independent risk factor for UIAs. Previous research on risk factors for aSAH has shown a trend towards a decrease in risk with regular exercise,[8,10] but two case-crossover studies have also shown that in the acute phase physical exercise can

trigger the rupture of an intracranial aneurysm.[6,15] However, the population attributable risk of physical exercise as a trigger factor is small and exercise also has a beneficial effect on other cardiovascular diseases. Therefore, we still advise patients at risk for UIAs and aSAH to engage in regular physical exercise.[6,15,16]

Selection bias is a potential limitation of our study, which may have influenced our results. First, we were unable to study family history of aSAH or history of stroke as risk factors, since this was the reason for imaging in many patients with UIAs and therefore influenced by selection bias. Second, in our multivariable analysis only hypertension and smoking were statistically significant risk factors associated with an increased risk of UIA development. Since smoking and hypertension are risk factors for atherosclerosis and many patients with an UIA had cerebral imaging because of atherosclerotic disease, we considered the possibility that the results on smoking and hypertension had been influenced by selection bias. In multivariable analysis only hypertension and smoking were statistically significant atherosclerotic risk factors associated with an increased risk. To study the possible effect of selection bias on our results for smoking and hypercholesterolaemia, we did two sensitivity analyses excluding patients screened for atherosclerotic disease or with a history of stroke, and found that point estimates for smoking hypercholesterolaemia remained virtually the same. Third, the risk of smoking could be somewhat underestimated, because former smokers were classified as non-smokers.

Our study has several strong points. First, since both patients with UIAs and controls came from the same catchment area, we were able to study risk factors for aneurysmal rupture in a rather defined population. Second, we only selected UIA patients without a history of aSAH. Thirdly, we had access to individual patient data that allowed multivariable analysis including a large number of potential risk factors and allowed us to study the interaction between the two most well established risk factors.

Current smoking and hypertension increase the risk of UIA and have combined a higher risk than the sum of the separate risks. Smoking and hypertension are also important risk factors for subarachnoid haemorrhage. Whether the increased risk for aSAH from smoking and hypertension is only caused by an increased risk for UIA or also by an increased risk of rupture of an already existing UIA should be investigated in future studies. Improving life style by not smoking, treating hypertension and regular exercise, probably reduces the risk of UIA and maybe also that of aSAH. Why hypercholesterolaemia, on one hand, is associated with an increased risk of atherosclerotic diseases and, on the contrary, with a decreased risk of UIAs, should be further investigated. If the risk decreasing effect of hypercholesterolaemia is mediated by statin use, statins might be an additional treatment option for decreasing the prevalence of UIAs and thereby the incidence of aSAH.

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Supplemental Table S6.1 Sensitivity analyses on atherosclerosis

Risk factor	SENS 1		SENS 2	
	Univariable analysis	Multivariable analysis	Univariable analysis	Multivariable analysis
Smoking	2.4 (1.7-3.5)	2.8 (1.6-4.0)	2.2 (1.5-3.2)	2.2 (1.4-3.5)
Hypercholesterolaemia	0.7 (0.4-1.2)	0.4 (0.2-0.9)	0.6 (0.3-1.2)	0.4 (0.2-0.8)
Hypertension	2.4 (1.6-3.6)	2.8 (1.7-4.6)	2.6 (1.7-4.0)	2.8 (1.7-4.7)
Family history of stroke	1.6 (1.1-2.3)	-	1.8 (1.2-2.7)	2.0 (1.2-3.2)
Physical exercise	0.6 (0.4-0.9)	0.5 (0.3-0.8)	0.6 (0.4-0.9)	0.5 (0.3-0.9)

Values are odds ratios and corresponding 95% confidence intervals.
SENS 1= Analysis excluding patients with an unruptured intracranial aneurysm who were screened for atherosclerosis; SENS 2= Analysis excluding all patients with an unruptured intracranial aneurysm or aneurysmal subarachnoid haemorrhage with a history of stroke.

7

Risk of rupture of an intracranial aneurysm based on patient characteristics: a case-control study

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ABSTRACT

Background: Knowledge about risk factors contributes to understanding the pathophysiological mechanisms that cause intracranial aneurysm rupture and helps to develop possible treatment strategies. We aimed to study life style and personal characteristics as risk factors for the rupture of intracranial aneurysms.

Methods: We performed a case-control study with 250 patients with an aneurysmal subarachnoid haemorrhage (aSAH) and 206 patients with an unruptured intracranial aneurysm (UIA). All patients with an aSAH and patients with an UIA were asked to fill in a structured questionnaire about their life style and medical history. For patients with an UIA we also collected data on the indication for imaging. With logistic regression analysis we identified independent risk factors for aneurysmal rupture.

Results: Reason for imaging in patients with an UIA were atherosclerotic disease (23%), positive family history (18%), headache (8%), preventive screening (3%), and other (46%). Factors that increased risk for aneurysmal rupture were smoking (odds ratio [OR] 1.9, 95% confidence interval [CI] 1.2-3.0) and migraine (OR 2.4, 95% CI 1.1-5.1); hypercholesterolaemia decreased this risk (OR 0.4, 95% CI 0.2-1.0), whereas a history of hypertension did not independently influence the risk.

Conclusions: Smoking, migraine and, inversely, hypercholesterolaemia are independent risk factors for aneurysmal rupture. Data from the questionnaire are insufficient to conclude whether the hypercholesterolaemia or its treatment with statins exert a risk reducing effect. The pathophysiological mechanisms through which smoking and migraine increase the risk of aneurysmal rupture should be investigated in further studies. Although a history of hypertension does not increase risk of rupture, a sudden rise in blood pressure might still trigger aneurysmal rupture.

INTRODUCTION

Three percent of the general population harbours an unruptured intracranial aneurysm (UIA).[1] Reducing the risk of rupture of an UIA is an important method for reducing the incidence of aneurysmal subarachnoid haemorrhage (aSAH), which has remained relatively stable over the last decades.[2]

Little is known about modifiable patient characteristics as risk factors for aneurysmal rupture. Smoking is a risk factor in many, but not all studies.[3-7] Data on hypertension remain even more controversial[3,5-9] and only few studies report on other risk factors, such as alcohol, diabetes and hypercholesterolaemia.[6-8]

Knowledge about risk factors for aneurysmal rupture contributes to understanding the pathophysiological mechanisms that cause aneurysm rupture and helps to develop possible treatment strategies other than invasive interventions to reduce this risk. We compared the characteristics of patients with an UIA and patients with an aSAH to study data on life style, clinical condition and family history as risk factors for the rupture of UIAs.

METHODS

Study population

Between September 2006 and September 2009 we included 250 consecutive patients who were admitted for aSAH at the Utrecht Stroke Center of the University Medical Center Utrecht in a case-crossover study.[10] Patients were eligible if they were 18 years or older and spoke Dutch or English or had a proxy who did so. Informed consent was given by either the patient or the proxy. aSAH was defined as an abrupt onset of severe headache or loss of consciousness with or without focal neurological signs and subarachnoid blood proven by CT or lumbar puncture, and an aneurysm proven with CT angiography, MR angiography or conventional angiography. The patients included a previous case-crossover study now served as cases in the current case-control study.[10]

As comparison group, we included 206 patients with an UIA from the same catchment area, who were treated at or referred to the Utrecht Stroke Center. Eligible were patients who had an UIA, who never had an aSAH, and were 18 years or older. The unruptured IA had to be confirmed by CT angiography, MR angiography or conventional angiography. The study protocol was approved by the medico-ethical review committee of our hospital.

Data collection

All patients with an aSAH and patients with an UIA were asked to fill in a structured questionnaire about their life style, clinical condition and family history prior to their aSAH or the discovery of their UIA. We collected data on demographics (age, sex), height and weight, medical history (diabetes mellitus, heart disease, hypertension, hypercholesterolaemia, migraine), smoking, use of alcohol and physical exercise.[10] We also asked for family history of stroke (other than aSAH). We excluded aSAH in family history of stroke, since this was often a reason for screening in patients with an UIA and therefore might lead to selection bias. Smoking was defined as smoking at time of aSAH or diagnosis of the UIA. Heart disease included myocardial infarction, angina pectoris, coronary artery bypass grafting and percutaneous transluminal coronary arterioplasty. Diagnoses of diabetes, hypertension, heart disease and hypercholesterolaemia were checked against medical records to confirm that the diagnosis was made prior to discovery of the UIA or aSAH. Family history was based on the information from the questionnaire. Excessive alcohol use was defined as ≥18 units (i.e. ≥150 grams) per week.[11] Lean body mass was defined as a body mass index (BMI) <22. Regular physical activity was defined as vigorous physical exercise (metabolic equivalent >6) more than three times a week.[12]

For patients with an UIA we also collected data on the indication for imaging from their medical records and predefined five categories: atherosclerotic disease (including transient ischaemic attack and stroke), positive family history for UIA or aSAH, any type of headache, preventive screening without medical reasons, and other.

Statistical analysis

All variables listed in Table 7.1 were assessed as possible risk factors. Univariable analysis was performed to calculate crude odds ratios (OR) with 95% confidence intervals (CI). Subsequently, we performed a multivariable backward stepwise logistic regression analysis to identify independent risk factors for rupture. Risk factors with p-value under 0.05 were considered statistically significant. Only family history of aSAH and a medical history of stroke were not used for multivariable analysis, because this was often the reason for screening and therefore may cause selection bias.

The initial analysis for migraine was based on self report on the questionnaire. We did a sensitivity analysis including only patients of whom migraine was documented as such in the medical records.

Because many patients with an UIA had imaging because of atherosclerotic disease, we performed two additional sensitivity analyses to investigate the role of selection bias. First

Table 7.1 Characteristics of the 250 patients with a ruptured aneurysm and 206 patients with an unruptured intracranial aneurysm

Characteristic	Ruptured (n=250)	Unruptured (n=206)
Men, n (%)	62 (24.8)	68 (33.0)
Mean age, y (sd)	54.7 (12.5)	54.6 (11.6)
Smoking, n (%)	155 (62.0)	96 (46.8)*
Alcohol use, n (%)	197 (79.1)*	173 (84.0)*
Alcohol ≥18 units/week, n (%)	42 (16.9)*	26 (12.8)*
Body mass index <22, n (%)	62 (26.3)†	44 (22.6)*
Vigorous exercise ≥3 times/week, n (%)	35 (17.2)*	43 (17.5)*
Medical history		
Stroke, n (%)	24 (12.2)*	54 (21.9)*
Hypertension, n (%)	61 (24.6)*	77 (38.1)*
Hypercholesterolaemia, n (%)	13 (5.4)*	26 (14.4)‡
Diabetes, n (%)	6 (2.4)	9 (4.4)*
Atrial fibrillation, n (%)	7 (2.8)*	5 (2.6)*
Heart disease, n (%)	15 (6.0)	12 (6.0)*
Migraine, n (%)	39 (17.2)*	14 (7.0)*
In medical record	21 (9.3)	5 (2.5)
Family history		
aSAH, n (%)	53 (22.5)†	56 (28.4)*
Stroke, n (%)§	70 (30.9)†	62 (32.5)†
Myocardial infarction, n (%)	26 (11.6)†	22 (11.4)†
Time diagnosis to questionnaire (mean, weeks)	6	303

sd= standard deviation; aSAH= aneurysmal subarachnoid haemorrhage.
* <5% missing data.
† 5-10% missing data.
‡ 10-15% missing data
§ Including ischaemic and haemorrhagic stroke, but excluding subarachnoid haemorrhage.

we did an analysis excluding patients with an UIA who were screened for atherosclerosis. Second, we did an analysis excluding all patients with an UIA or aSAH with a history of stroke.

RESULTS

Study population

The baseline characteristics of patients with an aSAH and patients with an UIA are summarised in Table 7.1. Reasons for imaging in patients with an UIA were atherosclerotic disease (23%), positive family history (18%), headache (8%), preventive screening (3%), and other (46%).

Risk factors for rupture

In the univariable analysis we found an increased risk of aneurysm rupture with smoking and a history of migraine and a decreased risk with hypercholesterolaemia, hypertension, diabetes and a history of heart disease. Only current smoking (OR 1.9, 95% CI 1.2-3.0), hypercholesterolaemia (OR 0.4, 95% CI 0.2-1.0), and history of migraine (OR 2.4, 95% CI 1.1-5.1) were independent risk factors (Table 7.2). Family history of aSAH also decreased the risk of aSAH in univariable analysis, but this factor was not considered in multivariable analysis, since it was often the indication for imaging.

