Neurosurgery
Characteristics of unruptured compared to ruptured intracranial aneurysms: a multicentre case-control study
--Manuscript Draft--

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Manuscript Region of Origin: UNITED KINGDOM

Abstract:

ABSTRACT
Background Only a minority of intracranial aneurysms rupture to cause subarachnoid haemorrhage.
Objective We tested the hypothesis that unruptured aneurysms have different characteristics and risk factor profiles compared to ruptured aneurysms.
Methods We recruited patients with unruptured aneurysms or aneurysmal subarachnoid haemorrhage at 22 UK hospitals between 2011-2014. Demographic, clinical, and imaging data were collected using standardized case report forms. We compared risk factors using multivariable logistic regression.
Results 2334 patients (1729 with aneurysmal subarachnoid haemorrhage, 605 with unruptured aneurysms) were included (mean age 54.22 years). In multivariable analyses, the following variables were independently associated with rupture status: black ethnicity (OR 2.42; 95% CI 1.29-4.56; compared to white); aneurysm location (anterior cerebral artery/anterior communicating artery [OR 3.21; 95% CI 2.34-4.40], posterior communicating artery [OR 3.92; 95% CI 2.67-5.74], or posterior circulation [OR 3.12; 95% CI 2.08-4.70], compared to middle cerebral artery). The following variables were inversely associated with rupture status: antihypertensive medication (OR 0.65; 95% CI 0.49-0.84), hypercholesterolemia (0.64 OR; 95% CI 0.48-0.85), aspirin use (OR 0.28; 95% CI 0.20-0.40), internal carotid artery location (OR 0.53; 95% CI 0.38-0.75), and aneurysm size (per mm increase) (OR 0.76; 95% CI 0.69-0.84).
Conclusion We show substantial differences in patient and aneurysm characteristics between ruptured and unruptured aneurysms. These findings support the hypothesis that different pathological mechanisms are involved in the formation of ruptured aneurysms and incidentally detected unruptured aneurysms. The potential protective effect of aspirin in the two cohorts might justify randomized prevention trials in patients with unruptured aneurysms.
### Significance of the Work:

Please include a brief statement summarizing the significance of the work and in particular how it differs from and advances existing literature.

Aneurysmal subarachnoid haemorrhage (SAH) is a devastating subset of stroke, occurring in relatively young people with a high mortality rate. Understanding risk factors may be helpful in identifying patients at high risk for aneurysmal SAH and consequently prevention. In our large multicentre case-control study, we have identified differing potential risk factors when comparing unruptured intracranial aneurysms with aneurysms causing SAH; in particular, aspirin use was found to be protective, independent of confounding by indication, and might merit further investigation. Our findings are relevant for neurologists and neurosurgeons when making clinical decisions in patients with an unruptured intracranial aneurysm.

### Compliance with Research Reporting Guidelines:

*Neurosurgery* endorses several reporting guidelines and requires authors to submit their research articles in accordance with the appropriate guideline statement(s) and checklist(s). Completed applicable checklists and flow diagrams must be included with submissions.

Research articles that must be submitted according to the appropriate reporting guideline(s) include, but are not limited to: randomized trials, systematic reviews, meta-analyses of interventions, meta-analyses of observational studies, diagnostic accuracy studies, and observational epidemiological studies (eg, case series, cohort, case-control, and cross-sectional studies). Consult the EQUATOR Network, which maintains a useful, up-to-date list of guidelines as they are published, with links to articles and checklists: http://www.equator-network.org.

Please confirm below that information is reported according to the relevant reporting guideline(s) and any required materials are included with the submission:

Yes - Submission Adheres to Appropriate Reporting Guideline(s) and Applicable Checklists/Materials Are Included

Please indicate which reporting guideline(s) the study adheres to (eg, STROBE, PRISMA, CONSORT).

as follow-up to "Compliance with Research Reporting Guidelines: *Neurosurgery* endorses several reporting guidelines and requires authors to submit their research articles in accordance with the appropriate guideline statement(s) and checklist(s). Completed applicable checklists and flow diagrams must be included with submissions.

Research articles that must be submitted according to the appropriate reporting guideline(s) include, but are not limited to: randomized trials, systematic reviews, meta-analyses of interventions, meta-analyses of observational studies, diagnostic accuracy studies, and

STROBE
observational epidemiological studies (e.g., case series, cohort, case-control, and cross-sectional studies). Consult the EQUATOR Network, which maintains a useful, up-to-date list of guidelines as they are published, with links to articles and checklists: http://www.equator-network.org.

Please confirm below that information is reported according to the relevant reporting guideline(s) and any required materials are included with the submission:

### Statistical Analysis:
For manuscripts that report statistics, the Editor requires that the authors provide evidence of statistical consultation or expertise.

If your article includes statistics, has the information reported been evaluated by an expert? **Yes**

### IRB/Ethics Approval:
Please indicate if your study has received institutional review board/ethics approval. If yes, these materials are readily available should the Editor request them. **Yes**
20th September 2016

Dr Nelson M. Oyesiku, MD PhD, FACS, Editor-in-Chief
Editor, Neurosurgery

Dear Dr Oyesiku,

Re: Characteristics of unruptured compared to ruptured intracranial aneurysms: a multicentre case-control study

We would be grateful if the above paper could be considered for publication in Neurosurgery as an article. Aneurysmal subarachnoid haemorrhage (SAH) is a devastating subset of stroke, occurring in relatively young people with a high mortality rate. Understanding risk factors may be helpful in identifying patients at high risk for aneurysmal SAH and consequently prevention. In our large multicentre case-control study, we have identified differing potential risk factors when comparing unruptured intracranial aneurysms with aneurysms causing SAH; in particular, aspirin use was found to be protective, independent of confounding by indication, and might merit further investigation. Our findings are relevant for neurologists and neurosurgeons when making clinical decisions in patients with an unruptured intracranial aneurysm.

I take full responsibility for the data, the analyses and interpretation, and the conduct of the research; I have full access to all of the data; the author has the right to publish any and all data separate and apart from any sponsor. A regional review board has approved the use of human subjects for this study.

All authors have read and approved the submitted manuscript; the manuscript has not been submitted elsewhere nor published elsewhere in whole or in part. I sign for and accept responsibility for this material on behalf of all co-authors. None of the authors have any conflict of interest to report.
This study was conducted in compliance with the current version of the Declaration of Helsinki, and GCP as well as all national legal and regulatory requirements.

The GOSH study is funded by the Stroke Association. This work was partly undertaken at UCLH/UCL who received a proportion of funding from the Department of Health’s NIHR Biomedical Research Centres funding scheme.

Yours sincerely,

David Werring PhD FRCP FESO
Professor of Clinical Neurology
Consultant Neurologist
RESPONSE TO REVIEWERS

Dear reviewers

RE: Characteristics of unruptured compared to ruptured intracranial aneurysms: a multicentre case-control study

We are grateful for the opportunity to resubmit a secondary revised version. Our itemized point-by-point responses are given below, and are underlined in our revised manuscript.

