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The trend of cerebral aneurysms over the past two centuries: Need for early screening - An observational study

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Abstract

Objective

Cerebral aneurysms (CAs) are linked to variations in the cerebral arterial network (CBAN). The aim of this study was to find the optimal age for screening to detect brain arterial variations and predict aneurysms before rupture.

Design and setting

This is an observational, quantitative, and retrospective research. The study analyzed 1127 cases of CAs published from 1761 to 1938. Additionally, Computed Tomography Angiography images of 173 patients treated at the Royal Adelaide Hospital (RAH) between 2011 and 2019 were examined for the presence and the location of aneurysms in CBAN.

Participants

Patients of various medical centres from different countries, males and females of full age range up to 100-years.

Results

Data from 1761 to 1938 included CAs cases of 526-males, 573-females, and 28-unknown sexes. The age of these patients varied from 18 months to 89-years (mean age = 42, SD = 18). Approximately 11.5% of the CAs occurred in patients less than 20-years old. Among the 1078 aneurysms whose location was reported, 76% were located in the internal carotid (IC), middle cerebral (MC), and anterior communicating artery complex (AcomAC) regions, while the remaining 24% were in the vertebrobasilar (VB) region. Among 173 patients from the RAH aged between 18 and 100 years, (male=83 and female=90, mean age=60, SD=16), 94% of the CAs were found in the IC, MC, and AcomAC regions. The pattern of aneurysm occurrence, as indicated by values at the 25th, 50th, and 75th percentiles, along with the minimum and maximum patient ages, has remained consistent from 1761 to 2019.

Conclusion

The distribution pattern of cerebral aneurysms in relation to sex, age and locations in the CBAN, remained steady over the last 260-years resulting in risk of strokes early in life. Therefore, early screening for CBAN segment variations is advised for stroke prevention.

Funding

None

Key words

Subarachnoid haemorrhage; Childhood Aneurysm; Stroke; Hemodynamics; Cerebral Arteries.

Strengths and limitations of this study:

- To our knowledge, the patterns of distribution and trends of occurrence of cerebral aneurysms have not been systematically studied over the past 260 years.
- The prevalence of cerebral aneurysms in every 50 to 100 years has been investigated for the first time.
- Aneurysms can develop at any age in the presence of variations in cerebral basal arterial network (CBAN). Early detection of variations in CBAN in infant using non-invasive ultrasound technique recommended and continuing screening regularly as needed.
- Reported cases from the medical centres are not a random representation of the general population.
- This investigation is not a continuous study.

Anatomical variations among components of the cerebral basal arterial network (CBAN) have been linked to the formation of cerebral aneurysms (CAs)¹ and such variations develop during the period of embryonic life.² The period taken for the development of CAs may vary among individuals and once formed they may enlarge, compress the surrounding tissues, and rupture leading to subarachnoid haemorrhage (SAH).³

Cerebral aneurysms of all sizes have been observed to cause SAH in adults⁴ (incidence 6-10/100000), however, they also occur in the age group 0-20 years (incidence rate=1.4-2 per 100000).⁵⁻⁷ It is not clear that the occurrence of anatomical variation-related aneurysms is limited to any specific age. The management of complicated CAs is costly and the CAs can leave permanent disabilities or even become fatal costing millions of dollars to families and governments.⁷⁻¹² The majority of childhood SAH (i.e., incidence 1.4-2 per 100000 children) are caused by the pre-existing cerebral aneurysms.¹³ About 5% of the total cerebral aneurysmal cases diagnosed in the clinical setup were in the age group 0 to 19 years and the incidence of childhood SAH is significantly greater in the older age children.¹³ The clinical manifestation of aneurysmal cases seen later in life might be the consequence of aneurysms that developed in early childhood. Therefore, this study aims to review CAs cases from a tertiary medical center and the literature to investigate the recent pattern of CAs and how it has changed over the past 260 years.

Material and method

Study design, and setting

Two types of data were used in this study.

Type-1 data are composed of 1127 cerebral aneurysmal cases that were published in the 407 papers¹⁴ from 1761 to 1938. These CAs were identified at autopsy and included patients of all ages (average age=41.7 years, mode age=41, median age=41, SD=17.7, age range 1.5 to 89 years) (Supplementary Table 1 and Supplementary File 1).

Type-2 data were Cerebral Computed Tomography Angiography (CTA) images obtained from 173 randomly selected patients, who visited the Royal Adelaide Hospital (RAH), South Australia, between January 2011 and December 2019 for a variety of cranial pathologies; their age ranged from 18 to 100 years, males = 83, female = 90, mean age=60 years, median age=62 years, mode age=61, SD=15.72) with (n=102) or without (n=71) aneurysms (Supplementary Table 1 and Supplementary File 2). These images were anonymised, stored in the Carestream data registry system and the patients have given their consent to use their clinical information for research activities. The consent documents taken from each patient were not provided to the researchers to ensure privacy. The Human Ethics permit (approval number: H2014-176, Research Ethics Committee, Office of Research Ethics, Compliance and Integrity, Faculty of Health Sciences, University of Adelaide) granted permission to access and use the deidentified data set from the Carestream data registry system (Vue-RIS-version-11.0.14.35) for research. Thus, the research materials used in this study comprised 1229 observed cases of CAs that spread across all age groups, spanning a period of approximately 260 years.

Data sources and size

Type-1 data: A range of variables (such as, the year CAs was detected, age, sex, location of the aneurysm) related to 1127 cases of CAs reported in publications from 1761 to 1938, ¹⁴ were transferred into an excel data file, rearranged and subjected to analysis (Supplementary File 1). Type-2 data: The cerebral CTA of 173-patients recorded from 2011 to 2019 in RAH were accessed to study the presence and absence of CAs in different locations of CBAN based on diagnoses made by clinicians. Some cases had multiple aneurysms located in the various segments of CBAN (Supplementary File 2).