In the sensitivity analysis on migraine as documented in the medical records, the OR of migraine in univariable analysis was 3.7 (95% CI 1.7-10). In multivariable analysis migraine was no longer an independent risk factor.

Table 7.2 Risk factors for rupture of an intracranial aneurysm

	Univariable analysis (n=456)	Multivariable analysis (n=317)
Men	0.67 (0.45-1.01)	-
Age (per year)	1.00 (0.99-1.02)	-
Smoking	1.8 (1.2-2.6)	1.9 (1.2-3.0)
Alcohol ≥18 units/week	1.3 (0.8-2.4)	-
Body mass index <22	1.2 (0.8-2.9)	-
Vigorous exercise ≥3 times/week	1.0 (0.6-1.7)	-
Medical history		
Stroke	0.3 (0.2-0.5)	NC
Hypertension	0.5 (0.3-0.8)	-
Hypercholesterolaemia	0.3 (0.1-0.5)	0.4 (0.2-1.0)
Diabetes	0.3 (0.1-0.7)	-
Atrial fibrillation	1.1 (0.3-3.6)	-
Heart disease	0.5 (0.2-0.9)	-
Migraine	2.7 (1.4-5.2)	2.4 (1.1-5.1)
Family history		
aSAH	0.7 (0.5-1.1)	NC
Stroke*	0.9 (0.6-1.4)	-
Myocardial infarction	1.0 (0.6-1.9)	-

Values are odds ratios and corresponding 95% confidence intervals.
NC= Not calculated because of inclusion bias; aSAH= aneurysmal subarachnoid haemorrhage.
* Including ischaemic and haemorrhagic stroke, but excluding subarachnoid haemorrhage.

With the analysis excluding patients with an UIA who were screened for atherosclerosis and with the analysis excluding all patients with an UIA or aSAH with a history of stroke in which we studied the influence of atherosclerosis. We found that point estimates for smoking, a history of migraine and hypercholesterolaemia remained virtually the same, although the OR for hypercholesterolaemia was no longer statistically significant (Supplemental Table S7.1).

DISCUSSION

Current smoking and a history of migraine increase the risk of rupture of an intracranial aneurysm. Hypercholesterolaemia decreases this risk, whereas hypertension does not independently affect the risk of rupture.

In previous studies from the same catchment area we reported that smoking is an independent risk factor for aneurysmal formation as well as for aSAH.[13,14] Although smoking increased the risk of rupture, we also previously reported that smoking is not a trigger factor for aneurysmal rupture.[5,10] This suggests that smoking weakens the wall of the UIAs, making them more vulnerable to trigger factors and thus rupture. The weakening of the vessel wall in smokers may be caused by an increased aneurysm growth,[4,8] or by inflammation of the vessel wall, rendering it more prone to rupture.[15,16]

Migraine was also an independent risk factor for aneurysmal rupture, but we could not find other studies reporting on migraine as risk factor for aneurysmal rupture. So far there is no reliable information about a possible pathway through which migraine might increase the risk of rupture. Migraine is not a trigger factor for aneurysmal rupture,[10] so, like smoking, migraine may lead to weakening of the aneurysmal wall. The pathway through which migraine may weaken the aneurysmal wall is unknown. It might be a migraine related process, but also a process influenced by anti-migraine drugs.

Hypercholesterolaemia independently decreased the risk of rupture. Recently a Japanese case-control study reported similar results,[3] whereas others found no effect on risk of rupture.[6,7] It is unknown whether the reduction in risk of rupture is caused by the hypercholesterolaemia itself or by the use of statins.

Although hypertension is a risk factor for developing UIAs and aSAH, and although circumstances that lead to a sudden rise in blood pressure are a trigger factor for aSAH, we found no effect of hypertension on the risk of aneurysmal rupture.[3,4,7,10,13,14] A possible explanation for these findings is that hypertension (when it is not yet known by the patient) leads to aneurysm formation, but that treatment of hypertension reduces the further

growth of aneurysms and thereby the risk of rupture on the long term, whereas sudden bouts of hypertension still may provoke aneurysm rupture. In patients known to have an UIA, hypertension might be more thoroughly treated than in patients with hypertension who are not aware of having an UIA. From this point of view aneurysmal rupture may be seen as a failure of treatment of hypertension. Also our comparison group of patients with an UIA often had a history of atherosclerotic disease, which was frequently the reason for imaging, which may again lead to better treatment of hypertension. In further studies the time relation between diagnosis of hypertension, installment of treatment, success of treatment and aneurysmal rupture should be further investigated.

Our study has some limitations. Firstly, selection bias by indication for screening should be considered, in particular when studying atherosclerotic risk factors. Almost half the patients with UIAs, of whom the indication for imaging was known, were investigated because of atherosclerotic disease or a family history of IA or aSAH. The large proportion of patients with atherosclerosis in the UIA group also resulted in a higher frequency of atherosclerotic risk factors in the UIA group compared with the aSAH group. The low risk of rupture for history of diabetes, hypertension, heart disease, and family history of stroke in the univariable analysis, probably reflects the selection bias. Also the risk of rupture for smoking might be potentially lowered by the selection bias. In multivariable analysis hypercholesterolaemia and smoking were the only statistically significant atherosclerosis associated risk factors for rupture. To study the possible effect of selection bias on our results for smoking and hypercholesterolaemia, we did two sensitivity analyses excluding patients screened for atherosclerotic disease or with a history of stroke, and found that point estimates for smoking and hypercholesterolaemia remained virtually the same. This shows that smoking and hypercholesterolaemia are indeed associated with risk of aneurysmal rupture and that this finding is not explained to a considerable extent by selection bias. Secondly, headaches might have been misclassified as migraine, since we based the diagnosis on self reporting from the questionnaire and not on a formal interview using the International Classification of Headaches to establish the diagnosis of migraine. Other types of headache, previous warning leaks and even aSAH might be mistaken for a migraine attack. Also, recall bias may have played a role, since patients with aSAH or their proxies might remember bouts of headaches more often than patients with unruptured intracranial aneurysms. Our sensitivity analyses, however, showed that misclassification and recall bias do not explain our results. Finally, recall bias for factors other than headache may have influenced our results, since the time lag between diagnosis and questionnaire in patients with an aSAH is much shorter than in patients with an UIA.

Our study also has several strong points. Firstly, since both patients with an aSAH and patients with an UIA came from the same catchment area, we were able to study risk factors for aneurysmal rupture in a rather defined population. Secondly, the inclusion of only first-ever cases of aSAH reduced selection and misclassification bias. Thirdly, we had access to individual patient data, which allowed multivariable analysis including a large number of potential risk factors with specific attention for patient characteristics instead of aneurysm characteristics. Fourthly, there was a uniform way of classification of characteristics since all participants were seen at the same hospital.

Currently, small aneurysms (<7 mm) are often left untreated and monitored over time. However, some rupture during follow-up. Based on our results, patients who harbour an aneurysm should be even more strongly advised to quit smoking. Also, our results support the need for further pathophysiological studies on how migraine and hypercholesterolaemia exert their effects on risk of rupture of aneurysms. This knowledge may lead to new treatment strategies to reduce the risk of rupture of UIAs. If the risk decreasing effect of hypercholesterolaemia is mediated by statin use, statins might be an additional treatment option for decreasing the prevalence of UIAs, and thereby the incidence of aSAH, and should also be further investigated. In contrast, if the risk due to migraine is caused by the use of anti-migraine medication, the use of anti-migraine medication should be discussed with the patients.

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Supplemental Table S7.1 Sensitivity analyses on atherosclerosis

	SENS1		SENS 2	
	Univariable analysis	Multivariable analysis	Univariable analysis	Multivariable analysis
Smoking	2.1 (1.4-3.2)	2.7 (1.6-4.7)	2.5 (1.6-3.8)	2.7 (1.6-4.6)
Hypercholesterolaemia	0.5 (0.2-1.1)	-	0.5 (0.2-1.3)	-
Migraine	2.4 (1.2-4.8)	2.3 (1.0-5.1)	2.6 (1.3-5.2)	2.4 (1.0-5.7)

Values are odds ratios and corresponding 95% confidence intervals.
SENS1= Analysis excluding patients with an unruptured intracranial aneurysm who were screened for atherosclerosis; SENS2= Analysis excluding all patients with an unruptured intracranial aneurysm or aneurysmal subarachnoid haemorhage with a history of stroke.

8

Life-time risks for aneurysmal subarachnoid haemorrhage: multivariable risk stratification

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ABSTRACT

Background: The overall incidence of aneurysmal subarachnoid haemorrhage (aSAH) in western populations is around 9 per 100,000 person-years, which confers to a life-time risk of around half a percent. Risk factors for aSAH usually are expressed as relative risks and suggest that absolute risks vary considerably according to risk factor profiles, but such estimates are lacking. We aimed to estimate incidence and life-time risks of aSAH according to risk factor profiles.

Methods: We used data from 250 patients admitted with aSAH and 574 sex- and age-matched controls, who were randomly retrieved from general practitioners files. We determined independent prognostic factors with multivariable logistic regression analyses and assessed discriminatory performance using the area under the receiver operating characteristic curve (AUC). Based on the prognostic model we predicted incidences and life-time risks of aSAH for different risk factor profiles.

Results: The four strongest independent predictors for aSAH, namely current smoking (odds ratio [OR] 6.0, 95% confidence interval [CI] 4.1-8.6), a positive family history for aSAH (OR 4.0, 95% CI 2.3-7.0), hypertension (OR 2.4, 95% CI 1.5-3.8) and hypercholesterolaemia (OR 0.2, 95% CI 0.1-0.4), were used in the final prediction model. This model had an AUC of 0.73 (95% CI 0.69-0.76). Depending on sex, age and the four predictors, the incidence of aSAH ranged from 0.4/100,000 to 298/100,000 person-years and life-time risk between 0.02% and 7.2%.

Conclusion: The incidence and life-time risk of aSAH in the general population vary widely according to risk factor profiles. Whether persons with high risks benefit from screening should be assessed in cost-effectiveness studies.

INTRODUCTION

Aneurysmal subarachnoid haemorrhage (aSAH) has an overall incidence of 9 per 100,000 person-years,[1] and carries a poor prognosis and a considerable economic burden.[2-4] Since part of the poor prognosis of aSAH is caused by the initial haemorrhage,[2] a possible method to reduce the considerable burden of aSAH is screening and preventive treatment of those persons at high risk. Modeling studies have shown that screening is cost-effective in persons with two or more affected first-degree relatives. However, around 90% of patients with aSAH do not have a positive family history or have only one affected first-degree relative. Several other risk factors, such as smoking and hypertension, have been identified.[5] Risks for these factors are usually expressed as relative risks. It is likely that absolute risks vary considerably according to risk factor profiles, but estimates of absolute risks according to risk factor profiles are lacking. Accordingly, it is unknown whether, based on risk factor profiles, persons can be identified to have a high enough risk to make screening worthwhile to consider.

We assessed predictors for aSAH and developed a prognostic model to estimate incidence and life-time risks of aSAH for persons in the general population based on age, sex and risk factor profile.

METHODS

Design and study population

Between September 2006 and September 2009 we included 250 consecutive patients who were admitted for aSAH at the Utrecht Stroke Center of the University Medical Center Utrecht in a case-crossover study.[6] Patients included in the case-crossover study served as cases in the current case-control study. They were eligible if they were 18 years or older and spoke Dutch or English or had a proxy who did so. Informed consent was given by either the patient or the proxy aSAH was defined as an abrupt onset of severe headache or loss of consciousness with or without focal neurological signs and subarachnoid blood proven by CT or lumbar puncture, and an aneurysm proven with CT-, MR- or conventional angiography.

Between January 2009 and January 2010 we recruited 574 controls from five different general practices in the referral region of the Utrecht Stroke Center. They were randomly selected and frequency matched for age and sex with the cases. The study protocol was approved by the medico-ethical review committee of our hospital.