Reviewer 1:

This revised manuscript, which describes a case control study identifying differences in ruptured and unruptured aneurysms, has been revised to adequately address our comments. This new version better defines the limitations of their study, especially regarding potential biases in the study groups. Even with its flaws, this study contributes to our current body of data and will further discussion on differences between ruptured and unruptured aneurysms.

We thank the reviewer for the useful comments and improvement on our manuscript.

Reviewer 2:

The authors did a great job addressing the reviewer’s concerns.

We thank the reviewer for the useful comments and improvement on our manuscript.

Reviewer 3:

1. The manuscript has now been improved by deleting obvious concerns and faults. However, the study design and patient selection predisposes yet for misconceptions which are not necessarily true but preferably association between different confounding factors which are difficult to be controlled for. Further analyses are needed.

We thank the reviewer for the useful comments and improvement on our manuscript. We have checked that we have undertaken all of the analyses suggested (see our response to point 4, below).

2. The study consists of 2334 patients (1729 with aneurysmal subarachnoid haemorrhage, 605 with unruptured aneurysms (UIAs)) were included (mean age 54.22 years). Patients with UIAs had clearly larger aneurysm than has previously been published (see ref 1. Vlak et al.) meaning that this population with UIAs is a more selected one than in previous studies.

We agree with this point. Indeed, we had a larger mean UIA size compared to Vlak et al. which could indicate selection bias, a limitation of any hospital-based study. However, an important
3. Patients with high BP values, long-term hypertension and large aneurysms die more likely than survive after SAH and do not reach treatment in secondary and tertiary clinics. For this issue there is only one study (Juvela S. Prehemorrhage risk factors for fatal intracranial aneurysm rupture. Stroke 2003;34:1852-1857). Some autopsy studies also suggest that patients with ruptured MCA aneurysms with space occupying are more common autopsy studies than in clinical studies. So patients with hypertension, large aneurysms and MCA aneurysms may be underestimated in ruptured aneurysm group.

We agree that our study cannot include patients with severe SAH who die before reaching hospital, and that these patients might have different characteristics to those included (e.g. larger aneurysms or co-morbidities), potentially introducing selection bias. This is a limitation of any study on ruptured aneurysms, which we acknowledge and discuss (Page 6, lines 178-182).

4. Patients with UIAs were older, had more diseases and medications (hypertension and antihypertensive medication, diabetes, hypercholesterolemia and statin use, previous stroke, coronary artery disease, cardiac disease, and because of several vascular diseases and risk factors also aspirin use. All these factors were more common in patients with UIAs than in those with SAH. Authors have picked aspirin as a "protecting factor" for rupture. Only in Table 3 were odds ratios adjusted for one of these confounders, previous stroke, which had also a lower association with SAH! By which mechanism? The reason seems that in cross-sectional retrospective study factors may associate without a causal relationship. Very sick patients likely die of other diseases than of aneurysm rupture. Because authors have interviewed and collected data from patients authors should present also indications of aspirin treatment. Aspirin was used likely for vascular diseases which shorten life-expectancy.

We thank the reviewer for addressing this important point. We can clarify that aspirin was shown to be “protective” in a pre-planned and systematic analysis, described in our methods, and was not specifically “picked”. We adjusted for all of the above-mentioned factors in a multivariable backward stepwise logistic regression analysis: diabetes, statin use, cardiovascular disease such as myocardial infarction, angina, and PVD. On page 7, lines 227-229 we mention this: “even after fully adjusting for potential confounders (ischemic heart disease, peripheral vascular disease, and diabetes)…”. We agree that a cross-sectional study cannot prove causation, or mechanisms of association. We agree that association between previous stroke and unruptured aneurysms is unlikely to be causal; for example, one possibility is that patients with a stroke have more careful management of their vascular risk factors, which might reduce future rupture risk.

Unfortunately, we cannot provide the detailed information about aspirin indication as requested by the reviewer. Nevertheless, the assumption can be made that patients either received aspirin due to an underlying cardiovascular condition (MI [35 on aspirin], angina [29 on aspirin], PVD [12 on aspirin], previous ischemic stroke [51 on aspirin], DM [34 on aspirin]) or as primary prevention (it has become a widespread practice of GP’s to start
patients above a certain age on aspirin). One hypothesis why patients with UIA use aspirin more frequently is that there are actively investigated for other potential risk factors, i.e. cardiovascular risk factors. Therefore, these patients could potentially have higher levels of aspirin use.

5. I am a little bit surprised that authors have not noted possibility of Berkson's bias in their study. A classic example is association of lung cancer both with smoking and yellow fingers. Yellow fingers may associate with lung cancer more significantly than smoking yes/no. I think that nobody can insist yellow fingers to cause lung cancer because it is not biologically plausible. This same seems to be here when authors assume that aspirin may prevent aneurysm bleeding. The only real treatment method is occlusion of aneurysm.

We agree that Berkson’s bias might affect our results, as in any study where cases and controls are recruited from a hospital (so that controls may not reflect the full population outside hospital). It is also possible that some of our associations are not causal, as in the example given by the reviewer. However, we have performed careful and systematic adjustment for all potential confounding factors to minimise the effect of potential bias and confounding. Our discussion clearly acknowledges the potential selection bias in our hospital-based study.

We also agree with the reviewers that the only definitive treatment of an UIA is its occlusion. However, our data and several other studies report an interesting potential protective effect of aspirin on aneurysm rupture1-3. Aneurysm wall inflammation might be reduced by the anti-inflammatory properties of aspirin, which might attenuate growth and reduce rupture risk2. To prove or disprove this hypothesis, a randomized trial would be needed. Indeed, we note that such trials are planned (e.g. clinicaltrials.gov NCT03063541). Although we agree that we cannot conclude that aspirin can prevent UIA rupture, we think our data are nevertheless of interest in supporting further investigation of this idea.

Therefore, it is unlikely that Berkson’s bias accounts for the possible effect of aspirin. The only way to definitively conclude whether aspirin does or does not have a protective effect is through a randomized controlled trial, which is beyond the scope of our study.

6. Authors should reanalyze results of Table 3 adjusting all above mentioned cardiovascular diseases and risk factors for association between aneurysm groups to see whether aspirin use and hypercholesterolemia are true independent factors. It seems that aspirin use is a proxy of several other factors since, e.g. patients with diabetes commonly use aspirin to prevent ischemic diseases. If some diseases/factors are too uncommon to be tested factors these can be combined as factors such as cardiovascular diseases and cardiovascular risk factors.

We agree that it is important to adjust for all of these factors (confounding by indication). We have therefore included all of them in our analyses (see page 7, lines 227-229 where we mention, “even after fully adjusting for potential confounders (ischaemic heart disease, peripheral vascular disease, and diabetes)”. For the purposes of clarity, and in line with standard statistical practice, some of these factors which were not statistically significant do not appear in the final models in Table 2 and Table 3.

