Long-term cognitive outcome following aneurysmal subarachnoid haemorrhage

Running title: Cognitive outcome following SAH

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All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Ben Gaastra. The first draft of the manuscript was written by Ben Gaastra and Ian Galea, all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Abstract

Objectives: Survivors of aneurysmal subarachnoid haemorrhage (aSAH) frequently suffer from cognitive dysfunction. The aim of this study was to assess, in a large sample size with long term follow-up, the characteristics of cognitive dysfunction following aSAH and explore whether cognitive deficits mediate employment outcome.

Materials and methods: In this retrospective case-controlled study, aSAH survivors (n=884) were identified from the UK Biobank and compared to matched controls (n=3536). Controls were propensity score matched according to age, sex, Townsend deprivation score, educational status and relevant medications known to influence cognition. Cognitive outcomes and employment status were compared between cases and controls using group comparison and cross-tabulation tests. A regression-based mediation analysis was performed to assess whether cognitive deficits mediate employment status following aSAH.

Results: Psychomotor reaction time and employment status significantly differed between aSAH cases and controls with slower reaction times ($p < 0.001$) and more unemployment or inability to work due to illness ($p < 0.001$) in the aSAH cohort at a mean follow-up of 125 months. Psychomotor slowing was estimated to mediate a significant proportion (6.59%) of the effect of aSAH on employment status.

Conclusions: Psychomotor reaction time and employment status differed significantly between aSAH cases and control matched individuals in the UK Biobank. Psychomotor slowing following aSAH had a discernible impact on employment status. Psychomotor reaction time and employment status are practical to acquire and can be used as surrogate measures of outcome in future studies of aSAH survivors.

Introduction

Aneurysmal subarachnoid haemorrhage (aSAH) is a devastating form of stroke associated with significant morbidity and mortality. Survivors of aSAH frequently suffer from cognitive impairment[1, 2], however the prevalence, characteristics and impact of the cognitive dysfunction needs further study.

The majority of clinical trials following aSAH use traditional outcome scales[3], including the modified Rankin score (mRS)[4] and the Glasgow Outcome Scale (GOS)[5]. These scales have their limitations since they are relatively insensitive to hidden disabilities such as cognitive outcome. For example, in one study half the patients with a mRS of zero (no symptoms) after aSAH exhibited significant cognitive impairment when evaluated neuropsychologically[6]. In other studies, of those previously in full or part-time employment, 40-50% were unemployed at one to three years after aSAH[7, 8]. A large number of studies have examined cognitive deficits after aSAH[1, 2, 9], but more work is needed to determine whether they persist in the very long-term, which domains are most affected and how these relate to return to employment. In particular, the mediation of employment status by cognitive dysfunction has not been studied.

The UK Biobank is a large-scale biomedical database. Participants underwent detailed cognitive testing and their employment status was recorded during their assessment visits. Within the UK Biobank cohort there are a subset of participants who have suffered aSAH. This makes it the largest database of long-term aSAH cognitive outcomes and the ideal tool to answer some of the outstanding questions about cognitive outcome after aSAH.

The aim of this study was to explore cognitive dysfunction in a larger sample size with longer follow-up compared to other studies, as is possible in the UK Biobank. We hypothesized that: (1) cognitive measures and employment status differ between aSAH cases and controls (2) cognitive deficits mediate employment outcome following aSAH.

Methods

This research has been conducted using the UK Biobank Resource[10]. Study design consisted of a retrospective case-controlled study, as part of application ID 49305. The study was performed under National Research Ethics Committee Approval 16/NW/0274 and institutional approval (ERGO 49253). The study has been reported in accordance with the STROBE statement for case-control studies[11]. This study uses information on 502 490 participants, with informed consent, recruited in the UK between 2006 and 2010.

Outcome measures

In order to assess cognitive outcome five cognitive tests were included as they have been shown in previous studies to detect cognitive impairment in the context of neurological disease in the UK Biobank[12]. All tests were administered on a touch screen at assessment centre visits.

Cognition was measured in the majority of participants (98%) using two tests. The "reaction time" test (data field 20023) asked participants to press a button as soon as matching pairs of symbols were presented and therefore measured psychomotor reaction time. Visual memory was assessed using a pairs matching test (data field 399) during which three or six pairs of matching symbol cards were displayed to participants for three seconds, then turned face down, and participants were asked to identify matched pairs.