Data collection

With a structured questionnaire, detailed data were obtained on age, sex, smoking status, diabetes, hypertension, hypercholesterolaemia and family history for aSAH or an intracranial aneurysm (IA).[6] Diagnoses of diabetes, hypertension and hypercholesterolaemia were checked against medical records to confirm that the diagnosis was made prior to the aSAH, since 40% of the interviews with aSAH patients were completed six weeks or more after the aSAH.[6] For cases and controls a positive family history for aSAH or an IA was defined as one or more affected first-degree relatives. Smoking was defined as current smoking. Excessive alcohol use was defined as ≥18 units per week.[5] Lean body mass was defined as a body mass index (BMI) <22. Regular physical activity was defined as vigorous physical exercise (metabolic equivalent >6) more than three times a week.[7]

Model development

To identify independent predictors and to develop a prognostic model, logistic regression analysis was performed with aSAH as an outcome measure. Eight clinical variables that have been previously identified as risk factors for aSAH, namely smoking, excessive alcohol use, a positive family history of an aSAH or IA, hypercholesterolaemia, hypertension, diabetes and a lean body mass, were entered into the model,[5,8-11] irrespective of their univariable association with aSAH.[12] They were step by step excluded from the multivariable model if the likelihood ratio test had a p-value >0.15. The discriminative performance, i.e. the extent to which a model enables discrimination between patients with and without aSAH, was described by the area under the receiver operating characteristic curve (AUC).

Model validation

Models based on multivariable regression analysis often overestimate regression coefficients. Therefore, we internally validated our models with bootstrapping techniques, where in each bootstrap sample the entire modeling process was repeated.[13] This resulted in a shrinkage factor for the regression coefficients.[14] The bootstrap procedure was also used to correct the AUC for overoptimism. This corrected AUC can be considered an estimate of discriminative ability expected in future similar patients.

Data were analysed with SPSS and R (version 2.11.1; http://www.r-project.org) with help of the libraries Foreign and Design of Harrell.[15]

Calculation of incidences and life-time risks

Because our prognostic model was derived from a subset and not the entire Dutch population, we had to calculate a correction factor for the intercept of the logistic regression model with the following formula: $a_1 = \ln [(N_D/N_C)/(n_D/n_C)]$, where N_D= incidence of aSAH in the general population (i.e. 0.00009), N_c= risk of no aSAH in the general population (0.99991), n_D= number of patients with aSAH in study population, and n_C= number of controls in the study population.[1,16] With these corrected intercepts, the incidence for aSAH could be calculated for men and women of different ages for each combination of the four predictors.[17] In addition we calculated the life-time risks for each sex and age category.

RESULTS

Table 8.1 summarises the baseline demographic data, clinical characteristics of patients and controls and odds ratios from univariable analysis. Multivariable logistic regression analysis yielded six predictors of aSAH, namely current smoking, a family history of aSAH

Table 8.1 Characteristics of the 250 patients with aSAH and 574 controls with univariable odds ratios

Characteristic	Patients (n=250)	Controls (n=574)	Odds ratio (95% CI)
Men, n (%)	62 (24.8)	177 (30.8)	*
Mean age, y (sd)	54.7 (15.8)	54.8 (15.8)	*
Current cigarette smoking, n (%)	155 (62.0)†	138 (24.1)†	5.1 (3.7-7.1)
Alcohol use, n (%)	197 (79.1)†	475 (83.1)†	0.8 (0.5-1.1)
Alcohol ≥18 units/week, n (%)	42 (16.9)†	67 (13.3)†	1.5 (1.0-2.3)
Body mass index <22, n (%)	62 (26.3)‡	112 (20.1%)†	1.4 (1.0-2.0)
Vigorous exercise >3 times/week, n (%)	43 (17.5)†	147 (25.7)†	0.6 (0.4-0.9)
Medical history, n (%)			
aSAH, n (%)	5 (2.0)	0	NE
Hypertension, n (%)	61 (24.6)†	104 (19.0)†	1.4 (1.0-2.0)
Diabetes, n (%)	6 (2.4)	26 (4.6)	0.5 (0.2-1.2)
Hypercholesterolaemia, n (%)	13 (5.4)†	76 (14.9)§	0.3 (0.2-0.6)
Positive family history for aSAH, n (%)‖	53 (22.5)‡	36 (6.4)†	4.2 (2.7-6.6)

aSAH= aneurysmal subarachnoid haemorrhage; n= number of patients; CI= confidence interval; sd= standard deviation; NE= not estimable.
* matching factors, OR not calculated.
† <5% missing data.
‡ 5-10% missing data.
§ 11-16% missing data.
‖ At least one first-degree relative with aSAH or intracranial aneurysm.

or IA, hypertension, hypercholesterolaemia, excessive alcohol use and regular physical exercise (Table 8.2). Lean body mass and diabetes had no predictive value. Since we wanted to develop a model that can be easily used in clinical practice, we compared the complete model with all six predictors with a model including only the four strongest predictors. The AUC was similar for the full model and simple model (0.74; 95% CI 0.70-0.78 vs 0.73; 95% CI 0.69-0.76); therefore, we used the simple model as final model for further calculation of risks. This model was based on 716 subjects.

Incidences and life-time risks

Figure 8.1 displays the predicted incidence of aSAH for each combination of the four predictors in the final model for men and women of different ages. The number of persons with each combination of predictors is provided in Supplemental Figure S8.1. Figure 8.2 displays the life-time risks of aSAH for men and women of different ages for each combination of the four predictors in the final model. Depending on age, sex and the presence or absence of the four predictors, the incidence of aSAH can lower 23-fold or increase 33-fold compared with the overall incidence of 9.1/100,000.[1] Annual risks of aSAH ranged from 0.4/100,000 to 298/100,000 person-years and life-time risk between 0.02% and 7.2%.

Table 8.2 Multivariable predictors for aneurysmal subarachnoid haemorrhage in 2 prognostic models of decreasing complexity

	Model 1* (n=705)	Model 2* (n=716)
Current smoking	5.9 (4.1-8.6)	6.0 (4.1-8.6)
Positive family history of aSAH	4.3 (2.4-7.5)	4.0 (2.3-7.0)
History of hypertension	2.3 (1.5-3.7)	2.4 (1.5-3.8)
Hypercholesterolaemia	0.2 (0.1-0.4)	0.2 (0.1-0.4)
Excessive alcohol use (≥18 units/week)	1.3 (1.0-2.8)	-
Vigorous exercise >3 times/week	0.6 (0.4-1.0)	-
AUC curve†	0.74 (0.70-0.78)	0.73 (0.69-0.76)

Values are odds ratios and corresponding 95% confidence intervals.
aSAH= aneurysmal subarachnoid haemorrhage, AUC= area under the curve; * Model 1 contains all 6 prognostic factors, model 2 only the four strongest predictors, † adjusted for overoptimism with bootstrapping techniques; model 1 was shrunk by 4 % and model 2 by 5%.

		No smoking				Current smoking			
		No hypertension		Hypertension		No hypertension		Hypertension	
Men, 35-45									
Family	No	0.7	3.1	1.6	7.1	3.7	16.7	8.4	38.3
History	Yes	2.5	11.5	5.8	26.4	13.7	62.2	31.5	142.9
		Yes	No	Yes	No	Yes	No	Yes	No
		Hypercholesterolaemia		Hypercholesterolaemia		Hypercholesterolaemia		Hypercholesterolaemia	
Women, 35-45									
Family	No	0.4	2.0	1.0	4.6	2.4	10.9	5.5	25.0
History	Yes	1.6	7.5	3.8	17.2	8.9	40.6	20.6	93.4
		Yes	No	Yes	No	Yes	No	Yes	No
		Hypercholesterolaemia		Hypercholesterolaemia		Hypercholesterolaemia		Hypercholesterolaemia	
Men, 45-55									
Family	No	1.1	5.0	2.5	11.4	5.9	26.7	13.5	61.5
History	Yes	4.1	18.5	9.4	42.6	22.0	99.7	50.5	229.0
		Yes	No	Yes	No	Yes	No	Yes	No
		Hypercholesterolaemia		Hypercholesterolaemia		Hypercholesterolaemia		Hypercholesterolaemia	
Women, 45-55									
Family	No	1.0	4.5	2.3	10.3	5.4	24.4	12.4	56.1
History	Yes	3.7	16.8	8.5	38.6	20.1	91.1	46.1	209.1
		Yes	No	Yes	No	Yes	No	Yes	No
		Hypercholesterolaemia		Hypercholesterolaemia		Hypercholesterolaemia		Hypercholesterolaemia	
Men, 55-65									
Family	No	1.2	5.6	2.8	12.9	6.7	30.3	15.4	69.7
History	Yes	4.6	20.9	10.6	47.9	24.9	113.1	57.3	259.6
		Yes	No	Yes	No	Yes	No	Yes	No
		Hypercholesterolaemia		Hypercholesterolaemia		Hypercholesterolaemia		Hypercholesterolaemia	
Women, 55-65									
Family	No	1.4	6.4	3.2	14.7	7.7	34.8	17.6	80.0
History	Yes	5.3	23.9	12.1	55.0	28.6	129.7	65.7	297.8
		Yes	No	Yes	No	Yes	No	Yes	No
		Hypercholesterolaemia		Hypercholesterolaemia		Hypercholesterolaemia		Hypercholesterolaemia	

≤ overall incidence for this age and sex[1]

1-2 times overall incidence for this age and sex

> 2 times overall incidence for this age and sex

Figure 8.1 Incidence of subarachnoid haemorrhage per 100,000 person-years for each combination of the four predictors according to strata of age and sex.

		No smoking				Current smoking			
		No hypertension		Hypertension		No hypertension		Hypertension	
Men, 35-45, RLT 39.6y, RLR 0.36%									
Family history	No	0.03	0.12	0.06	0.28	0.15	0.66	0.33	1.51
	Yes	0.10	0.45	0.23	1.04	0.54	2.43	1.24	5.50
		Yes	No	Yes	No	Yes	No	Yes	No
		Hypercholesterolaemia		Hypercholesterolaemia		Hypercholesterolaemia		Hypercholesterolaemia	
Women, 35-45, RLT 43.6y, RLR 0.40%									
Family history	No	0.02	0.09	0.04	0.20	0.10	0.47	0.24	1.08
	Yes	0.07	0.33	0.16	0.75	0.39	1.75	0.89	3.98
		Yes	No	Yes	No	Yes	No	Yes	No
		Hypercholesterolaemia		Hypercholesterolaemia		Hypercholesterolaemia		Hypercholesterolaemia	
Men, 45-55, RLT 30.2y, RLR 0.27%									
Family history	No	0.03	0.15	0.08	0.34	0.18	0.80	0.41	1.84
	Yes	0.12	0.56	0.28	1.28	0.66	2.97	1.51	6.69
		Yes	No	Yes	No	Yes	No	Yes	No
		Hypercholesterolaemia		Hypercholesterolaemia		Hypercholesterolaemia		Hypercholesterolaemia	
Women, 45-55, RLT 34.0y, RLR 0.31%									
Family history	No	0.03	0.15	0.08	0.35	0.18	0.83	0.42	1.89
	Yes	0.13	0.57	0.29	1.30	0.68	3.05	1.56	6.87
		Yes	No	Yes	No	Yes	No	Yes	No
		Hypercholesterolaemia		Hypercholesterolaemia		Hypercholesterolaemia		Hypercholesterolaemia	
Men, 55-65y, RLT 21.4y, RLR 0.19%									
Family history	No	0.03	0.12	0.06	0.27	0.14	0.65	0.33	1.48
	Yes	0.10	0.45	0.23	1.02	0.53	2.39	1.22	5.41
		Yes	No	Yes	No	Yes	No	Yes	No
		Hypercholesterolaemia		Hypercholesterolaemia		Hypercholesterolaemia		Hypercholesterolaemia	
Women, 55-65y, RLT 25.0y, RLR 0.23%									
Family History	No	0.04	0.16	0.08	0.37	0.19	0.87	0.44	1.98
	Yes	0.13	0.60	0.30	1.37	0.71	3.19	1.63	7.18
		Yes	No	Yes	No	Yes	No	Yes	No
		Hypercholesterolaemia		Hypercholesterolaemia		Hypercholesterolaemia		Hypercholesterolaemia	

Low risk Intermediate risk High risk

Figure 8.2 Life-time risk (%) of subarachnoid haemorrhage for each combination of the four predictors according to strata of age and sex. RLT= remaining life-time risk in the general population; RLR= life-time risk in the general population. Risks are based on remaining life expectancies for the average age of each age category.[17] Low risk was defined as a risk lower than the risk in the general population for persons with the same life expectancy; high risk was defined as twice the risk for patients with the same life expectancy and only one affected first-degree relative.[1,8,18]

DISCUSSION

We found that using only four easily retrievable predictors for aSAH and a simple risk chart risks can be stratified over a considerable range. We found that the incidence of aSAH varies from 0.4 to 298/100,000 person-years, depending on sex, age and risk factor profile, while the overall incidence of aSAH is known to be approximately 9 per 100,000 person-years.[1] Life-time risks vary between 0.02 and 7%.