7. Authors state in Discussion: "By contrast, the majority of stable unruptured aneurysms would be expected to have low rupture rates, even if this increases with increasing aneurysm size, consistent with observational data reporting that only a very
small minority of incidentally detected unruptured aneurysms will rupture to cause
aneurysmal SAH (incidence 9 in 206 100,000)." This statement is not true and most UIAs
are smaller than those in this study. Incidence rate is right but UIAs grow with a rate of
3-4% per year in a follow-up of even low-risk UIAs. These do not likely rupture because
patients are dying of unrelated causes. However, if UIA is growing the rupture risk is
clearly higher and more than 50% of growing UIAs are rupturing during follow-up
(Juvela S, Poussa K, Porras M. Factors affecting formation and growth of intracranial
aneurysms: a long-term follow-up study. Stroke 2001;32:485-491). This should be noted
and cited in discussion since risky UIAs were not selected by aneurysm occlusion at
baseline of follow-up in this study. This study also had highest study quality and lowest
study bias according to recent meta-analyses of UIA growth (Brinjikji W, Zhu YQ,
aneurysms: a systematic review and meta-analysis. Am J Neuroradiol
2016;37:615-620; and Backes D, Rinkel GJ, Laban KG, Algra A, Vergouwen MD. Patient-
and aneurysm-specific risk factors for intracranial aneurysm growth: systematic

We thank the reviewer for this comment and agree that the wording of our sentence was not
fully clear (“By contrast, most stable unruptured aneurysms would be expected to have low
rupture rates, even if this increases with increasing aneurysm size”). We have changed the
wording and included a new sentence focused on the increase in size of a specific unruptured
aneurysm. The reference has been added. Please see:
- Page 6, lines 197-200.

8. Comments on evidence of aspirin for treatment of UIAs are not based on unbiased high
grade studies. Author has cited one post hoc study of ISUIA. One must remember that
ISUIA was a highly selected patient population study with a low rupture risk UIAs. At
baseline already 58% were excluded from follow-up because of an aneurysm occlusion
and additional 32% were treated during follow-up before a possible rupture (see refs 22
and 23). If 71% of patients with UIAs are excluded totally or partially from a short-term
follow-up, the remaining patients are likely similar to those patients with UIAs in the
present study, i.e. patients with several cardiovascular diseases or risk factors using
aspirin and statins and thought not to be benefit from aneurysm treatment. Patient with
risk factors for cardiovascular diseases and aspirin use likely die untimely and likely not
from aneurysm rupture because of a shorter life-expectancy. Post hoc study used logistic
regression which cannot also discriminate timing of deaths. These results cannot be
generalized to all patients with UIAs.

We agree with the reviewer that the level of evidence for the effectiveness of aspirin on
prevention of aneurysm rupture is low. However, evidence exists that aspirin harbors a
preventive effect (see our comment to point 5, above). The only way to definitely approach this
is to conduct a randomized trial on patients with UIA and aspirin intake. We agree that the
ISUIA data cannot be generalized to all populations of patients with UIAs.

9. Authors underestimate risks of aspirin stating that it is safe. In a primary prevention
study aspirin use decreased risk of myocardial infarction but increased 2-fold risk of
hemorrhagic stroke, most likely primary intracerebral hemorrhage (ICH)(Steering
Committee of the Physicians' Health Study Research Group. Final report on the aspirin
In addition, pre-ictal use of aspirin increases case fatality after ICH (Thompson BB, Béjot

We thank the reviewer for his useful comments regarding the safety of aspirin; we have tried to implement them into our discussion. We have added a statement regarding the potential adverse effects of aspirin on intracerebral haemorrhage and SAH outcome (Page 8, 238-239).

We agree that no strong evidence exists on the net clinical benefit of aspirin in preventing aneurysm rupture, potential increase in hemorrhage severity or increase in frequency of hemorrhagic stroke. Only a randomized controlled trial would give us a definitive answer to this question.

- Page 7/8, lines 236-239
- Page 8, lines 245-246
- Page 10, lines 319-320

10. It is yet highly doubtful whether aspirin really prevents SAH. These aspects make it difficult to estimate whether (low risk) UIAs should be studied in a placebo-controlled randomized trial to see prevention of bleeding. Study may need to continue decades to see effect and compliance of aspirin/placebo intake for a long-term time may be modest when risks of gastrointestinal and intracranial bleedings are noted by patients. It is well-known that appropriate completion of a randomized trial of any treatment is a time consuming and includes several difficulties. Recommendation of such trial without careful evaluation is not reasonable.

We agree with the reviewer that randomized treatment trials are time consuming, cost-consuming and might be very challenging due to the length of follow up. We note that a small proof-of-concept randomized trial has already been conducted2 and that others are planned (clinicaltrials.gov NCT03063541).

Once again, we are most grateful for the carefully considered, thorough and constructive comments from the reviewer. We hope that the paper will be considered of interest to the readers of Neurosurgery and suitable for publication.

Please contact us if further information is required.

Yours sincerely,

The author and co-authors


Characteristics of unruptured compared to ruptured intracranial aneurysms: a multicentre case-control study

Isabel C Hostettler MD1, Varinder S Alg MBBS1, Nichole Shahi MD1, Fatima Jichi PhD2, Stephen Bonner PhD3, Daniel Walsh PhD4, Diederik Bulters FRCS5, Neil Kitchen PhD6, Martin M Brown FRCP1, Henry Houlden PhD7, Joan Grieve MD6, David J Werring PhD FRCP1,# on behalf of the Genetics and Observational Subarachnoid Haemorrhage (GOSH) Study investigators

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3 Department of Anaesthesia, The James Cook University Hospital, Middlesbrough, UK
4 Department of Neurosurgery, King’s College Hospital NHS Foundation Trust, London, UK
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Previous presentations
This study has been presented as a poster at the European Stroke Organisation Conference (ESOC), in Barcelona, Spain 05/2016.

Financial Disclosure
The GOSH study is funded by the Stroke Association. This work was partly undertaken at UCLH/UCL who received a proportion of funding from the Department of Health’s NIHR Biomedical Research Centres funding scheme.
**Acknowledgments**

We thank the many NIHR Clinical Research Network Practitioners and the investigators at participating centres for their assistance with this study, and the patients for taking part.
STROBE Statement—checklist of items that should be included in reports of observational studies

Please fill out the page numbers on this form and upload the file as a supplemental file when you submit your revision