After UK Biobank recruitment started, three other tests were added in succession, and consequently these tests were done in less than 40% of participants. A "fluid intelligence" test (data field 20016) measured verbal and numeric reasoning. Prospective memory (data field 20018) was assessed by asking participants at the start of the assessment to memorize a certain shape from an array of shapes, and after the whole assessment, they were asked to recall the shape. Working memory was also assessed by the "numeric memory" test (data field 4282) during which participants were asked to repeat in reverse a string of numbers presented to them.

All cognitive tests report a continuous score apart from prospective memory which was dichotomised into correct on first attempt (good outcome) or not (poor outcome). The UK Biobank website and prior publications[12] provide more detail on these cognitive tests.

Employment status (data field 6142) was dichotomised into good and poor outcome, with poor outcome defined as “unable to work because of sickness or disability” or “unemployed”. For the aSAH cohort, the outcome measure was taken at the first available follow-up assessment following diagnosis of aSAH; most patients only had one assessment. Hence there is only one outcome datapoint for each aSAH patient in this study. For the control cohorts the outcome measure was taken at first assessment in the UK Biobank.

aSAH cohort

aSAH cases were identified from the UK Biobank using ICD-9 (data field 41271) and ICD-10 codes (data field 41270) from hospital inpatient data; read code information from primary care data (data field 42040); and self-reported medical conditions (data field 20002) reported at baseline or subsequent assessment centre visits. Cases were excluded if there was significant evidence that they were not actually aneurysmal in nature and likely to have been miscoded. This was defined using ICD-9 and ICD-10 codes from hospital inpatient and primary care data. Cases with a traumatic event code within 30 days of diagnosis of aSAH were excluded (Supplementary Table 1 for inclusion and exclusion codes). Cases were cross-checked against the algorithmically generated subarachnoid haemorrhage diagnosis (data field 42012) and first occurrence database for ICD-10 code I60 (data field 131360). Cases were included if there was data available in at least one outcome measure subsequent to the date of diagnosis.

Control cohorts

To allow for comparison of aSAH patients and controls four separate matched control populations were generated. Propensity score matching was performed with a nearest neighbour method and a case: control ratio of 1:4. All four control populations were matched to the aSAH cohort according to the following variables, known to influence outcome and cognition following aSAH: age at time of outcome assessment in the UK Biobank (data field 21003), sex (data field 31), Townsend deprivation score[13] (data field 189), and education status dichotomised into individuals holding a college or university degree at time of initial assessment in the UK Biobank or not (data field 6138). Sex and education status were treated as binary, age and Townsend deprivation score were treated as continuous variables.

Three of the control populations were additionally matched for the presence of medications which have been shown in a detailed study to influence verbal-numerical reasoning, memory and reaction time in the UK Biobank[14]. This is of particular relevance as these three cognitive domains are directly tested by the cognitive outcome measures used in this study. Medications were categorised according to therapeutic subgroup (for example beta blocking agents) for the purpose of this study. Three binary medication variables were created to indicate, for each individual in the UK Biobank, whether they were taking a medication within a therapeutic subgroup which influences reasoning, visual memory and psychomotor reaction time. Each of these three medication variables was used in addition to the above four covariates to generate three matched control cohorts, to study the corresponding cognitive outcomes (reasoning, visual memory and psychomotor reaction time). The fourth control cohort was not matched for medications influencing cognition to allow analysis of other outcome measures which have not been shown to be affected by medications in the UK Biobank. To generate the matched populations, individuals with missing variables were excluded from the analysis.

Statistical analysis

In order to identify which outcome measures differ between aSAH and control cohorts the raw outcome scores were compared. A t-test was performed for continuous outcome measures and a chi-squared test for binary outcome measures. The six outcome measures (five cognitive tests and employment status) were considered separately and compared to the relevant matched control population (see Table 1). Individuals with missing outcome data were excluded from the analysis for the outcome of interest.

In order to assess whether cognitive deficits following aSAH influence employment status a regression-based mediation analysis was performed using PROCESS[15]. For this analysis aSAH case versus control status was used as the independent variable, employment status was used as the dependent variable and any significant cognitive measure considered as the mediator. The relevant control population matched to the cognitive measure of interest was used. Significance of the indirect effect was tested using 5000 bootstrapped samples.