Current smoking, a family history of aSAH or IA, hypertension, hypercholesterolaemia, excessive alcohol use and regular physical exercise were all independent predictors. Because we wanted to make a simple risk chart, we compared a model including only the four strongest predictors without excessive alcohol use and regular physical exercise with the full model of all six predictors and found a comparable AUC. This does not mean that physical exercise or excessive alcohol use are not important predictors, but these variables have limited added value for the prediction of aSAH when data on current smoking, a family history of aSAH or IA, hypertension, and hypercholesterolaemia are already accounted for.

Life-time risks for patients between age 35 and 65 varied between 0.02% and 7% depending on risk factor profile. The life-time risk in the general population is 0.7%, 1.5% for patients with only one affected first-degree relative and 26% for patients with two affected first-degree relatives.[1,18] In the current study, we identified several high-risk groups with life-time risks higher than 5%, all with a positive family history for an aSAH or IA. We found that persons with a fist-degree relative with an aSAH or IA were at an even higher risk of aSAH when they smoke or have high blood pressure. This is in line with a previous study that shows that smoking and hypertension have an additional risk for IA formation in persons with a positive family history.[19] Risks for patients without such a family history are lower, but when they smoke or have high blood pressure, the life-time risks can be as high as 1.4%, which is twice as high as the average life-time risk and comparable to the life-time risk of patients with one affected first-degree relative.[1,18] So far, screening has only been proven to be cost-effective for persons with two affected first-degree relatives.[8] Which patient categories may benefit from screening for and preventive treatment of unruptured aneurysms needs to be assessed in cost-effectiveness studies. Also, further studies should be done on whether patients with a positive family history should all be screened or only those who smoke or have high blood pressure or whether these persons should be screened with higher frequency.

Our study also has some limitations. Cases and controls were approximately matched for sex and age, thus we were not able to study these factors as potential risk factors and

predictors. However, the incidence of aSAH is known for different sex and age categories, thus we were still able to calculate incidence and life-time risks for patients of different sex and age.[1] Because the majority of our study population was between 35 and 65 years of age, we considered contribution of patients aged <35 and >65 too small for reliable risk estimation for those age categories. Also, the clinical relevance of predicting the life-time risk of aSAH of patients 65 and older is limited, since it is unlikely that in clinical practice these elderly patients would be offered screening for cerebral aneurysms based on their risk factor profile.

Furthermore, our study lacks external validation. Although bootstrapping techniques were applied, there might be an overestimation of the true performance. Also, the inclusion of patients in a relatively good clinical condition may have led to survival bias if certain risk factors also affect prognosis after aSAH. However, we found no important difference between the frequency of risk factors based on the medical records of patients who were included in our study and those who were not (data not shown). In addition, one may question the generalisability of our data to Finland and Japan, since the incidence of aSAH in these countries is higher.[1] Recently, a Japanese study also identified smoking and hypertension and, inversely, hypercholesterolaemia as independent risk factors.[20] Therefore, it is likely that our model is also applicable in Japan if the higher incidence of aSAH in this country is taken into account. Finally, the effect of family history might be overestimated, since family histories are known to be insufficiently accurate to prove or disprove the diagnosis of familial aSAH.[21,22] False positive recording of a positive family history of aSAH or IA might be higher in aSAH patients than in controls.

Strengths of our study are that we had access to a comprehensive set of clinical variables for all patients and controls. Therefore, we could assess the independent contribution of each predictor and could develop a prognostic model to provide estimates of the incidence and life-time risk of aSAH for people with different combinations of predictors and with different sex and age. We used bootstrapping techniques to shrink regression coefficients in order to correct for over-optimism (internal validation), providing more reliable risk estimates. Also all prognostic factors we found have been previously identified as risk factors for aSAH, which adds to the reliability.[5] Since we used population based control we reduced referral bias and can apply our findings to the general population.

In conclusion, the incidence and life-time risks for aSAH for people in the general population can be calculated reliably based on four easily retrievable prognostic factors: hypertension, hypercholesterolaemia, current smoking and family history of aSAH. These risk calculations may serve as basis for future cost-effectiveness studies on screening for and preventive treatment of persons in the high risk categories we identified.

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Supplemental Figure S8.1 Number of persons with each combination of the four predictors

		No smoking				Current smoking			
		No hypertension		Hypertension		No hypertension		Hypertension	
Family history	No	22	303	24	68	13	188	10	19
	Yes	1	4	3	9	4	27	2	10
		Yes	No	Yes	No	Yes	No	Yes	No
		Hypercholesterolaemia		Hypercholesterolaemia		Hypercholesterolaemia		Hypercholesterolaemia	

9

General discussion

General discussion

The risk of aneurysmal subarachnoid haemorrhage (aSAH) can be divided into several components, namely the risk of developing an unruptured intracranial aneurysm (UIA) and the risk of rupture of an UIA. This risk of rupture can be further subdivided into chronic factors that make the aneurysm more prone to rupture, and acute factors that trigger aneurysmal rupture (Figure 9.1). This thesis focused on the risk of aSAH and the

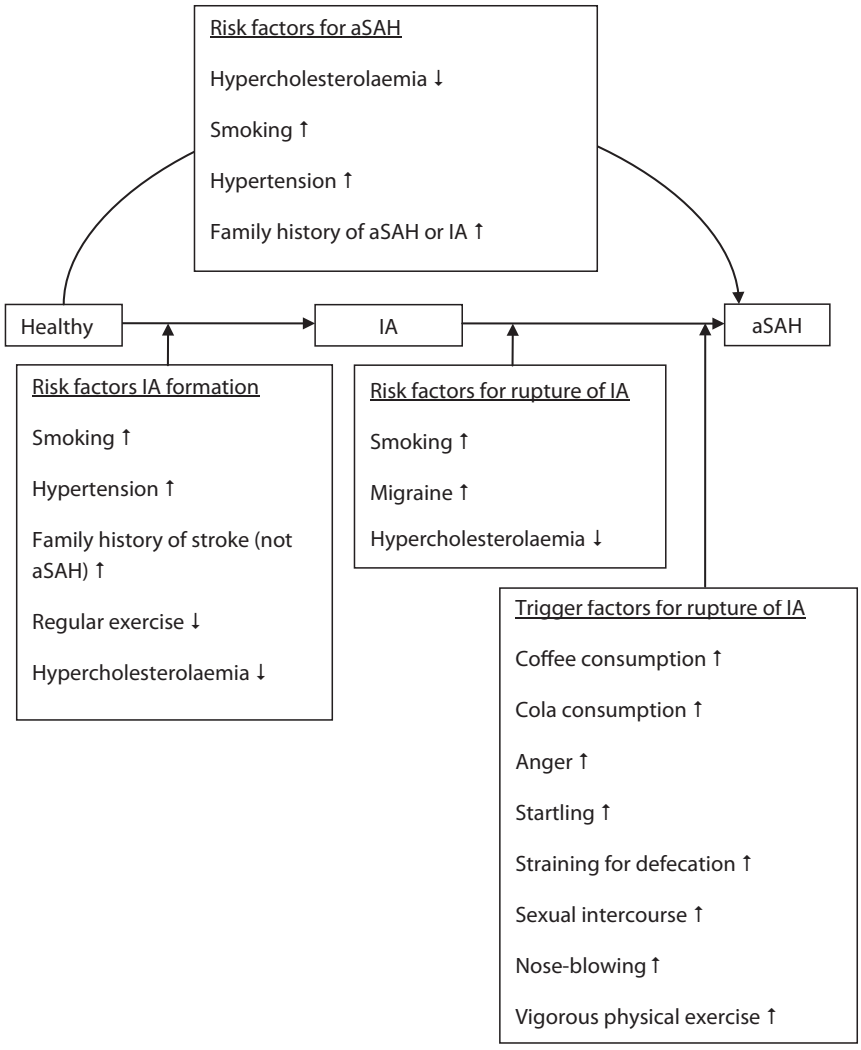

Figure 9.1 Risk factors for the different steps that lead tot aneurysmal subarachnoid haemorrhage. IA= intracranial aneurysm; aSAH= aneurysmal subarachnoid haemorrhage; ↑= associated with increased risk; ↓= associated with decreased risk.

three components that make up that risk. In addition we identified prognostic factors for aSAH and developed a prognostic model to estimate incidence and life-time risks of aSAH for persons in the general population based on age, sex and risk factor profile.

The prevalence of unruptured intracranial aneurysms

A prerequisite for having an aSAH is having an UIA, therefore we first concentrated on finding the prevalence of UIAs. We found that about 3.2% of the population harbours an UIA, which is 40% higher than reported previously.[1,2] In patients with a family history of aSAH or UIA or a history of autosomal dominant polycystic kidney disease (ADPKD) we found an increased prevalence ratio compared to patients without risk factors.[2] The prevalence of UIAs is not increased in patients with a brain tumour or pituitary adenoma. Also, we found no statistically significant higher prevalence of UIA in patients with atherosclerosis, even though smoking and hypertension are risk factors for harbouring an UIA.[2,3] However, in our study on the prevalence of UIAs we had no data on hypertension or smoking status, which probably explains the absence of a clear association.

Risk factors for aSAH: piecing the puzzle together

In order to unravel the different components that compose the risk of aSAH (namely risk factors for developing an UIA, risk factors for rupture and trigger factors), we compared three different groups: controls, who were randomly selected from the general population, patients with an UIA and patients with an aSAH.[3-5]

There is now overwhelming evidence, also from data presented in this thesis, that smoking and hypertension are important risk factors for aSAH, and that they have an additive joint effect.[5-12] We have shown that smoking increases the risk of aSAH by an increased risk of harbouring an UIA.[3] Smoking also increased the risk of aneurysmal rupture, although it does not trigger aneurysmal rupture.[4,13] This suggests that smoking weakens the wall of the UIAs, making it more vulnerable to trigger factors and thus rupture. The weakening of the vessel wall in smokers may be caused by increased aneurysm growth or by inflammation of the vessel wall.[14-17] Although smoking does not trigger the actual rupture, patients who are diagnosed with an UIA should be strongly advised to quit smoking to decrease the growth rate of their aneurysm and thereby the risk of rupture.

The risk of aSAH is increased in patients with a history of hypertension.[5,9] This increased risk is caused by a higher risk of developing an UIA, not by a higher risk of rupture.[3,4] If patients with high blood pressure also smoke, the risk of harbouring an UIA is even higher than can be expected based on the individual risks associated with hypertension

and smoking. This suggests a synergism between these two prominent risk factors in the development of UIAs. In contrast to our finding that the risk of rupture is not increased in patients with hypertension, we hypothesize that the common characteristic of the trigger factors for aneurysmal rupture is a sudden and short lasting rise in blood pressure caused by the trigger factor.[4,13] Possibly untreated hypertension leads to aneurysm formation, but treatment of hypertension reduces the further growth of aneurysms and thereby the risk of rupture on the long term, whereas sudden bouts of hypertension still may provoke aneurysm rupture. In patients known to have an UIA, hypertension might be more likely to be diagnosed and more thoroughly treated compared with patients with hypertension without a known UIA. From this point of view aneurysmal rupture may be seen as a failure of treatment of hypertension. Unfortunately, we were unable to investigate the role of anti-hypertensive drugs in our studies due to insufficient data on type of medication, duration of use and effectiveness of treatment.

Hypercholesterolaemia, a known risk factor for atherosclerosis, decreases the risk of aSAH.[5,9,10,18] In our study this is caused by both a decreased risk of UIA development and a decreased risk of rupture.[3,4,10] The mechanism through which hypercholesterolaemia lowers the risk of UIA development and rupture remains unclear. Since most patients with high cholesterol are treated with statins, it is possible that it is not the hypercholesterolaemia itself, but the statins that lower the risk through a protective effect on the vascular wall.[19-21] Some animal studies suggested that statins suppress aneurysmal formation and progression and ameliorate the inflammatory state in atherosclerosis.[22-24] However, a recent clinical study failed to confirm a beneficial effect of statin use on the risk of development of UIAs.[25] In contrast, cessation of statin use increases the risk of aSAH, presumably by an increased risk of rupture.[26] Unfortunately, we had insufficient data on statin use to study whether the hypercholesterolaemia or its treatment with statins exert a risk reducing effect on either UIA development or the risk of rupture.