<table>
<thead>
<tr>
<th>Item No</th>
<th>Recommendation</th>
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<tr>
<td><strong>Title and abstract</strong></td>
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<td>1</td>
<td>(a) Indicate the study’s design with a commonly used term in the title or the abstract</td>
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<td>(b) Provide in the abstract an informative and balanced summary of what was done and what was found</td>
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<td><strong>Introduction</strong></td>
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<td>Explain the scientific background and rationale for the investigation being reported</td>
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<td><strong>Methods</strong></td>
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<td>4</td>
<td>Present key elements of study design early in the paper</td>
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<td>5</td>
<td>Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection</td>
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<td>6</td>
<td>(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</td>
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<td>Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls</td>
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<td>Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants</td>
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<td>(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed</td>
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<td>6</td>
<td>Case-control study—For matched studies, give matching criteria and the number of controls per case</td>
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<td>7</td>
<td>Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable</td>
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<td><strong>Variables</strong></td>
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<td>8*</td>
<td>For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group</td>
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<td>9</td>
<td>Describe any efforts to address potential sources of bias</td>
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<td>Explain how the study size was arrived at</td>
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<td>11</td>
<td>Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why</td>
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<td><strong>Statistical methods</strong></td>
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<td>12</td>
<td>(a) Describe all statistical methods, including those used to control for confounding</td>
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<td>(b) Describe any methods used to examine subgroups and interactions</td>
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<td>(c) Explain how missing data were addressed</td>
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<td>(d) Cohort study—If applicable, explain how loss to follow-up was addressed</td>
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<td>Case-control study—If applicable, explain how matching of cases and controls was addressed</td>
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<td>12</td>
<td>Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy</td>
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<td>(e) Describe any sensitivity analyses</td>
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<td><strong>Results</strong></td>
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<td><strong>Participants</strong></td>
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<td>13*</td>
<td>(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed</td>
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<td>(b) Give reasons for non-participation at each stage</td>
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<td>(c) Consider use of a flow diagram</td>
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<td><strong>Descriptive data</strong></td>
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<td>14*</td>
<td>(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders</td>
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<td>(b) Indicate number of participants with missing data for each variable of interest</td>
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<td><strong>Outcome data</strong></td>
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<td>15*</td>
<td>Cohort study—Report numbers of outcome events or summary measures over time</td>
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<td>Case-control study—Report numbers in each exposure category, or summary measures of exposure</td>
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<td><strong>Main results</strong></td>
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<td>16</td>
<td>(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval)</td>
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confidence interval). Make clear which confounders were adjusted for and why they were included (a).

(b) Report category boundaries when continuous variables were categorized

(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 5 |

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<th>Discussion</th>
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<td>Key results</td>
<td>18</td>
<td>Summarise key results with reference to study objectives</td>
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<td>Limitations</td>
<td>19</td>
<td>Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias</td>
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<td>Interpretation</td>
<td>20</td>
<td>Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence</td>
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<td>Generalisability</td>
<td>21</td>
<td>Discuss the generalisability (external validity) of the study results</td>
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<tr>
<td>Funding</td>
<td>22</td>
<td>Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based</td>
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*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.
ABSTRACT

Background Only a minority of intracranial aneurysms rupture to cause subarachnoid haemorrhage.

Objective We tested the hypothesis that unruptured aneurysms have different characteristics and risk factor profiles compared to ruptured aneurysms.

Methods We recruited patients with unruptured aneurysms or aneurysmal subarachnoid haemorrhage at 22 UK hospitals between 2011-2014. Demographic, clinical, and imaging data were collected using standardized case report forms. We compared risk factors using multivariable logistic regression.

Results 2334 patients (1729 with aneurysmal subarachnoid haemorrhage, 605 with unruptured aneurysms) were included (mean age 54.22 years). In multivariable analyses, the following variables were independently associated with rupture status: black ethnicity (OR 2.42; 95% CI 1.29-4.56; compared to white); aneurysm location (anterior cerebral artery/anterior communicating artery [OR 3.21; 95% CI 2.34-4.40], posterior communicating artery [OR 3.92; 95% CI 2.67-5.74], or posterior circulation [OR 3.12; 95% CI 2.08-4.70], compared to middle cerebral artery). The following variables were inversely associated with rupture status: antihypertensive medication (OR 0.65; 95% CI 0.49-0.84), hypercholesterolemia (0.64 OR; 95% CI 0.48-0.85), aspirin use (OR 0.28; 95% CI 0.20-0.40), internal carotid artery location (OR 0.53; 95% CI 0.38-0.75), and aneurysm size (per mm increase) (OR 0.76; 95% CI 0.69-0.84).

Conclusion We show substantial differences in patient and aneurysm characteristics between ruptured and unruptured aneurysms. These findings support the hypothesis that different pathological mechanisms are involved in the formation of ruptured aneurysms and incidentally detected unruptured aneurysms. The potential protective effect of aspirin in the two cohorts might justify randomized prevention trials in patients with unruptured aneurysms.

Running Title
Characteristics of aneurysm types

Key words
Characteristics, predisposition to rupture, risk factors, subarachnoid haemorrhage, unruptured intracranial aneurysms.
INTRODUCTION

About 3% of the population have an unruptured intracranial aneurysm but only a minority rupture to cause a subarachnoid haemorrhage (SAH); the overall risk of subarachnoid haemorrhage for unruptured intracranial aneurysms is about 1% per year. SAH causes 5% of all strokes, yet, with young age of onset and approximately 50% mortality, it substantially reduces productive life-years despite improvements in risk stratification, imaging, surgical and intensive care treatment. Up to 76% of patients who survive have permanent cognitive deficits, and only 6-17% of survivors return to employment. Hence, predicting (and reducing) the risk of rupture of an intracranial aneurysm is an important clinical and socio-economic need.

Previous studies assumed common causal mechanisms for ruptured and unruptured aneurysms, but it is also possible that their underlying risk factors and pathophysiological mechanisms are different. For example, several studies report that ruptured aneurysms causing SAH are smaller than unruptured aneurysms, suggesting that they might form rapidly and quickly rupture, potentially due to different underlying mechanisms.

Although many potential risk factors are associated with intracranial aneurysms (e.g. aneurysm location, aneurysm size, smoking, number of aneurysms, age, female sex, hypertension, hypercholesterolemia, previous history of SAH, heart disease, and aspirin use), most show inconsistent results, which might in part relate to rupture status. We therefore tested the hypothesis that incidentally detected unruptured aneurysms have different characteristics and risk factor profiles compared to aneurysms that cause SAH.

METHODS

Patients

We collected data from patients with aneurysmal SAH or unruptured aneurysm without previous SAH enrolled in the Genetic and Observational Subarachnoid Haemorrhage (GOSH) study (designed to examine the genetic and clinical characteristics of patients with ruptured and unruptured aneurysms), which recruited at 22 neurosurgical centres in the UK between 2011-2014. Written informed consent was obtained from participants, or from a representative in case of lack of capacity. We excluded patients with perimesencephalic SAH (63 patients) (defined by the characteristic distribution of blood (i.e. mainly or only in the cisterns around the midbrain) and absence of an identified intracranial aneurysm by the local
principle investigator and SAH due to trauma or mycotic aneurysms. Recruitment was as
inpatient or from outpatient neurovascular clinics following either new diagnosis or previous
diagnosis as an inpatient. Standardised case report forms were completed by trained stroke
research practitioners. Medical history was obtained from patient self-reporting and/or
available medical records. Hypertension, hypercholesterolemia and diabetes mellitus were
defined as present if the patient or medical records indicated hypertension,
hypercholesterolemia or hyperglycaemia for which either drug treatment, lifestyle or other
advice had been provided. We defined antihypertensive drug use, statin use, and aspirin use
by patient self-reporting or available documentation on regular intake at the time of either
admission with aneurysmal SAH or of being diagnosed with an unruptured aneurysm.
Recreational drug use was assessed for cocaine, cannabis, amphetamine and opiates by patient
self-reporting or from relatives. Smoking and alcohol use were defined as on-going use.
Family history of aneurysmal SAH and intracranial aneurysm was defined as presence of at
least one relative with the relevant disorder. Internal carotid artery location was considered as
an aneurysm in the cavernous segment of the internal carotid artery and onwards. The study
was approved by a Research Ethics committee.