The proportion of the mediator effect on employment status was calculated using the method described by VanderWeele[16].

Analyses were performed in statistical software R (version 3.6.2, R Foundation for Statistical Computing) and SPSS Statistics (version 27.0, IBM Corporation). A p value of <0.05 was considered significant with Bonferroni correction for multiple testing where appropriate.

Results

Patients

888 aSAH patients were identified from the UK Biobank. Four aSAH patients were excluded from the matching process due to missing data regarding educational status meaning 884 were used in the final analysis (see Figure 1 for flow chart of inclusion of patients; see Table 2 for demographics of aSAH patients). The mean follow-up time at first assessment following aSAH was 125 months (range 12 days - 662 months).

501 609 individuals were available in the UK Biobank to generate the matched control cohorts. 5260 participants were excluded from the potential control pool due to missing data on age (n=1), Townsend deprivation score (n=623) and educational status (n=4636). Four matched control populations (n=3536) were generated with the average standard mean difference after matching across all variables <0.04.

Outcome data availability

Three of the cognitive outcome measures (reasoning, prospective memory and working memory) were introduced late after recruitment had started in the UK Biobank, and therefore data for these variables was available in less than half the participants. Missingness analysis did not reveal any systematic differences between aSAH and controls (Supplementary Tables 2 and 3).

Comparison of aSAH cases versus controls

aSAH patients had significant psychomotor slowing in comparison to the matched control cohort (589 ms (standard deviation $\pm$ 138 ms) versus 569 ms (standard deviation $\pm$ 121 ms);

t = 3.84, p <0.001). No other significant difference was identified between the aSAH cohort and the relevant matched control cohort for the other four cognitive tests (see Table 3). For outcomes with missing data (reasoning, prospective memory and working memory), the complete case analysis was followed by multiple imputation, with similar results (p >0.2). In another sensitivity analysis, control populations were additionally matched for neurological/psychiatric diagnoses; results were similar (Supplementary Table 4).

A significant difference in employment status between the aSAH and matched control cohort was identified (82.8% versus 94.0%; χ^2 = 116.8, p <0.001), with aSAH patients more likely to be unemployed or unable to work because of sickness or disability.

Mediation analysis

Mediation analysis was performed to assess whether the psychomotor slowing had a discernible impact on employment status following aSAH (see Figure 2). The control cohort matched for medications influencing psychomotor reaction time was used. The indirect effect of aSAH on employment status mediated by psychomotor slowing was significant, with an odds ratio of 1.05 (95% confidence intervals 1.02-1.08). The odds ratio for the direct effect of aSAH on employment status was 3.09 (95% confidence intervals 2.45-3.89). The proportion of the effect of aSAH on employment status mediated by psychomotor slowing was estimated to be 6.59%.

Discussion

In this study we demonstrate that psychomotor reaction time and employment status differ significantly between aSAH survivors and matched control individuals in the UK Biobank. This study had a relatively long follow-up time of just over 10 years and shows that the cognitive impact of aSAH in survivors is long-lasting. This study is significantly larger than previous cognitive outcome studies with 884 cases, most prior studies have fewer than 200 patients[1, 2]. Findings here support the use of psychomotor reaction time and employment status as alternative measures of outcome in future studies of aSAH survivors. Both types of outcome data are practical to collect; the psychomotor reaction time test is based on 12 rounds of the card-game 'Snap', and a variety of online and digital versions are available.

The results are clinically relevant and will help clinicians to advise aSAH survivors and their relatives regarding cognition and employment outcomes in the long term. As psychomotor reaction time deficits mediate poor employment outcomes future studies should consider methods to optimise this cognitive domain in the long term as it may be beneficial in promoting quality of life and return to work following aSAH.

Changes in employment status following aSAH have been described previously with up to 50% of individuals either delayed or unable to return to their normal work following aSAH[2]. There is, however, minimal information on how psychomotor reaction time changes following aSAH and its impact on the patient's life. One small retrospective study of 58 patients following aSAH demonstrated longer reaction times[17] and another showed a trend towards slower reaction times following aSAH[18]. We demonstrate that psychomotor slowing has a discernible impact on employment after aSAH. It was surprising to be able to detect this effect in view of the multifactorial nature of the ability to remain in employment; this emphasises that cognitive deficits following aSAH are clinically meaningful, with effects extending to employment.