Physical exercise decreases the risk of cardiovascular disease.[27] We found that the risk of harbouring an UIA is decreased in patients who do regular physical exercise.[4] Although regular physical exercise was not a risk factor for aneurysmal rupture, heavy physical exercise does trigger aneurysmal rupture.[5,13] Apparently physical exercise has a positive influence on the changes of the vascular wall associated with the development of an UIA. Once an UIA has developed, there is an elevated risk during or just after exercise which subsides soon thereafter. The population attributable risk of physical exercise is small, therefore we would not advise patients to refrain from physical exercise. The fact that exercise lowers the risk of developing an UIA, possibly also the development of new UIAs, strengthens this advice.

Data on whether the use of (excessive) alcohol increases the risk of aSAH remain contradictive.[6,7,9-11] In our study on risk factors for aSAH, excessive alcohol intake was not an independent risk factor for aSAH in the multivariable analysis after we accounted for smoking status;[5] probably this is caused by the strong relationship between alcohol consumption and cigarette smoking. Excessive alcohol use did also not increase the risk of developing an aneurysm or the risk of rupture, nor was it a trigger factor for rupture.[3,4,13]

From literature and from data presented in this thesis it is known that patients with a family history of UIA or aSAH are at increased risk of having an aSAH.[5,28-31] From our review on the prevalence of UIAs we concluded that patients with a positive family history have a 3.4 times higher prevalence of UIAs compared with the general population.[2] The risk of aSAH is about 50 times higher in patients with two first-degree relatives than in patients with no affected first-degree relatives.[28] This suggests a higher risk of rupture, which has been previously reported by others.[32] Because a large proportion of UIA patients was screened because of a positive family history our data were biased by this indication and we were thus not able to study family history of aSAH as risk factor for UIAs or aneurysmal rupture.[3,4]

It is well recognized that women have a higher risk of aSAH, which is mainly caused by a higher incidence in women over 55 years of age.[33] In our review on UIAs we found that women have a 1.5 times higher prevalence of UIAs, which seemed to start in the fifth decade.[2] However, this trend alone does not fully explain the higher incidence of aSAH in older women. This suggests that older women have a higher risk of rupture. In our review we found that populations with more women also have more aneurysms >5 mm, which are known to have a higher rupture rate, but age could not be taken into account.[2] Previously, a higher age was already associated with a higher risk of rupture, but sex-specific data were not reported.[34] It has also been postulated that hormonal factors, especially a post-menopausal status, plays a role in the higher incidence of aSAH in older women.[33] Several studies, including a recent systematic review, described an increased risk of aSAH for postmenopausal women, but the pathophysiological mechanism remains unclear.[35-37] Unfortunately, we were not able to further investigate sex, age and hormonal factors as a risk factor in our studies. The cause of the higher risk of aSAH, the higher prevalence of UIAs and the higher risk in rupture in women, especially older women, needs to be further investigated.

Another well known non-modifiable risk factor for aSAH is age. In our review on the prevalence of UIAs, we found that, compared with patients older than 80 years, there was a statistically significantly lower prevalence in patients under the age of 30, but not when compared with other age groups.[2] Others have suggested that patients over the age of 60 have a higher risk of rupture.[34] Since our control patients were frequency matched for sex

and age with the patients with an aSAH (and thereby virtually also matched with UIA patients) we were unable to investigate age in our studies on risk factors for aSAH, risk factors for UIAs and risk of rupture.

The incidence of aSAH in Finnish and Japanese populations is significantly higher than in other parts of the world.[33] Interestingly, we found no higher prevalence of UIAs in Finland and Japan.[2] This implies that the risk of rupture is higher in these countries. Indeed, previous meta-analyses found a higher rupture rate in patients of Japanese and Finnish descent.[34] The reason for this higher risk of rupture is still unknown. There is no higher proportion of high risk aneurysms (i.e. larger than 5 mm or located in the posterior circulation) in Finnish and Japanese populations.[2] Other factors, such as a higher growth rate, a higher susceptibility to trigger factors or a genetic predisposition for weaker aneurysms may play a role in the higher rupture rate in these populations.

The absolute risk of aSAH

The proportion of years of potential life lost from aSAH is similar to that of ischaemic stroke and a recent calculation found a total economic burden of £510 million annually for aSAH in the UK.[38,39] A possible method to reduce aSAH is screening and preventive treatment of persons at high risk for aSAH. So far, screening has shown to be cost effective in patients with two or more first-degree relatives with aSAH or UIA, who carry a 26% life-time risk.[40] Screening of patients with only one affected first-degree relative (life-time risk 1.5%) was not cost-effective. About 90% of patients with an aSAH does not have a positive family history; therefore, it is important to identify other high risk groups on basis of their risk factor profile.[41,42]

In this thesis we have developed age and sex stratified risk charts for the risk of aSAH with only four easily retrievable predictors for aSAH, namely hypertension, smoking, hypercholesterolaemia and a family history of aSAH or UIA (one or more affected first-degree relatives).[5] The overall incidence of aSAH is approximately 9 per 100,000 person-years, but we have shown that the incidence varied from 0.4 to 298/100,000 person-years, depending on sex, age and risk factor profile.[5,33] Life-time risks varied between 0.02 and 7%.

The life-time risks for patients with a positive family history in the cost-effectiveness study mentioned above were calculated with a remaining life-time of 80 years, which is almost twice the remaining life-time we used for calculating absolute risks.[5,28,40] We have demonstrated a large increase in absolute risk of aSAH when patients with one or more affected first-degree relative also smoke or have hypertension.[5] Even without a positive family history, some patients who smoke or have high blood pressure have a life-time risk

of aSAH higher than the average risk of patients with one affected first-degree relative alone.[5,40] Whether it is cost-effective to screen patients who smoke or have high blood pressure, especially with one or more affected relatives with an UIA or aSAH, is not yet known. In terms of decreasing the risk of UIAs as well as other cardiovascular diseases, patients who smoke and have hypertension need to be treated for their high blood pressure and should be strongly advised to quit smoking, especially if they have one or more first-degree relatives with an aSAH or UIA.

Implications for future research

Many new research questions arise from the data presented in this thesis, but future research projects should first focus on our most consistent findings.

Smoking was a risk factor for rupture, but not a trigger factor. Future research should study the pathophysiological pathway through which smoking exerts its effect on the vascular wall and stimulates aneurysmal growth. Previous investigators already found that patients who quit smoking during follow-up have the same risk of rupture as patients who were non-smokers.[14,15] This suggests that in UIA patients who quit smoking the growth rate decreases, but the pathophysiological mechanism through which smoking increases growth or rupture still needs to be further investigated. Also the time lag after which the beneficial effect of cessation of smoking is noticeable is unknown.

Further studies should also try to answer the question whether the protective effect for hypercholesterolaemia on aneurysms and aSAH is related to the hypercholesterolaemia itself or to treatment with statins. If indeed use of statins decrease the risk of aneurysmal development and rupture, statin use might become a treatment strategy to prevent aneurysmal development and aneurysmal rupture.

Trigger factors for aSAH are a new field of research and the study presented in this thesis has studied the largest number of trigger factors for aSAH to date.[13] However, more research on trigger factors is needed to study their role in aSAH. Firstly, studying trigger factors in populations with a high risk of rupture could be considered. It is known that the rupture rate is higher in Finnish and Japanese populations, whereas these populations do not have a higher proportion of large aneurysms or aneurysms in the posterior circulation.[2,34] Therefore, it is possible that the higher rupture rate is due to an increased susceptibility for trigger factors or possibly new trigger factors. Secondly, a higher susceptibility to trigger factors might also play a role in familial aSAH. However, due to the rarity of familial aSAH, it will be difficult to gather enough patient data. Thirdly, we have suggested previously in this thesis that patients with an UIA or patients with an aSAH awaiting treatment might benefit

from changes in lifestyle. Whether reducing caffeine consumption or treating patients with laxatives may lower the risk of aneurysmal rupture needs to be further investigated. Furthermore, it is unknown whether the use of anti-hypertensive drugs affects the surge in blood pressure after a trigger factor, which should first be studied in animal studies.

Finally, future researchers might consider a cost-effectiveness study including patients with one or more affected first-degree relatives, who also smoke or have high blood pressure. The life-time risks for patients without a positive family history does not exceed the 2%; therefore screening for UIAs in these patients is unlikely to be cost-effective.

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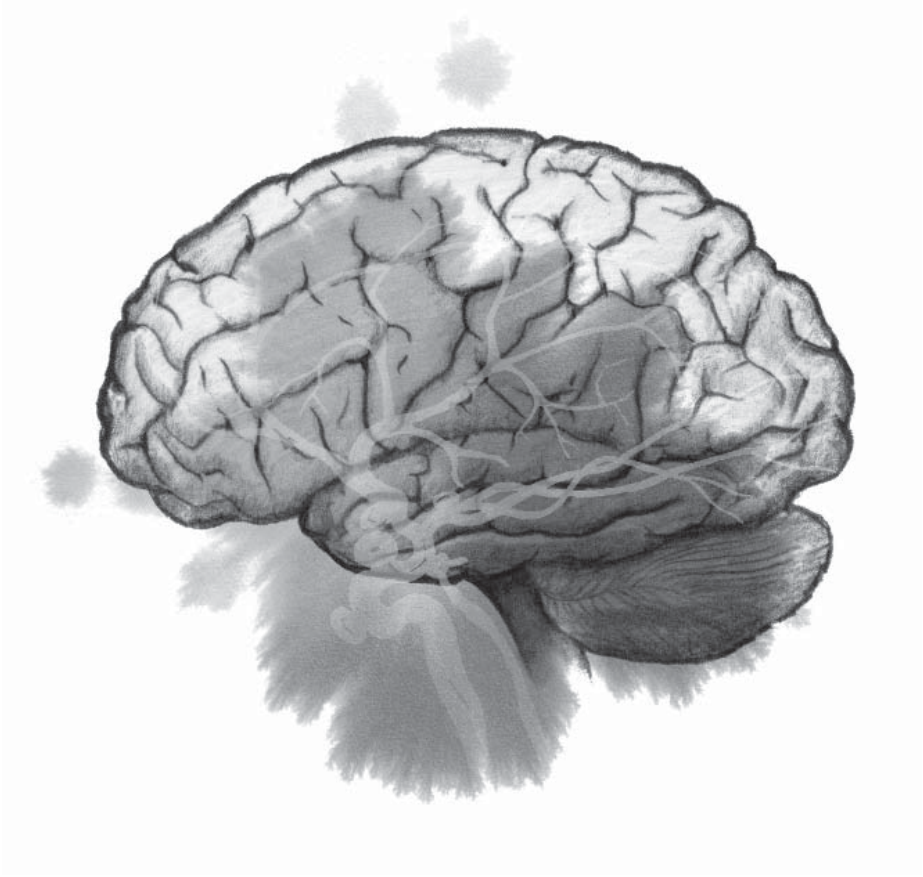


Summary

SUMMARY

Rupture of an intracranial aneurysm causes an aneurysmal subarachnoid haemorrhage (aSAH), which is an important subtype of stroke. Knowledge about risk factors for aSAH is necessary to better understand the pathophysiological mechanisms and to develop possible preventive measures.

The risk of aSAH consists of three different components, namely the risk factors for developing an unruptured intracranial aneurysm (UIA), risk factors for aneurysmal rupture and trigger factors, which cause the actual rupture. In the present thesis we tried to identify risk factors for the different components that make up the risk of aSAH and to develop a prognostic model based on these risk factors.

In **Chapter 2** we systematically reviewed the literature on the prevalence of UIAs. We found that the prevalence in persons without comorbidity was 3.2% (95% confidence interval [CI] 1.9-5.2). In the past 50 years the prevalence has not changed significantly. The prevalence is similar in patients with a brain tumour (including pituitary tumours) or atherosclerosis, but is much higher in patients with polycystic kidney disease (prevalence ratio [PR] 6.9, 95% CI 3.5-14) or a positive family history of UIA or aSAH (PR 3.4, 95% CI 1.9-5.9). However, the high incidence of aSAH in patients with a positive family history is only partly explained by a higher prevalence of UIAs.