**Statistical analysis**

Demographic, clinical and radiological data were first assessed in univariable analysis
comparing patients with aneurysmal SAH to those with unruptured aneurysm [Table 1].
Variables for multivariable analysis were chosen based on univariable analysis, as well as
previous studies and biological plausibility. We conducted a multivariable backward stepwise
logistic regression analysis to identify factors independently associated with aneurysmal
SAH. We excluded family history of SAH or unruptured aneurysm and previous history of
stroke from the multivariable analysis, due to potential selection bias in the unruptured
aneurysm group. A sensitivity analysis was conducted including these variables. As a
further sensitivity analysis, we used multiple imputation for missing data values. The level of
statistical significance was set at 5% (p-value=0.05). Statistical analysis was performed using
STATA 13 (StataCorp. 2011. *Stata Statistical Software: Release 13*. College Station, TX:
StataCorp LP).

**RESULTS**

Baseline characteristics are summarized in Table 1. We included 2334 patients: 1729 with
ruptured intracranial aneurysms (1215 females [70.3%], 514 males [29.7%], mean age 53.24,
12.70 SD) and 605 patients with unruptured aneurysms (425 females [70.25%], 180 males [29.75%] mean age 57.03, 12.17 SD).

Associations of potential risk factors with incidental intracranial aneurysms and aneurysmal SAH

In univariable analysis factors associated with aneurysmal SAH as opposed to incidentally-detected unruptured aneurysms were: hypertension not treated (OR 2.54; 1.65-3.93 95% CI; p <0.001), ethnicity (black ethnicity (compared to the baseline group [white ethnicity]), OR 2.31; 1.37-3.90 95% CI; p=0.003); smoking (OR 1.31; 1.09-1.59 95% CI; p=0.005); recreational drug use (OR 1.73; 1.09-2.90 95% CI; p=0.02); aneurysm location (anterior cerebral artery and anterior communicating artery, posterior communicating artery, and posterior circulation (compared to aneurysms of the middle cerebral artery) with location in the anterior cerebral artery or anterior communicating artery having the largest impact [OR 3.50; 2.64-4.64 95% CI]) [Table 1]. Factors that were inversely associated with aneurysmal SAH (i.e. which were apparently protective) were: older age at diagnosis (as a continuous variable OR 0.98; 0.97-0.98 95% CI; p <0.001; as a categorical variable by every 10 year increase of age the odds ratio of aneurysm rupture status was 0.21; 0.14-0.26 95% CI); hypertension (OR 0.53; 0.44-0.64 95% CI; p <0.001); anti-hypertensive medication use (OR 0.45; 0.37-0.54 95% CI; p <0.001); hypercholesterolemia (OR 0.45; 0.37-0.55 95% CI; p <0.001); diabetes mellitus (OR 0.60; 0.40-0.90 95% CI; p=0.013); previous stroke (OR 0.18; 0.12-0.26 95% CI; p <0.001); angina (OR 0.45; 0.27-0.77 95% CI; p=0.002); heart disease (OR 0.53; 0.35-0.81 95% CI; p=0.003); use of aspirin (OR 0.22; 0.17-0.28 95% CI; p <0.001), positive family history of intracranial aneurysm or SAH (OR 0.63; 0.49-0.80 95% CI; p <0.001; [positive family history of aneurysmal SAH separately (OR 0.79; 0.69-0.90 05% CI; p=0.001), positive family history of unruptured intracranial aneurysm separately (OR 0.66; 0.54-0.81 95% CI; p <0.001]), location of aneurysm in the internal carotid artery (OR 0.47; 95% CI 0.35-0.62); and aneurysm size (OR 0.91; 0.90-0.93 95% CI; p <0.001; 406 missing values). For the univariable analysis we also analysed aneurysm size as a categorical variable dividing it into 5mm step categories, which also showed that larger aneurysms are independently associated with a decreased risk of aneurysmal SAH (coefficient -0.089; -0.11-(-0.07) 95% CI; p <0.001.

Most aneurysms were smaller than 7.0 mm. Unruptured aneurysms tended to be larger (mean aneurysm size 9.0mm, SD 6.3mm; median 7.0mm) compared to ruptured aneurysms (mean
aneurysm size 6.6mm, 4.2mm SD; median 5.7mm). The mean duration of antihypertensive
treatment was 8.12 years (7.81 SD; median 5); however, this was not associated with
aneurysmal SAH in the univariable analysis (OR 1.00; 0.98-1.02 95% CI; p=0.977).

Of 119 patients with recreational drug use, 93 reported consumption of cannabis, 30 cocaine,
17 ecstasy, and 5 opiates. Forty-one patients had consumed multiple drugs.

In the multivariable regression analysis, following factors were independently associated with
aneurysmal SAH in the final adjusted model [Table 2]: black ethnicity compared to white
ethnicity (OR 2.42; 1.29-4.56 95 % CI; p=0.013 overall categorical variable); and aneurysm
location (location in the posterior communicating artery had the largest influence [OR 3.92;
2.67-5.74 95% CI]; p <0.001 overall categorical variable; internal carotid artery location was
inversely associated with aneurysmal SAH status). Independent factors inversely associated
with aneurysmal SAH status were: treatment with antihypertensive medication (OR: 0.65;
0.49-0.84 95% CI; p=0.001); hypercholesterolemia (OR 0.64; 0.48-0.85 95% CI; p=0.002);
aspirin use (OR 0.28; 0.20-0.40 95% CI; p <0.001); increasing aneurysm size (OR 0.76, 0.69-
0.84 95% CI; p <0.001), and internal carotid artery location (OR 0.53; 0.38-0.75 95% CI).

In a sensitivity analysis including family history of aneurysm and previous history of stroke in
the final model, the associations with aneurysmal SAH did not significantly change; Asian
ethnicity became a significant predictor for aneurysmal SAH ([OR 2.13; 1.02-4.46 95% CI],
p=0.012 overall categorical variable), and the model’s prediction increased (likelihood ratio
test p <0.001, Pseudo R2 increasing from 0.18 to 0.20) [Table 3]. A further sensitivity
analysis using multiple imputation for missing data in the variables aneurysm size (406
missing values) and aneurysm location (148 missing values) showed no change in OR (data
not shown).