Deficits in multiple domains of cognitive function have been demonstrated following aSAH including visual and verbal memory[6, 19, 20], yet we could only demonstrate dysfunction in psychomotor reaction time, and not in other domains including visual memory, reasoning, prospective memory and working memory. Two factors may contribute to this finding.

Firstly, for reasoning, prospective memory and working memory scores, there was a high percentage of missing data in the UK Biobank as a whole, and therefore within the aSAH and control cohorts (Supplementary Table 2). This is because these three tests were not performed during most assessment visits at the UK Biobank; all three tests were introduced in the last two years of recruitment and working memory was subsequently removed due to assessment time constraints. The proportion of missing data was similar across aSAH cohorts, control cohorts and the UK Biobank as a whole (Supplementary Table 2). There was no evidence that participants with missing cognitive outcome data performed disproportionally poorly in other cognitive domains to suggest difficulty experienced during testing (Supplementary Table 3).

Secondly, the mean follow-up time following aSAH in the UK Biobank was 125 months. Cognitive outcome studies after aSAH are usually of much shorter duration, around 12 months, with the majority under 60 months[2]. Follow-up time in the UK Biobank was therefore significantly longer than that of the previous studies. Longer follow-up may allow for recovery of cognitive deficits explaining why no significant differences were identified in this study. In keeping with this explanation, one study has demonstrated significant improvements in motor, psychomotor, verbal and visual memory, executive function and intelligence between three and 12 months following aSAH[21]. On the other hand, the same study showed that motor function did not recover to the normative mean by 12 months post-aSAH[21], which may explain why psychomotor reaction time is the only cognitive test to demonstrate a significant difference at a mean follow-up of 125 months. The follow-up time within the UK Biobank cohort was not a significant predictor of psychomotor reaction time (Supplementary Results), which may indicate that some irreversible residual disability occurs after SAH, even if some improvement occurs in the first few years.

The presence of hydrocephalus has been shown to be a significant predictor of outcome following aSAH in some[22] but not other studies[6, 23]. A sensitivity analysis was performed to assess whether the presence of hydrocephalus following aSAH, as defined using ICD-9 and ICD-10 codes, influenced cognitive and employment outcomes, in our cohort. Hydrocephalus was not a significant predictor of psychomotor reaction time (p=0.384) or employment status (p=0.977), controlling for age, Townsend score, sex, relevant medications, education status and time to follow-up.

This study has a number of strengths and limitations. It has a large sample size, long follow-up and employment data. Case ascertainment was more detailed than the algorithmically generated SAH diagnosis field already available in the UK Biobank (data field 42012)[24]. Employment status was dichotomised into good and poor outcome, with poor outcome defined as “unable to work because of sickness or disability” or “unemployed”. The UK Biobank data does not specify the reason for inability to return to work. Granular detail regarding the precise reason for the inability to return to work might have delivered additional insight into the frequency and nature of neurological deficits linked to the

inability to return to work. Future studies of employment should include more detailed assessment. The World Federation of Neurological Surgeons (WFNS) score is a marker of early brain injury following aSAH and a strong predictor of outcome[25], but it was not available and could not be controlled for in this analysis. However, since length of stay in hospital is strongly associated with WFNS score[26], we considered using it as a surrogate marker of the WFNS score (n=551). Length of stay was not a significant predictor of psychomotor reaction time (p=0.071) or employment status (p=0.053), controlling for age, Townsend score, sex, relevant medications, education status and time to follow-up. This is not unexpected as recruitment to the UK Biobank was likely to be biased towards aSAH survivors with a short length of stay and good outcome, due to the need to attend multiple detailed assessments. It should also be noted that aSAH cases who died in the acute phase of their illness would not have been recruited to the UK Biobank study. Hence the findings of this study are most transferable to aSAH survivors who have recovered sufficiently to undertake detailed cognitive assessment. In the aSAH cohort the year of haemorrhage ranges from 1953 to 2016, and there have been significant changes in the management of aSAH over this time period[27]. As improvement in management over this period may have influenced outcome, a sensitivity analysis was performed. Year of aSAH was not a significant predictor of psychomotor reaction time (p=0.612) or employment status (p=0.687). Finally, in the majority of aSAH cases cognitive measures and employment status were only assessed at a single time point, so it was not possible to assess change over time. Future studies to assess the change in these outcome measures over time and over a range of follow-up periods would provide further insight.