Women had a higher prevalence of UIAs than men (PR 1.6, 95% CI 1.0-2.5), with a trend towards an even higher prevalence in older women. We found no differences according to age, except for patients <30 years of age who had a lower prevalence.

The higher aSAH incidences in Finnish and Japanese populations are not explained by a higher prevalence of UIAs. This suggests higher risks of rupture in these populations, which we conclude is not due to a higher proportion of high risk aneurysms (i.e. larger than 5 mm or located in the posterior circulation).

Patients with stroke, especially aSAH, are often in poor clinical condition, in which case physicians and researchers have to rely on information given by proxies. **Chapter 3** describes the results of a study to investigate the reliability of proxy responses regarding trigger factors for stroke. For exposure to risk factors and average frequency of exposure in the past year, non-response is low and the level of agreement is high for most risk factors; for last time of exposure non-response is higher, but proxies who could respond provided reliable estimates of last time of exposure to most trigger factors. We therefore concluded that proxies provide reliable information on exposure to chronic risk factors and trigger factors for stroke.

In **Chapter 4** we aimed to identify and quantify trigger factors for aneurysmal rupture. In total, 250 patients with an aSAH completed a structured questionnaire regarding exposure to 30 potential trigger factors in the period soon before aSAH (hazard period) and for usual frequency and intensity of exposure. Eight triggers increased the risk for aSAH: coffee consumption (relative risk [RR] 1.7, 95% CI 1.2-2.4), cola consumption (RR 3.4, 95% CI 1.5-7.9), anger (RR 6.3, 95% CI 4.6-25), startling (RR 23.3, 95% CI 4.2-128), straining for defecation (RR 7.3, 95% CI 2.9-19), sexual intercourse (RR 11.2, 95% CI 5.3-24), nose-blowing (RR 2.4, 95% CI 1.3-4.5), and vigorous physical exercise (RR 2.4; 95% CI 1.2-4.2). All triggers we identified potentially induce a sudden and short increase in blood pressure, which seems a possible common cause for triggering the aneurysmal rupture. The highest population-attributable risks (i.e. the proportion of aSAHs that can be contributed to a specific trigger factor) were found for coffee consumption (10.6%) and vigorous physical exercise (7.9%).

In **Chapter 5** we investigated whether the relative risks associated with the trigger factors we identified in Chapter 4, differed according to sex and age or according to site and size of the ruptured aneurysm. Of all eight trigger factors, only the risk associated with physical exercise differed slightly according to patient and aneurysm characteristics. The risk of rupture after exercise is higher in patients over the age of 60. There was no sex difference. Patients with aneurysms <5mm in the anterior communicating artery might have a higher risk of rupture after exercise.

Chapter 6 describes a case-control study in which we compared 206 patients with an UIA with 574 controls in an attempt to identify independent risk factors for the presence of UIAs from life style and medical history data. Current smoking (odds ratio [OR] 3.0, 95% CI 2.0-4.5), hypertension (OR 2.9, 95% CI 1.9-4.6) and family history of stroke (OR 1.6, 95% CI 1.04-2.5), increase the risk of UIA, with smoking and hypertension having an additive effect (OR 8.3, 95% CI 4.5-15.2), whereas hypercholesterolaemia (OR 0.5, 95% CI 0.3-0.9) and regular physical exercise (OR 0.6, 95% CI 0.3-0.9) decrease this risk. Since patients and controls were virtually matched for sex and age, these risk factors could not be taken into account.

In **Chapter 7** a second case-control study is described in which 206 patients with an UIA were compared with 250 patients with an aSAH in order to study life style and personal characteristics as risk factors for the rupture of UIAs. Smoking (OR 1.9, 95% CI 1.2-3.0), migraine (OR 2.4, 95% CI 1.1-5.1) and, inversely, hypercholesterolaemia (OR 0.4, 95% CI 0.2-1.0) were independent risk factors for aneurysmal rupture, whereas hypertension did not independently affect the risk. Data were insufficient to determine whether the hypercholesterolaemia or its treatment with statins exerted a risk reducing effect. The

pathophysiological mechanisms through which smoking and migraine increase the risk of aneurysmal rupture should be investigated in further studies.

Unfortunately, patients with an aSAH and patients with an UIA were virtually matched for sex and age, thus these risk factors could not be taken into account. In this study 18% of patients with an UIA were screened because of a positive family history; therefore this factor could not be studied since this would have caused inclusion bias.

In **Chapter 8** we aimed to estimate incidence and life-time risks of aSAH according to risk factor profiles. We performed a case-control study in which 250 patients with aSAH and 574 sex-and age-matched controls, who were randomly retrieved from general practitioners files, were compared. We found six independent prognostic risk factors for aSAH. The four strongest independent predictors were also risk factors for aSAH, namely current smoking (OR 6.0, 95% CI 4.1-8.6), a positive family history for aSAH (OR 4.0, 95% CI 2.3-7.0), hypertension (OR 2.4, 95% CI 1.5-3.8) and hypercholesterolaemia (OR 0.2, 95% CI 0.1-0.4), and were used in the final prediction model to estimate incidence and life-time risks.

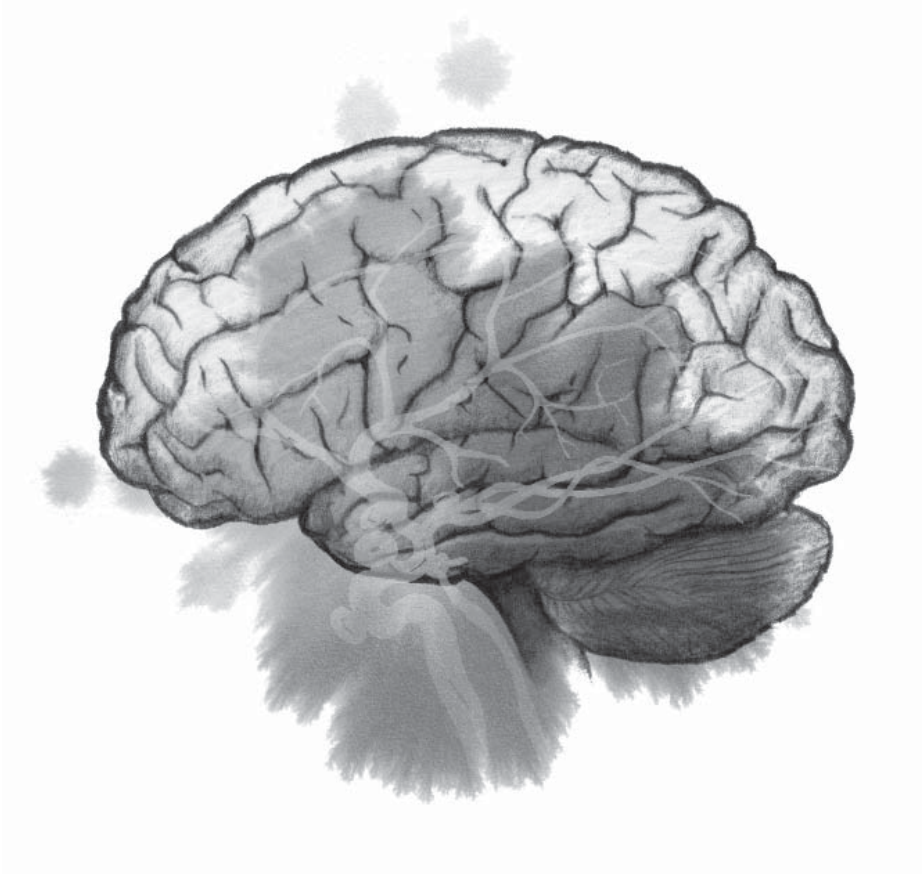
The overall incidence of aSAH in western populations is around 9 per 100,000 person-years. We estimated that, depending on sex, age and the four predictors, the incidence of aSAH varies from 0.4/100,000 to 298/100,000 person-years and life-time risk between 0.02% and 7.2%. Whether persons with high risks benefit from screening should be further assessed in cost-effectiveness studies.

In **Chapter 9** we attempt to put some of the pieces of the aSAH puzzle together. We have found that smoking and hypertension are very important risk factors for aSAH, which have an additive joint effect in the development of UIAs. Smoking increases the risk of aSAH by an increased risk of harbouring an UIA and an increased risk of rupture, although smoking does not trigger aneurysmal rupture. A history of hypertension increases the risk of aSAH by a higher risk of developing an UIA, not by a higher risk of rupture. However, we do hypothesize that a sudden and short lasting rise in blood pressure caused by trigger factors may elicit the actual rupture.

Hypercholesterolaemia decreases the risk of rupture by both a decreased risk of UIA development and a decreased risk of rupture. The mechanism through which hypercholesterolaemia lowers the risk of UIA development and rupture, and the role of statin use remain unclear.

We have shown that physical exercise decreases the risk of developing an UIA, thereby decreasing the risk of aSAH. Once an UIA has developed, there is an elevated risk during or just after exercise which subsides soon thereafter, but exercise has no long term effect on risk of rupture.

Our studies have been limited, since we were not able to take well known risk factors for aSAH such as sex, age and family history of aSAH or UIA into account. Therefore other pieces of this puzzle still need to fall into place to complete the 'picture' of risk factors for aSAH and their interrelationships…



Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Een subarachnoïdale bloeding (SAB) is een bloeding in de subarachnoïdale ruimte, de ruimte die zit tussen de hersenen en het spinnenwebvlies. Een SAB wordt in 90% van de gevallen veroorzaakt door het knappen van een aneurysma, een uitstulping in een van de slagaders van de hersenen. Omdat een SAB vaak relatief jonge mensen treft en een hoge sterfte kent, is het een belangrijke vorm van een beroerte. Een manier om het aantal SAB's te laten dalen is de kans op het ontwikkelen van aneurysmata, alsook het knappen van aneurysmata te verlagen. Hiervoor is het belangrijk om te weten welke factoren het risico op een SAB verhogen dan wel verlagen.

Het risico op een SAB bestaat uit drie componenten: 1) risicofactoren voor het ontstaan van een aneurysma, 2) 'chronische' risicofactoren voor het knappen van een aneurysma, zoals vrouwelijk geslacht, leeftijd en bloeddruk, en 3) factoren, die het acute knappen van het aneurysma veroorzaken (triggerfactoren). In dit proefschrift is getracht om de risicofactoren van deze drie componenten te identificeren. Daarnaast is er een prognostisch model ontwikkeld waarmee voor mensen uit de algehele bevolking, op basis van hun risicoprofiel, een schatting kan worden gemaakt van het risico op een SAB.

Niet-invasieve beeldvormende technieken worden de afgelopen jaren in toenemende mate gebruikt voor het afbeelden van de hersenen en de hersenvaten. Dit heeft geresulteerd in een toename van het aantal ontdekte asymptomatische aneurysmata, maar ook in een toename van het aantal publicaties over dit onderwerp. Om een zo goed mogelijke schatting te maken van het relatieve voorkomen (prevalentie) van ongebarsten aneurysmata werd een review en meta-analyse uitgevoerd aan de hand van alle studies over dit onderwerp tot nu toe (**hoofdstuk 2**). Na screening van meer dan 5000 artikelen werden uiteindelijk 68 studies in de studie opgenomen. Er werd berekend dat de prevalentie van ongeknapte aneurysmata in een gemiddelde populatie (leeftijd gemiddeld 50 jaar, 50% mannen en geen co-morbiditeit) ongeveer 3,2% is. De prevalentie is in de afgelopen 50 jaar niet significant veranderd.

De prevalentie van aneurysmata is 6,9 keer (95% betrouwbaarheidsinterval [Engels: confidence interval (CI)] 3,5-14) zo hoog bij patiënten met cystenieren. Bij patiënten met een positieve familieanamnese voor SAB is het risico 3,4 maal (95% CI 1,9-5,9) verhoogd, wat slechts ten dele het vaker voorkomen van SAB's in deze patiëntencategorie verklaart. Patiënten jonger dan 30 jaar hebben een significant lager risico op een aneurysma; de overige leeftijdscategorieën hebben vergelijkbare prevalenties. Vrouwen bleken een 1,6 maal (95% CI 1,0-2,5) hogere prevalentie te hebben dan mannen. Het lijkt erop alsof dit vooral veroorzaakt wordt door een hogere prevalentie van aneurysmata bij vrouwen boven de 50 jaar.