DISCUSSION

In this large observational study, we show patients with incidentally detected unruptured
intracranial aneurysms have different patient and aneurysm characteristics and potential risk
factors compared to patients with ruptured aneurysms. Certain aneurysm locations (anterior
cerebral artery and anterior communication artery, posterior communicating artery, and
posterior circulation) and black ethnicity were independently associated with aneurysmal
SAH, compared to patients with an unruptured aneurysm. In addition, we found that location in the internal carotid artery is inversely associated with aneurysmal SAH. We also demonstrated antihypertensive medication use, aspirin use, hypercholesterolemia, and larger aneurysm size are independently associated with a decreased risk of aneurysmal SAH compared to the population of incidental intracranial aneurysms.

In our cohort, incidentally detected unruptured aneurysms were larger compared to those with aneurysmal SAH. Our findings are consistent with other studies that show the majority of ruptured aneurysms are less than 10 mm\(^1\). Indeed, in our study the size of unruptured aneurysms was larger than that reported in a previous meta-analysis\(^1\). This could indicate selection bias, a limitation of any hospital-based study. However, an important strength is that we have data on unruptured aneurysm size in 544 patients (90%); in the meta-analysis this was only available in 368 patients (25%)\(^1\).

Also in line with our data, is the International Study of Unruptured Intracranial Aneurysms (ISUIA), a lower risk of rupture was reported in intracranial aneurysms with a diameter of less than 10 mm; this observation that small unruptured aneurysms are at lower risk of future rupture than large unruptured aneurysms has been convincingly shown in other large prospective studies\(^20,36,37\). One explanation for this apparent inconsistency is that aneurysms that rupture to cause SAH and incidentally detected unruptured aneurysms have different pathological mechanisms making them behave differently\(^38\). Most intracranial aneurysms are considered to form over days to weeks, at which point they either rupture or stabilise due to remodelling of the arterial wall\(^10,11\). Whether early rupture or stabilisation occurs might be because of different underlying pathological haemodynamic and inflammatory mechanisms\(^39\).

Indeed, differences have been described in the histology of ruptured compared to unruptured aneurysms\(^9,10\). Our data are consistent with this hypothesis, in which rapidly developing aneurysms that rupture are expected to be small. By contrast, the majority of stable unruptured aneurysms would be expected to have low rupture rates, even if rupture rate is higher in larger aneurysm compared to smaller aneurysms\(^1,3,39,40\). Nevertheless, patients whose unruptured aneurysm increase in size during follow-up are at high risk of rupture and warrant further treatment\(^41,42\). An alternate explanation is that our results are due to selection bias. One could hypothesise that larger ruptured aneurysms were excluded due to prehospital death if they suffered more severe haemorrhages, while smaller unruptured aneurysms were excluded as they may not have been referred to tertiary care. Therefore, only tentative
conclusions can be drawn from this result and its meaning must be considered carefully. This could only be resolved in a longitudinal prospective large trial. However, a population of patients with unruptured aneurysms as in ISUIA and other studies would not suffice and it would require a healthy population with no prior diagnosis of an aneurysm. Due to the relatively low incidence of aneurysms and particularly SAH these would be logistically challenging.

The large sample size allowed us to investigate not only risk factors but also their treatments. A previous study has found a linear relationship between increase in systemic arterial pressure and pressure in the aneurysm sac\textsuperscript{43}. This finding supports the hypothesis that a rapid increase in blood pressure rather than a chronic increased blood pressure lead to aneurysm rupture. Patients with untreated hypertension had a higher OR for rupture. Furthermore, treatment rather than duration of treatment, appears to be associated with a decrease in aneurysmal SAH. These findings are most consistent with a rapid benefit from antihypertensive treatment, rather than a long-term remodelling of the aneurysm wall. The potentially protective effect of treatment is consistent with the hypothesis that a sudden rise in blood pressure might trigger the rapid formation of aneurysms that are prone to rupture early. Different antihypertensive drugs with different mechanisms of action might have differing influences on aneurysm formation and rupture other than purely through blood pressure control\textsuperscript{44}. However, we did not have data on specific antihypertensive agents, which should ideally be addressed in further prospective studies.

We found that regular aspirin use was significantly less common in patients with SAH than in patients with unruptured aneurysms even after fully adjusting for potential confounders (ischaemic heart disease, peripheral vascular disease, and diabetes; OR 0.28; 95% CI 0.20-0.40; p<0.001). This could mean that aspirin use protects against SAH in patients with unruptured aneurysms. Although it is possible that the use of aspirin results in more severe SAH, which might be excluded from our study (e.g. if patients die before reaching hospital), we did not find any association between aspirin use and severity of SAH (data not shown). Thus, this seems an unlikely explanation for the higher proportion of patients taking aspirin in the unruptured aneurysm group (25.45% versus 6.94% in the aneurysmal SAH group). A recent study also showed no association of aspirin or anticoagulation with mortality or complications; on the contrary, aspirin was associated with a shorter hospital stay\textsuperscript{45}; other studies showed a potential decrease in ischaemic events after SAH and increase in
asymptomatic survival\(^{46,47}\). However, further studies suggest aspirin given preventively might increase the risk of intracerebral haemorrhage and rebleeding after SAH\(^{46,48,49}\). Furthermore, our findings are in keeping with prospective data from the ISUIA and other studies, which showed a protective effect for regular aspirin use on intracranial aneurysm rupture\(^{25,47}\). Aspirin could potentially reduce the risk of aneurysm rupture by inhibiting inflammatory mediators (e.g. matrix metalloproteinases and tumor necrosis factor-alpha)\(^{50}\). Our findings suggest that unruptured aneurysms are not a contraindication to antiplatelet therapy for patients with a clear indication. Due to lack of definitive strong evidence, neither for a protective effect nor harmful effect, this requires further research. Indeed, our data strengthen the case for randomised trials testing the benefit of regular aspirin use on aneurysm rupture. We cannot fully explain the reason for aspirin use being higher in the unruptured aneurysm group; apart from a true biological effect, another possibility is that patients found to have an unruptured aneurysm are investigated for additional diseases that lead to aspirin prescription (e.g. hypertension, hypercholesterolaemia or previous stroke).

Our study also suggests that hypercholesterolaemia could have a protective effect on aneurysm rupture (OR 0.64; 95% CI 0.48-0.85; \(p=0.002\)). Previous smaller studies found a similar relationship, but were unable to determine whether this finding might be due to statin treatment rather than the underlying hypercholesterolaemia\(^{16,51}\). We were able to adjust for use of statins, and showed that hypercholesterolaemia was a protective factor for aneurysmal SAH, independent of the use of statin medications. The mechanism remains unclear. We suggest that part of the effect could emerge through stabilisation of the aneurysm wall and so preventing newly formed aneurysm from early rupture.