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Table Captions

Table 1 Control cohort used for each outcome measure in analysis. Data on medications influencing prospective and numeric memory test scores was not available. Data on medications influencing reasoning, visual memory and psychomotor reaction time within UK Biobank was from Nevado-Holgado AJ et al (see text)

Table 2 Demographics of aSAH patients included in study. SD: standard deviation. IQR: interquartile range. GP: general practitioner. ICD: International Classification of Diseases

Table 3 Comparison of aSAH cases and relevant matched populations with regard to outcome measure. * indicates $p<0.05$

Figure Captions

Fig 1 Flow diagram for identification of aSAH patients from the UK Biobank

Fig 2 Mediation analysis. Effect sizes (regression coefficients, B) reported for a: dependent variable on mediator; b: mediator on dependent variable, controlling for independent variable; c': independent variable on dependent variable. For the analysis aSAH case and control were coded as 1 and 0 respectively; and with regard to employment good outcome and poor outcome were coded as 0 and 1 respectively. * indicates $p<0.001$

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Supplementary information

Long-term cognitive outcome following aneurysmal subarachnoid haemorrhage

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Supplementary methods and results

Missingness analysis

There was no significant difference in missingness of the three cognitive outcomes with missing data (reasoning, prospective memory and working memory) between the aSAH cohort and the matched control population, or the whole UK Biobank, as assessed using the chi-squared test ($p \geq 0.05$) (Supplementary Table 2).

A further missingness analysis was performed within the aSAH cohort for these three cognitive outcome measures to compare the other cognitive outcome measures and covariates between patients with and without missing data (t-test for continuous data and chi-squared test for discrete data). There were some minor differences, but none survived Bonferroni's correction for multiple comparisons (Supplementary Table 3).

Sensitivity analyses

For outcomes with missing data (reasoning, prospective memory and working memory), the complete case analysis was followed by multiple imputation. Missing outcome measures were imputed using age at time of follow up, Townsend deprivation score, sex, medications if relevant (as Table 1), educational status, and the well populated outcome measures. Five datasets were generated. Multiple imputation was performed in the *MICE* package[1] in R using a linear regression imputation method with bootstrap for scalar data (reasoning and working memory) and logistic regression imputation for binary data (prospective memory). Results were similar with no significant difference between cases and controls ($p > 0.2$).

Neurological and psychiatric disease has been demonstrated to be associated with worse cognitive performance in the UK Biobank[2]. Survivors of aSAH have been shown to have a higher burden of psychiatric disease[3, 4]. In order to confirm that the presence of alterative neurological or psychiatric disorders does not contribute to outcome following aSAH in this study a sensitivity analysis was performed. In this analysis the control populations were additionally matched for the presence/absence of alternative neurological or psychiatric disorders defined by the hospital ICD-10 codes used by Cullen et al.[2] (excluding codes I600-7 and I609). Results were similar (Supplementary Table 4).

Time to follow-up

Time to follow-up after aSAH in the UK Biobank is not standardised due to the nature of the dataset. For each individual outcome measure a regression analysis was performed to assess whether time to follow-up was significantly associated with each outcome measure, controlling for age at time of follow-up, Townsend deprivation score, sex, medications if relevant (as Table 1) and educational status. Time to follow up in the aSAH cohort was not a significant predictor of outcome in any of the five cognitive tests for both the primary and sensitivity analyses.