Uit de literatuur is bekend dat Finse en Japanse populaties een hogere incidentie van SAB's kennen. Uit de meta-analyse bleek echter dat de prevalentie van ongeknapte aneurysmata in deze landen niet significant hoger is ten opzichte van die in andere landen. Dit lijkt erop te wijzen dat aneurysmata in Finse en Japanse populaties een grotere kans hebben om te knappen. Uit de meta-analyse bleek echter dat er in de Finse en Japanse populaties geen hogere prevalentie van aneurysmata met verhoogd risico voorkomt (d.w.z. >5 mm of gelegen in het achterste deel van de cirkel van Willis) dan bij andere populaties. Het blijft dus vooralsnog onduidelijk wat de oorzaak is van deze hogere knapkans in Finse en Japanse populaties.

Patiënten met een beroerte, vooral na een SAB, zijn er vaak slecht aan toe, waardoor artsen en onderzoekers regelmatig moeten terugvallen op informatie die door naasten gegeven wordt. Daarom werd in **hoofdstuk 3** gekeken naar de betrouwbaarheid van door naasten gegeven informatie over risicofactoren en triggerfactoren voor een beroerte. Er werd gevonden dat de non-respons over de (frequentie van) blootstelling aan risicofactoren in het afgelopen jaar laag was en dat de antwoorden van de patiënt goed overeenkwamen met die van de naaste(n). De non-respons was hoger op vragen over de laatste keer van blootstelling aan de risicofactoren, maar de schatting die naasten konden geven over de laatste blootstelling aan eventuele triggerfactoren was wel betrouwbaar. We concludeerden dan ook dat naasten voldoende betrouwbare informatie kunnen geven over risico- en triggerfactoren van beroertes, met name SAB's.

Sporten, seks, alcoholgebruik, roken en stress worden genoemd als activiteiten en omstandigheden die vaak voorafgaan aan een SAB. Voor de meeste factoren is echter nooit onderzocht of dit berust op toeval of dat ze daadwerkelijk het knappen van het aneurysma uitlokken. Alleen van lichamelijke inspanning is bekend dat het ook daadwerkelijk een triggerfactor is voor het knappen van een aneurysma. In **hoofdstuk 4** werd getracht om triggerfactoren voor een SAB te identificeren en te kwantificeren. Hiervoor hebben in totaal 250 patiënten een SAB vragenlijst ingevuld (met of zonder de hulp van een naaste) over de blootstelling aan 30 potentiële triggerfactoren. Patiënten werd gevraagd naar (frequentie van) blootstelling aan die factoren in het afgelopen jaar en vooral naar blootstelling in de periode kort voor de SAB. Voor de analyses werd gebruikgemaakt van de 'case-crossover'-methode, waarbij op basis van de frequentie van blootstelling in het afgelopen jaar de kans wordt berekend dat iemand ook in de periode vlak voor de SAB blootgesteld is aan een bepaalde factor. Als het aantal mensen dat aan een factor is blootgesteld in de periode voor de SAB hoger is dan op basis van de blootstellingsfrequentie van het afgelopen jaar verwacht zou mogen worden, dan kan gesproken worden van een triggerfactor. In totaal zijn acht triggerfactoren geïdentificeerd die de kans op het knappen van een aneurysma,

en dus het krijgen van een SAB, verhogen, namelijk: koffiedrinken (relatief risico (RR) 1,7, 95% CI 1,2-2,4), cola drinken (RR 3,4, 95% CI 1,5-7,9), boosheid (RR 6,3, 95% CI 4,6-25), schrikken (RR 23,3, 95% CI 4,2-128), persen voor ontlasting (RR 7,3, 95% CI 2,9-19), seksuele gemeenschap (RR 11,2, 95% CI 5,3-24), het snuiten van de neus (RR 2,4, 95% CI 1,3-4,5) en lichamelijke inspanning (RR 2,4, 95% CI 1,2-4,2). Van deze acht triggerfactoren is bekend dat ze een plotselinge en kortdurende bloeddrukverhoging kunnen geven wat mogelijk het daadwerkelijk knappen van het aneurysma veroorzaakt.

Naast het berekenen van het risico dat geassocieerd is met iedere triggerfactor, werd ook berekend welk percentage van alle SAB's kan worden toegeschreven aan iedere triggerfactor afzonderlijk, het zogenaamde 'population attributable risk'. Uit deze berekeningen bleek dat de hoogste percentages kunnen worden toegeschreven aan koffiedrinken (10,6%) en lichamelijke inspanning (7,9%). Ondanks het feit dat het relatieve risico van deze factoren laag is, zijn deze laatste toch voor een naar verhouding hoog percentage van de SAB's verantwoordelijk, omdat deze activiteiten gewoonweg veel voorkomen in de algehele populatie.

In **hoofdstuk 5** hebben we gekeken of geslacht en leeftijd van de patiënt en de grootte en locatie van het aneurysma invloed hebben op het relatieve risico van de acht gevonden triggerfactoren. Dit was alleen het geval bij lichamelijke inspanning, voor de overige triggerfactoren werd geen verschil gevonden. Het risico na lichamelijke inspanning was groter bij patiënten ouder dan 60 jaar. Ook werd gevonden dat patiënten met een klein aneurysma, vooral wanneer deze gelokaliseerd is in het voorste deel van de cirkel van Willis, een grotere kans hebben op het knappen van het aneurysma na lichamelijk inspanning. Geslacht had geen effect op het ruptuurrisico na lichamelijke inspanning.

Na het identificeren en kwantificeren van de triggerfactoren voor het knappen van een SAB in een aantal studies werd getracht getracht risicofactoren voor het ontwikkelen van een aneurysma en 'chronische' risicofactoren voor het knappen van een aneurysma te identificeren. Hiervoor werd gebruik gemaakt van het 'case-control'-onderzoek, waarin steeds twee groepen met elkaar vergeleken werden. In **hoofdstuk 6** werden 206 patiënten met een ongebarsten aneurysma vergeleken met 574 controlepatiënten uit de algehele bevolking. Hieruit bleek dat roken (odds ratio (OR) 3,0, 95% CI 2,0-4,5), hoge bloeddruk (OR 2,9, 95% CI 1,9-4,6) en beroertes in de familie (OR 1,6, 95% CI 1,04-2,5) allen de kans vergroten op het krijgen van een aneurysma. Patiënten die lijden aan hoge bloeddruk en daarnaast ook roken hebben zelfs een sterk verhoogd risico op een aneurysma (OR 8,3, 95% CI 4,5-15,2). Dit is een hoger risico dan op basis van de individuele risicofactoren verwacht mag worden, wat suggereert dat dit roken en deze hoge bloeddruk elkaar versterken. Verder werd gevonden dat een verhoogd cholesterolgehalte (OR 0,5, 95% CI 0,3-0,9) en

regelmatig sporten (OR 0,6, 95% CI 0,3-0,9) het risico op een aneurysma verlagen. Helaas konden leeftijd en geslacht, twee belangrijke factoren, niet meegenomen worden, omdat de groep patiënten met een aneurysma qua verdeling naar leeftijd en geslacht vrijwel gelijk was aan de controlegroep.

In **hoofdstuk 7** hebben we een tweede 'case-control'-studie gedaan, waarin 206 patiënten met een ongebarsten aneurysma werden vergeleken met 250 patiënten met een SAB. Hieruit bleek dat roken (OR 1,9; 95% CI 1,2-3,0) en migraine (OR 2,4; 95% CI 1,1-5,1) het risico op knappen verhogen, terwijl een verhoogd cholesterolgehalte de kans op knappen juist verlaagt (OR 0,4; 95% CI 0,2-1,0). Opvallend was dat hoge bloeddruk geen onafhankelijke risicofactor was voor het knappen van een aneurysma. Vooralsnog is niet duidelijk hoe migraine en cholesterol het knappen van een aneurysma beïnvloeden en welke rol medicatie daarbij speelt. Ongeveer 18% van de patiënten met een ongebarsten aneurysma waren gescreend, omdat ze een familielid met een SAB of aneurysma hadden. Daarom kon een positieve familieanamnese niet worden meegenomen als risicofactor voor het knappen van een aneurysma. Ook konden wederom leeftijd en geslacht niet worden meegenomen als risicofactor, omdat de groep met patiënten met een aneurysma qua verdeling naar leeftijd en geslacht vrijwel gelijk was aan de groep patiënten met een SAB.

De incidentie van een SAB is ongeveer 9 per 100.000 persoonsjaren. Wij vermoedden echter dat deze incidentie sterk uiteen kan lopen, afhankelijk van leeftijd, geslacht en risicoprofiel. In **hoofdstuk 8** hebben we daarom op basis van een viertal risicofactoren voor een SAB, namelijk roken, hoge bloeddruk, een verhoogd cholesterolgehalte en een positieve familieanamnese, een prognostisch model ontwikkeld. Hiermee konden op basis van leeftijd, geslacht en risicoprofiel schattingen worden gemaakt van de incidentie en 'life-time'- risico's (risico voor de nog resterende levensjaren) voor verschillende groepen patiënten. Uit het model bleek dat de incidentie van SAB varieerde tussen de 0,4 per 100.000 persoonsjaren en 298 per 100.000 persoonsjaren. Het life-time risico varieert tussen de 0,02% en de 7,2%. Tot dusver is alleen voor patiënten met ≥2 familieleden met een aneurysma of SAB aangetoond dat screenen kosteneffectief is (life-time risico 26%). Of het screenen van patiënten met een hoog risicoprofiel ook kosteneffectief is moet nog onderzocht worden door middel van kosteneffectiviteitstudies.

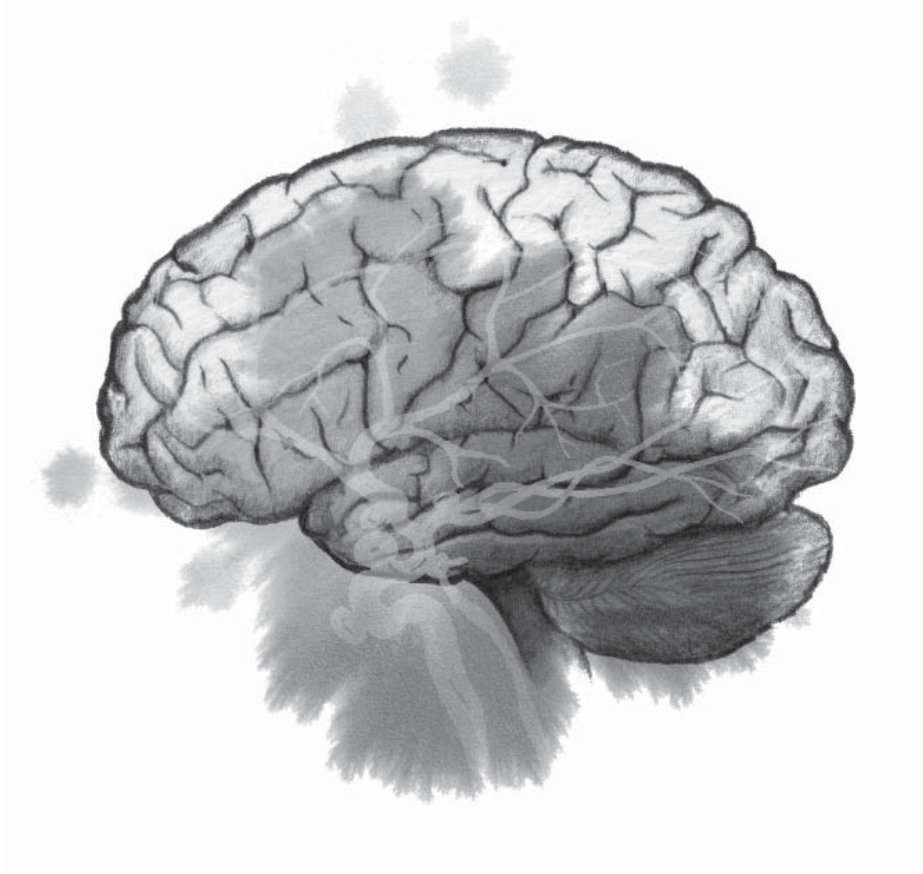
In **hoofdstuk 9** werd getracht de gevonden stukjes van de SAB-puzzel in elkaar te passen. Roken verhoogt het risico op een SAB door een verhoogd risico op een aneurysma, maar ook een verhoogd risico op het knappen van dat aneurysma, al blijkt het geen triggerfactor te zijn die het knappen uitlokt. Een hoge bloeddruk verhoogt het risico op een SAB door een grotere kans op het ontwikkelen van een aneurysma, wat verder versterkt wordt door ook te roken. Hoge bloeddruk geeft echter geen verhoogde knapkans. Wel is het mogelijk

dat een plotselinge en kortdurende bloeddrukstijging als gevolg van blootstelling aan een triggerfactor leidt tot het knappen van een aneurysma. Een verhoogd cholesterolgehalte verlaagt het risico op een SAB door het verlagen van het risico op een aneurysma, maar ook door het verlagen van het risico op het knappen van een aneurysma. Via welk mechanisme cholesterol deze risico's verlaagt en welke rol cholesterolverlagers daarbij spelen blijft vooralsnog onduidelijk.