We found black ethnicity to be independently associated with aneurysmal SAH, but whether this is due to genetic or environmental factors remains uncertain. Greater risk of aneurysmal SAH in black patients compared to white patients has been described before\(^{52}\). Another study found that patients who underwent treatment for unruptured aneurysms generally had higher socioeconomic status and were more likely to be white, female, or insured, suggesting the findings to be due to social implemented reasons rather than based on genetic differences\(^{53}\).

Our study has important strengths. We included a large sample from multiple neurosurgical centres throughout the UK. The participants with aneurysmal SAH and unruptured aneurysms were recruited from the same hospitals over the same time-period using standardized
inclusion criteria and report questionnaire with standardized definitions of all risk factors. Moreover, the unruptured aneurysm group is free of the disease (aneurysmal SAH). Our large sample size allowed us to undertake a multivariable analysis including many clinical and anatomical factors in our model.

Our study also has limitations. Selection bias towards patients with unruptured intracranial aneurysms with a family history of intracranial aneurysm or aneurysmal SAH, or with a previous stroke has been suggested (as these patients will be more likely to undergo brain imaging)\textsuperscript{16}. Indeed, common reasons for intracranial aneurysm screening were positive family history for aneurysmal SAH or unruptured aneurysm, or a previous history of stroke; 18.35\% of the unruptured aneurysm patients had a positive family history of SAH or intracranial aneurysms compared to 12.32\% with aneurysmal SAH (p <0.001). 11.9\% of the patients with unruptured aneurysms had a previous history of stroke compared to 2.3\% of those with aneurysmal SAH (p <0.001). Nevertheless, a sensitivity analysis controlling for these variables did not affect our findings [Table 3]. As the aim of our study was not to compare “risk factors” between two groups with the same underlying disease but to evaluate for differing characteristics and potential risk factors in two different diseases, selection bias should be negligible. The study was designed to examine the different genetic and clinical characteristics of patients with ruptured and unruptured aneurysms; we are here presenting the large amount of clinical data collected to explore clinical differences between these cohorts. Another limitation arises from the fact that patients who are diagnosed with an unruptured intracranial aneurysm might not be seen by a neurologist or neurosurgeon due to their advanced age or significant comorbidities. These patients could not be included in our study. We did not explicitly collect the information about why unruptured intracranial aneurysms were diagnosed, apart from the small symptomatic number (9 patients). The study also has potential for bias towards aneurysmal SAH survivors; patients who died before they could be recruited, or in whom no informant could provide consent, were excluded from our study. Another potential limitation of our study is the case-control design preventing any direct inferences on causality. However, an observational natural history study in a similar population of untreated intracranial aneurysms is unlikely to be either feasible or ethically acceptable; not all diagnosed unruptured aneurysms can be left untreated and be followed-up, which also introduces selection bias. Although it would be highly desirable that diagnosed unruptured aneurysms result from random screening of the population this is unlikely to
happen without large scale intracranial imaging studies, which are likely to be logistically, financially and ethically challenging.

CONCLUSION

We found that patients with aneurysmal SAH most likely have a different risk factor profile in comparison to patients with incidentally detected unruptured aneurysms. Aneurysm location and black ethnicity are associated with aneurysmal SAH in comparison to incidentally detected unruptured aneurysms. Antihypertensive medication, aspirin use, hypercholesterolemia, aneurysm location on the internal carotid artery, and aneurysm size are associated with unruptured intracranial aneurysms compared to aneurysmal SAH. These findings support the hypothesis that risk factors for the type of aneurysm that ruptures early are different to unruptured aneurysms or to those that rupture later. The large potentially protective effect of aspirin use justifies randomized clinical trials to prevent SAH in patients with unruptured aneurysms offering an alternative treatment option in small aneurysms, where the decision for invasive treatment is difficult. This would also hopefully resolve the controversial evidence on protective or harmful effects of aspirin.
REFERENCES


Table 1: Characteristics of the cohort and results of univariable analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ruptured aneurysm</th>
<th>Unruptured aneurysm</th>
<th>OR; 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, (mean) y</td>
<td>53.2 (12.7 SD)</td>
<td>57.0 (12.2 SD)</td>
<td>0.98; 0.97-0.98</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>1.0; 0.82-1.22</td>
<td>0.99</td>
</tr>
<tr>
<td>Male</td>
<td>514 (29.7%)</td>
<td>180 (29.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1215 (70.3%)</td>
<td>425 (70.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>- White</td>
<td>1484 (87.91%)</td>
<td>551 (93.39%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mixed</td>
<td>26 (1.54%)</td>
<td>5 (0.85%)</td>
<td>1.93; 0.74-5.05</td>
<td></td>
</tr>
<tr>
<td>- Asian</td>
<td>72 (4.27%)</td>
<td>17 (2.88%)</td>
<td>1.57; 0.92-2.69</td>
<td></td>
</tr>
<tr>
<td>- Black</td>
<td>106 (6.28%)</td>
<td>17 (2.88%)</td>
<td>2.32; 1.37-3.90</td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive Family History SAH/UIA</td>
<td>213 (12.3%)</td>
<td>111 (18.4%)</td>
<td>0.63; 0.49-0.80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Positive Family History of SAH</td>
<td>191 (11.1%)</td>
<td>98 (16.2%)</td>
<td>0.79; 0.69-0.90</td>
<td>0.001</td>
</tr>
<tr>
<td>Positive Family History of UIA</td>
<td>25 (1.5%)</td>
<td>19 (3.1%)</td>
<td>0.66; 0.54-0.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoker</td>
<td>765 (44.3%)</td>
<td>228 (37.7%)</td>
<td>1.31; 1.09-1.59</td>
<td>0.005</td>
</tr>
<tr>
<td>Drinker</td>
<td>1168 (67.6%)</td>
<td>392 (64.8%)</td>
<td>1.13; 0.93-1.37</td>
<td>0.215</td>
</tr>
<tr>
<td>Recreational drug use</td>
<td>99 (5.7%)</td>
<td>20 (3.3%)</td>
<td>1.78; 1.09-2.90</td>
<td>0.02</td>
</tr>
<tr>
<td>Medical History</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>Affected (N)</td>
<td>Untreated (N)</td>
<td>Odds Ratio (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>--------------</td>
<td>---------------</td>
<td>---------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Hypertension</td>
<td>542 (31.4%)</td>
<td>281 (46.5%)</td>
<td>0.53; 0.44-0.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension not treated</td>
<td>123 (80.9%)</td>
<td>29 (19.1%)</td>
<td>2.54; 1.65-3.93</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antihypertensive Medication</td>
<td>425 (24.6%)</td>
<td>255 (42.2%)</td>
<td>0.45; 0.37-0.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>350 (20.2%)</td>
<td>218 (36.0%)</td>
<td>0.45; 0.37-0.55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin medication</td>
<td>273 (15.8%)</td>
<td>192 (31.7%)</td>
<td>0.40; 0.33-0.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>69 (4.0%)</td>
<td>39 (6.5%)</td>
<td>0.60; 0.40-0.90</td>
<td>0.013</td>
</tr>
<tr>
<td>Previous Stroke</td>
<td>40 (2.3%)</td>
<td>72 (11.9%)</td>
<td>0.18; 0.12-0.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous ICH</td>
<td>9 (0.5%)</td>
<td>4 (0.7%)</td>
<td>0.79; 0.24-2.56</td>
<td>0.75</td>
</tr>
<tr>
<td>History of Myocardial infarction</td>
<td>41 (2.4%)</td>
<td>19 (3.1%)</td>
<td>0.75; 0.43-1.30</td>
<td>0.304</td>
</tr>
<tr>
<td>Coronary artery disease (Angina)</td>
<td>33 (1.9%)</td>
<td>25 (4.13%)</td>
<td>0.45; 0.27-0.77</td>
<td>0.002</td>
</tr>
<tr>
<td>Cardiac disease (myocardial infarction and angina)</td>
<td>58 (3.4%)</td>
<td>37 (6.1%)</td>
<td>0.53; 0.35-0.81</td>
<td>0.003</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>25 (1.5%)</td>
<td>15 (2.5%)</td>
<td>0.58; 0.30-1.10</td>
<td>0.09</td>
</tr>
<tr>
<td>Aspirin</td>
<td>120 (6.94%)</td>
<td>154 (25.45%)</td>
<td>0.22; 0.17-0.28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aneurysm location</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- MCA</td>
<td>341 (21.04%)</td>
<td>194 (34.34%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- ICA</td>
<td>135 (8.33%)</td>
<td>164 (29.03%)</td>
<td>0.47; 0.35-0.62</td>
<td></td>
</tr>
<tr>
<td>- ACA/Acom</td>
<td>572 (35.29%)</td>
<td>93 (16.46%)</td>
<td>3.50; 2.64-4.64</td>
<td></td>
</tr>
<tr>
<td>- Pcom</td>
<td>359 (22.15%)</td>
<td>63 (11.15%)</td>
<td>3.24; 2.35-</td>
<td></td>
</tr>
</tbody>
</table>
SD = standard deviation; ICH = intracerebral haemorrhage; MCA = middle cerebral artery; ICA = internal carotid artery; ACA = anterior cerebral artery; Acom = anterior communicating artery; Pcom = posterior communicating artery.