Supplementary tables

Data field	Code and definition
	Inclusion
Data field 41270 ICD 10 codes	I600 I60.0 Subarachnoid haemorrhage from carotid siphon and bifurcation I601 I60.1 Subarachnoid haemorrhage from middle cerebral artery I602 I60.2 Subarachnoid haemorrhage from anterior communicating artery I603 I60.3 Subarachnoid haemorrhage from posterior communicating artery I604 I60.4 Subarachnoid haemorrhage from basilar artery I605 I60.5 Subarachnoid haemorrhage from vertebral artery I606 I60.6 Subarachnoid haemorrhage from other intracranial arteries I607 I60.7 Subarachnoid haemorrhage from intracranial artery, unspecified I609 I60.9 Subarachnoid haemorrhage, unspecified Ruptured aneurysm
Data field 41271 ICD9	430 Subarachnoid haemorrhage 4309 Subarachnoid haemorrhage
Data field 42040 Primary care data	G60 Equates to ICD-10 code I609 G600 Equates to ICD-10 code I607 G601 Equates to ICD-10 code I600 G602 Equates to ICD-10 code I601 G603 Equates to ICD-10 code I602 G605 Equates to ICD-10 code I604 G606 Equates to ICD-10 code I605 G60X Equates to ICD-10 code I607 G60z Equates to ICD-10 code I609 Gyu60 Equates to ICD-10 code I606 Gyu6E Equates to ICD-10 code I607 X00Df Equates to ICD-9 code 430

	X00Dg Equates to ICD-10 code I609 X204F Equates to ICD-10 code I609 Xa01c Equates to ICD-10 code I606 Xa01h Equates to ICD-10 code I601 Xa01i Equates to ICD-10 code I606 Xa01j Equates to ICD-10 code I602 Xa01k Equates to ICD-10 code I603 Xa01l Equates to ICD-10 code I604 Xa01m Equates to ICD-10 code I606 Xa01o Equates to ICD-9 code 430
Data field 20002 Self-reported medical conditions	1086 Subarachnoid haemorrhage
Exclusion	
Data field 41270 ICD 10 codes	Q282 Q28.2 Arteriovenous malformation of cerebral vessels Q283 Q28.3 Other malformations of cerebral vessels S-T Injury, poisoning and certain other consequences of external causes V,W,X External causes of morbidity and mortality
Data field 41271 ICD9	74780 Arteriovenous aneurysm of brain 74781 Other anomalies of cerebral vessels 800-900 Trauma and injury
Data field 42040 Primary care data	P7y01 Equates to ICD-10 code Q282 P7y02 Equates to ICD-10 code Q283 S, U Equates to ICD-10 codes S,T,V,W,X and ICD-9 codes 800-900

Supplementary Table 1. Inclusion and exclusion codes for aSAH cases in the UK Biobank. ICD: International Classification of Diseases

	Number of participants with missing data (%)					
Outcome	aSAH cohort (n=884)	Matched controls (n=3536)	Matched controls, including for medications influencing reasoning (n=3536)	Matched controls, including for medications influencing visual memory (n=3536)	Matched controls, including for medications influencing psychomotor reaction time (n=3536)	Comparison of missingness between aSAH and matched control cohorts
Psychomotor reaction time (% missing in whole UKB: 1.2%)	18 (2.0%)				47 (1.3%)	$\chi^2 = 2.44$ p = 0.11
Visual memory 3 pair trial 6 pair trial (% missing in whole UKB: 0.9%)	 0 (0%) 1 (0.1%)			 0 (0%) 0 (0%)		
Prospective memory (% missing in whole UKB: 65.9%)	598 (67.6%)	2265 (64.1%)				$\chi^2 = 4.0$ p = 0.05
Reasoning (% missing in whole UKB: 67.1%)	614 (69.5%)		2397 (67.8%)			$\chi^2 = 0.91$ p = 0.34
Working memory (% missing in whole UKB: 89.7%)	782 (88.5%)	3128 (88.5%)				$\chi^2 = 0$ p = 1
Employment status (% missing in whole UKB: 0.2%)	0 (0%)	0 (0%)				

Supplementary Table 2. Percentage missing data for outcome measures in aSAH and control cohorts