We hebben ook aangetoond dat door regelmatig te sporten het risico op een aneurysma wordt verkleind. Indien een aneurysma zich eenmaal heeft ontwikkeld, dan is er een verhoogd risico op het knappen van het aneurysma gedurende en kort na lichamelijke inspanning, maar op de langere termijn heeft sporten geen effect op de knapkans. Omdat sporten ook andere cardiovasculaire voordelen heeft wordt patiënten met een aneurysma toch niet geadviseerd om zich niet meer lichamelijk in te spannen.

Doordat de patiëntengroep met een SAB, die met een ongeknapt aneurysma en de controlegroep qua leeftijd en geslacht op elkaar leken, konden deze belangrijke factoren niet worden meegenomen in de diverse studies naar risicofactoren. Ook de factor familieanamnese konden niet altijd bestudeerd worden.

In dit proefschrift is uiteengezet hoe factoren, zoals roken, hoge bloeddruk, inspanning en een verhoogd cholesterol, de kans op een SAB beïnvloeden en bij welke tot een SAB leidende stap in het proces deze factoren een rol spelen. Een deel van de puzzel lijkt hiermee opgelost; echter er blijven nog een aantal puzzelstukjes over die in de toekomst hopelijk zullen worden aangelegd om een compleet beeld te krijgen van de risicofactoren en hun onderlinge samenhang.



Dankwoord

DANKWOORD

Zeven jaar na het starten van mijn promotieonderzoek ligt er eindelijk een boekje waar ik ontzettend trots op ben. Rest mij nog het dankwoord te schrijven om diegenen te bedanken zonder wie dit proefschrift nooit tot een goed einde was gekomen…

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Ale, de snelheid waarmee je al mijn manuscripten nakeek deed niets af aan de nauwkeurigheid waarmee dat gebeurde; werkelijk alles werd nagerekend. Ook je vermogen om mij werkelijk iets te laten begrijpen van statistiek is uniek. Als ik weer eens niet meer uit mijn eigen woordenbrij kwam bij het schrijven van een artikel, dan was jouw advies heel eenvoudig: KISS (Keep It Stupidly Simple). Ik wil je bedanken voor de geweldige en ook gezellige begeleiding die je me al die jaren hebt gegeven!

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Drs. Brandenburg. Beste Raya, ook jij kwam als student een wetenschappelijke stage doen, oorspronkelijk voor 3 maanden. Dat werd 1,5 jaar, maar het resulteerde wel in een gezamenlijke publicatie in de Lancet Neurology. Ik vind het heel leuk dat je af en toe voor advies langskomt en dat je zelf nu ook besloten hebt promotieonderzoek te gaan doen. Je hebt in ieder geval een goede indruk gekregen van de te nemen hobbels bij het promoveren…

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Prof. Dr. Smit, Prof. Dr. Wokke, Prof. Dr. Groen, Prof. Dr. Verhaar en Dr. Braekkan, leden van de leescommissie. Veel dank voor het warme onthaal van mijn manuscript. Ik dank jullie voor de energie en de tijd die jullie in het doornemen ervan gestoken hebben.

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jullie mocht beginnen heb ik me toen niet ten volle gerealiseerd wat dat precies zou gaan inhouden… Dank voor de leuke opleidingstijd in Utrecht onder jullie bezielende leiding!

Arts-assistenten Neurologie. Het is mooi te zien hoe gezellig en hecht de assistentenclub uit Utrecht was, is en blijft. Ik heb genoten van de meer dan 10 jaar UMCU Neurologie met assistentenweekenden, Biemondfeestjes, congressen en Babinski-tripjes. Ik zal ze missen… Het ga jullie goed!

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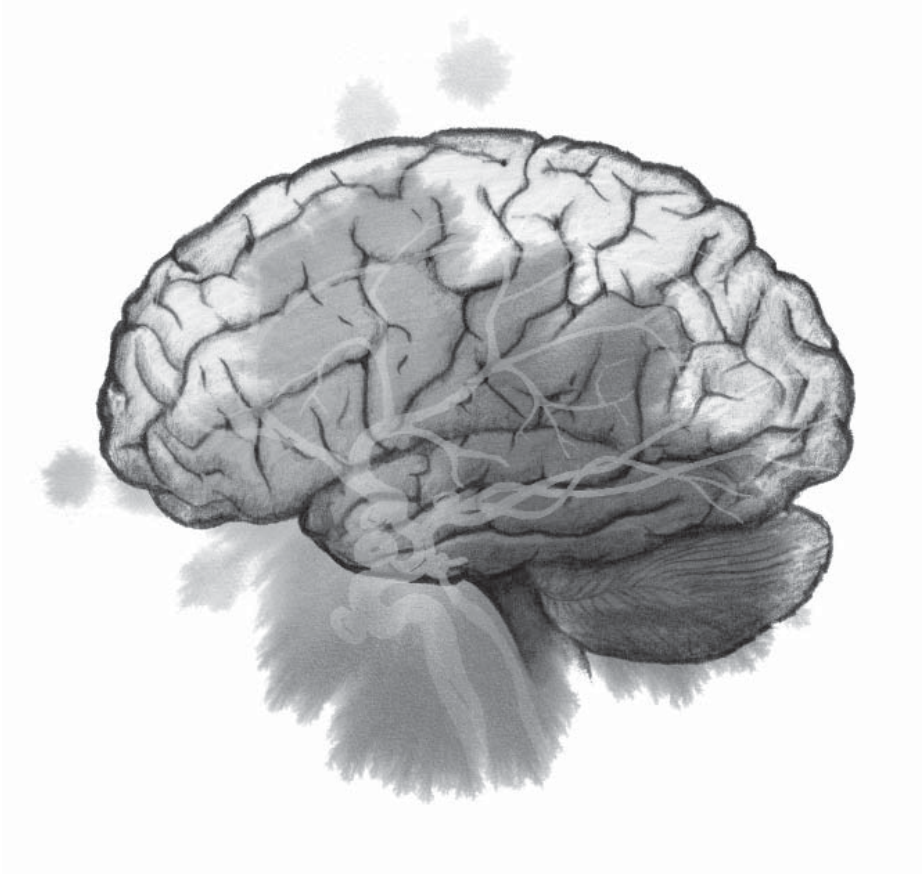
Lieve ouders, zonder jullie veilige nest zou ik nooit zo ver hebben durven uitvliegen. Pap, jij bent degene geweest die me gestimuleerd heeft te gaan promoveren en ook vol te houden als het wat moeizaam ging. Het was heerlijk je af en toe te kunnen bellen dat MHM weer een keer bovenaan de PubMed-pagina stond in plaats van JM. Ik ben nu beter gaan begrijpen waarom jij je leven aan de wetenschap hebt gewijd. Mam, jij bent degene

geweest die mijn artikelen nauwgezet doorgespit heeft op taalfouten en inconsistenties tussen de hoofdstukken. Zonder jouw inzet had ik de deadlines nooit gehaald. Je bent de liefste moeder die een kind (en promovenda) zich kan wensen!

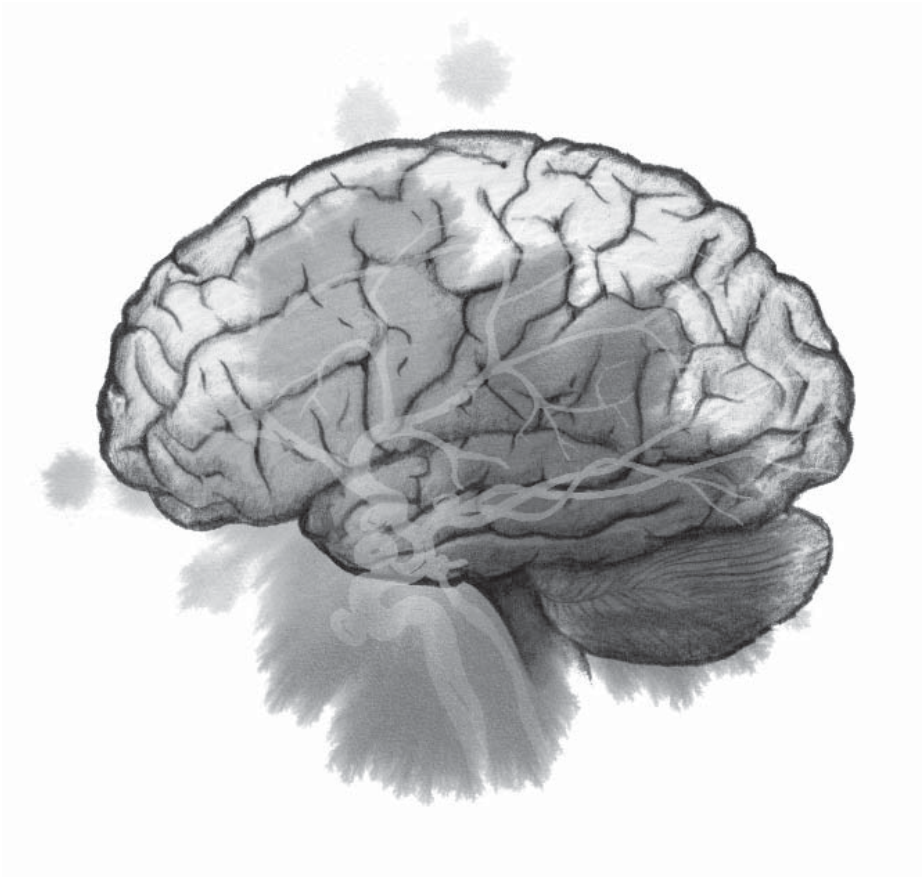
Lieve Guido, Dieuwke en Gijs, als deze inkt is opgedroogd houd ik al weer meer van jullie! Ik kijk ernaar uit samen met jullie verder van het leven te genieten…



Curriculum vitae

CURRICULUM VITAE

Monique Vlak was born on the 21st of September 1975 in Utrecht, the Netherlands. After graduating from the Christelijk Lyceum Veenendaal in 1993 she started to study Health Sciences at Maastricht University the same year. After successfully completing the first year, she changed to study Medicine at the Radboud University in Nijmegen. During this study she became interested in neurology and participated in various research projects on neuromuscular diseases under supervision of Prof.dr. B.G.M. van Engelen (Nijmegen) and Prof.dr. C. Angelini (Padua, Italy). In 2001 Monique obtained her medical degree and then worked as a resident at the Neurology Department of the Radboud Hospital in Nijmegen. In 2002 she started her neurology training at the University Medical Center in Utrecht under supervision of prof.dr. J. van Gijn and prof.dr. J.H.J. Wokke. Monique began her PhD project on risk factors for subarachnoid haemorrhage in 2006 under supervision of Prof.dr. A. Algra en Prof.dr. G.J.E. Rinkel. In 2011 she received the Junior Investigators Award at the European Stroke Conference in Hamburg/Germany for her research on subarachnoid haemorrhage. After finishing her neurology training in July 2010, Monique started practicing as a neurologist and sleep specialist at the Slotervaart Hospital in Amsterdam.



List of publications

LIST OF PUBLICATIONS

This thesis

1. **Vlak MH**, Rinkel GJ, Greebe P, Algra A. Risk of rupture of an intracranial aneurysm based on patient characteristics: a case-control study. *Stroke*. 2013, in press.
2. **Vlak MH**, Rinkel GJ, Greebe P, Algra A. Independent risk factors for intracranial aneurysms and their joint effect: a case-control study. *Stroke*. 2013, in press.
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