For aneurysm location there were 40 missing values in the ruptured and 108 in the unruptured group.

For aneurysm size there were 345 missing values in the ruptured and 61 in the unruptured group.

<table>
<thead>
<tr>
<th></th>
<th>Ruptured</th>
<th>Unruptured</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior circulation</td>
<td>214 (13.20%)</td>
<td>51 (9.03%)</td>
<td>2.39; 1.68-3.40</td>
</tr>
<tr>
<td>Aneurysm size (mean) mm</td>
<td>6.6 (4.16 SD)</td>
<td>9.0 (6.3 SD)</td>
<td>0.91; 0.90-0.93</td>
</tr>
<tr>
<td>Multiple aneurysms</td>
<td>447 (25.9%)</td>
<td>161 (26.6%)</td>
<td>0.96; 0.78-1.19</td>
</tr>
</tbody>
</table>
### Table 2: Multivariable analysis model evaluating differences between unruptured and ruptured intracranial aneurysms

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th><em>P</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.0</td>
<td>0.98-1.01</td>
<td>0.365</td>
</tr>
<tr>
<td>Sex (male vs female)</td>
<td>0.86</td>
<td>0.66-1.11</td>
<td>0.242</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td>0.013</td>
</tr>
<tr>
<td>- white (reference)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- black</td>
<td>2.42</td>
<td>1.29-4.56</td>
<td></td>
</tr>
<tr>
<td>- asian</td>
<td>2.00</td>
<td>0.98-4.08</td>
<td></td>
</tr>
<tr>
<td>- mixed</td>
<td>1.26</td>
<td>0.45-3.53</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>1.22</td>
<td>0.96-1.56</td>
<td>0.104</td>
</tr>
<tr>
<td>Use of antihypertensive medication</td>
<td>0.65</td>
<td>0.49-0.84</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>0.64</td>
<td>0.48-0.85</td>
<td>0.002</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>0.28</td>
<td>0.20-0.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aneurysm location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- MCA (reference)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- ICA</td>
<td>0.53</td>
<td>0.38-0.75</td>
<td></td>
</tr>
<tr>
<td>- ACA/Acom</td>
<td>3.21</td>
<td>2.34-4.40</td>
<td></td>
</tr>
<tr>
<td>- Pcom</td>
<td>3.92</td>
<td>2.67-5.74</td>
<td></td>
</tr>
<tr>
<td>- Posterior circulation</td>
<td>3.12</td>
<td>2.08-4.70</td>
<td></td>
</tr>
<tr>
<td>Aneurysm size</td>
<td>0.76</td>
<td>0.69-0.84</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
MCA = middle cerebral artery; ICA = internal carotid artery; ACA = anterior cerebral artery; Acom = anterior communicating artery; Pcom = posterior communicating artery.
Table 3: Multivariable analysis model, sensitivity analysis including positive family history of SAH or unruptured intracranial aneurysm and previous history of stroke

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.0</td>
<td>0.98-1.01</td>
<td>0.392</td>
</tr>
<tr>
<td>Sex</td>
<td>0.83</td>
<td>0.64-1.08</td>
<td>0.171</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td>0.012</td>
</tr>
<tr>
<td>- white (reference)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- black</td>
<td>2.41</td>
<td>1.27-4.56</td>
<td></td>
</tr>
<tr>
<td>- asian</td>
<td>2.13</td>
<td>1.02-4.46</td>
<td></td>
</tr>
<tr>
<td>- mixed</td>
<td>1.20</td>
<td>0.43-3.38</td>
<td></td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>0.69</td>
<td>0.52-0.90</td>
<td>0.007</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>0.69</td>
<td>0.52-0.92</td>
<td>0.011</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>0.32</td>
<td>0.22-0.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aneurysm location</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- MCA (reference)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- ICA</td>
<td>0.533</td>
<td>0.38-0.75</td>
<td></td>
</tr>
<tr>
<td>- ACA/Acom</td>
<td>3.23</td>
<td>2.34-4.44</td>
<td></td>
</tr>
<tr>
<td>- Pcom</td>
<td>4.07</td>
<td>2.75-6.01</td>
<td></td>
</tr>
<tr>
<td>- Posterior circulation</td>
<td>3.12</td>
<td>2.06-4.72</td>
<td></td>
</tr>
<tr>
<td>Aneurysm size</td>
<td>0.76</td>
<td>0.69-0.84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Positive Family History</td>
<td>0.61</td>
<td>0.44-0.85</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous Stroke</td>
<td>0.24</td>
<td>0.14-0.41</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
MCA = middle cerebral artery; ICA = internal carotid artery; ACA = anterior cerebral artery; Acom = anterior communicating artery; Pcom = posterior communicating artery.