	Not missing	Missing	p value
Missing analysis: prospective memory			
Age at time of follow up Mean (±SD) years	57.9 (7.4)	58.0 (7.0)	0.845
Sex Female (%) Male (%)	180 (62.9) 106 (37.1)	344 (57.5) 254 (42.5)	0.145
Townsend deprivation score Mean (±SD)	-1.0 (2.9)	-1.0 (3.4)	1
Education status No college or university degree (%) College or university degree (%)	194 (67.8) 92 (32.2)	457 (76.4) 141 (23.6)	0.009
Visual memory 3 pair trial 6 pair trial Mean (±SD)	0.6 (1.2) 4.8 (3.8)	0.6 (1.2) 4.2 (3.5)	1 0.020
Employment status Good outcome (%) Poor outcome (%)	243 (85.0) 43 (15.0)	489 (81.8) 109 (18.2)	0.279
Psychomotor reaction time Mean (±SD)	590.2 (161.3)	588.6 (126.4)	0.873
Presence of neurological or psychiatric diagnosis other than aSAH No (%) Yes (%)	130 (45.5) 156 (54.5)	261 (43.6) 337 (56.4)	0.664
Missingness analysis: reasoning			
Age at time of follow up Mean (±SD) years	58.0 (7.5)	58.0 (7.0)	1
Sex Female (%) Male (%)	170 (63.0) 100 (37,0)	354 (57.7) 260 (42.3)	0.160
Townsend deprivation score Mean (±SD)	-1.2 (2.9)	-0.9 (3.4)	0.207
Education status No college or university degree (%) College or university degree (%)	183 (67.8) 66 (24.4)	468 (76.2) 146 (23.8)	0.011
Visual memory 3 pair trial 6 pair trial Mean (±SD)	0.6 (1.2) 4.9 (3.7)	0.6 (1.2) 4.1 (3.6)	1 0.002
Employment status Good outcome (%) Poor outcome (%)	233 (86.3) 37 (13.7)	499 (81.3) 115 (18.7)	0.084
Psychomotor reaction time Mean (±SD)	590.0 (162.20)	588.7 (126.9)	0.898
Medication status Not taking medications influencing reasoning (%) Taking medications influencing reasoning (%)	74 (27.4) 196 (72.6)	142 (23.1) 472 (76.9)	0.201
Presence of neurological or psychiatric diagnosis other than aSAH No (%) Yes (%)	125 (46.3) 145 (53.7)	266 (43.3) 348 (56.7)	0.455
Missingness analysis: working memory			

Age at time of follow up Mean (±SD) years	58.5 (7.7)	57.9 (7.1)	0.427
Sex Female (%) Male (%)	64 (62.7) 38 (37.3)	460 (58.8) 322 (41.2)	0.515
Townsend deprivation score Mean (±SD)	-1.6 (2.7)	-0.9 (3.3)	0.040
Education status No college or university degree (%) College or university degree (%)	71 (69.6) 31 (30.4)	580 (74.2) 202 (25.8)	0.388
Visual memory 3 pair trial 6 pair trial Mean (±SD)	 0.5 (0.9) 4.5 (2.7)	 0.6 (1.2) 4.3 (3.7)	 0.417 0.598
Employment status Good outcome (%) Poor outcome (%)	90 (88.2) 12 (11.8)	642 (82.1) 140 (17.9)	0.160
Psychomotor reaction time Mean (±SD)	584.9 (166.2)	589.7 (134.7)	0.742
Presence of neurological or psychiatric diagnosis other than aSAH No (%) Yes (%)	 51 (50.0) 51 (50.0)	 340 (43.5) 442 (56.5)	 0.254

Supplementary Table 3. Missing data analysis for prospective memory, reasoning and working memory. p values are raw. Alpha corrected using Bonferroni's method is 0.002. SD: standard deviation

Outcome	aSAH cohort (n=884)	Matched: no medications (n=3536)	Matched: reasoning medications (n=3536)	Matched: visual memory medications (n=3536)	Matched: psychomotor reaction time medications (n=3536)	p value for comparison of SAH cohort and relevant matched population
Psychomotor reaction time At first assessment Mean (±SD)	589 (± 138)				574 (± 125)	0.002*
Visual memory 3 pair trial 6 pair trial Mean (±SD)	0.60 (±1.19) 4.35 (±3.62)			0.609 (±1.29) 4.21 (±3.37)		0.299 0.789
Prospective memory Correct on first attempt (good outcome) (%)	207 (72.4%)	902 (74.1%)				0.598
Reasoning Mean (±SD)	5.64 (±2.06)		5.70 (±2.18)			0.646
Numeric memory Mean (±SD)	6.31 (±1.63)	6.25 (±1.88)				0.736
Employment status Good outcome (%)	732 (82.8%)	3207 (90.7%)				<0.001*

Supplementary Table 4. Comparison of aSAH cases and relevant matched populations (including matching for additional neurological/psychiatric diagnoses) with regard to outcome measure. * indicates $p<0.05$

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