The above cases of CAs were grouped into age ranges 0-5, 6-10, 11-15, 16-20, 21-30, 31-40, 41-50, 51-60, 61-70, 71-80, and over 81 years and transferred into the SPSS v. 25 software, for analyses (Supplementary File 1). The observation error has been tested by repeating the observation of the location of CAs in the cerebral CTA images in 20-cases, a month after the first study. There was 100% agreement of repeated observations with

those of the first one. The sites of the formation of aneurysms were recorded as the left and right, internal carotid artery (ICA), middle cerebral artery (MCA), anterior cerebral artery (ACA), anterior communicating artery complex (AcomAC), posterior communicating artery (Pcama), posterior cerebral artery (Pcama), posterior cerebral artery (Pcama), posterior cerebral artery (Pcama), posterior inferior cerebellar artery (AICA), superior cerebellar (Scama), posterior inferior cerebellar artery (AICA), superior cerebellar (Scama), and pial arterial regions. In some cases, the areas of location of aneurysms seemed not to have been mentioned and those cases were tabulated under the heading of 'aneurysms located in CBAN (CBAN-an)'. Overall, the locations of nearly 1229 aneurysmal cases from both data sets were broadly divided into four categories: central and bilateral, left and right before being plotted in the bar charts to study the location and distribution trends of aneurysms in the arterial network over the past 260-years (Figure 1 and 2). The aneurysms located in the AcomAC, and basilar arterial regions were classified as the central group of aneurysms. Additionally, in a few cases aneurysms were located simultaneously on left and right sides and those cases were grouped as 'bilateral' (Supplementary File 1 and 2 and Figure 2).

Statistical methods

Data were analysed using Excel and Statistical Package for the Social Sciences (SPSS-IBM, version-25) program (e.g., descriptive, and Chi squared tests). The p values less than 0.05 were considered as statistically significant.

Patient and public involvement

Involving patients was challenging for conducting and planning this research, since researchers were allowed the access only to anonymised raw data recorded in the database. As per the ethics permit (details in the method section), we accessed retrospective anonymized data, precluding patient involvement in research planning and execution. Patients and families visiting the hospital will receive study updates. Input from participants will be encouraged via follow-ups, seminars, and email. Shared experiences and suggestions will be valued, with privacy respected. The shared outcome of this study will be informed to the public, families and patients who attend the RAH hospital for various clinical visits, through a series of meetings, seminars, and media releases.

Findings

This study reviewed 1127 aneurysmal cases of patients of all ages from a total of 407 published articles prior to the year 1939. The ages of these patients (male=526, female=573, unknown sex=28) ranged from 18 months to 89 years of age with an average of 41.70 years, mode of 41 years and median of 41 years (SD=17.7) (Supplementary Table 1, Figure 1a, Figure 1b, Figure 1c, Supplementary File 1). The second group of patients with CAs (44 males and 58 females, and n=102) from the RAH (2011 to 2019) with the age range 18-100 years showed that the most common age for diagnosis or complication of CAs ranged from 31-60 years with the calculated mean, median, mode, and standard deviation (SD), 57.60, 60.00, 48.00, and 13.12 years, respectively (Supplementary Figure 1 and Figure 1d). Analysis of both sets of data revealed that the majority of the patients who presented with complicated aneurysms were in their 3rd to 6th decades of life (Supplementary Table 1, Figure 1 a-d).

The most important aspect of the two sets of data was the wide age range of occurrence of CAs and the fact that some of the complicated aneurysmal cases appeared at an early age (Figure 1a, Figure 1b, Supplementary File 1). A separate analysis was conducted for 853 out of the 1127 cases of CAs recorded before 1938 (male=409, female=438, unknown sex=6), specifically focusing on the age range of 18 to 89 years to align the age groups with the RAH recorded data from 2011 to 2019 (Supplementary Table 1, Figure 1c and Figure 1d). The similarities of standard deviation (15.45) of those 853 cases (from 1761-1938) and the cases that were recorded from 2011 to 2019 in RAH (13.12 years) validated the comparability of our data and the findings (Supplementary Table 1). The values of the 25th, 50th, and 75th percentiles, as well as the minimum and maximum observed ages of patients with aneurysms, remained relatively stable from 1761 to 1938 (Figure 3a). Some of these percentile values increased slightly as life expectancy extended from 1761 to the 21st century (Figure 3b). Therefore, the SD, and age distribution of adult patients with ruptured or diagnosed CAs presented in the 2011-2019 dataset were consistent with those cases reported before 1938, indicating persistence of a pattern (Supplementary Table 1, Figure 1 and 3). Specifically, aneurysms are being frequently diagnosed in

In the type 2 dataset, a total of 135 aneurysms were identified in 102 individuals, with ages ranging from 18 to 83 years, across various components of CBAN (Figure 1d and Supplementary File 2). Among these aneurysms, 38(28.14%) were detected in the right MCA region, while 17(12.6%) were in the right ICA region. In comparison, the left MCA and ICA regions had 27(20%) and 12(8%) aneurysms, respectively, which appeared to be lower in number compared to the right MCA and ICA regions. When considering the distribution of aneurysms based on territory, 55 out of 135 aneurysms (40.74%) in 50 patients were found in the right ICA and MCA territories, whereas 39 out of 135 aneurysms (28.88%) in 37 patients were detected in the left ICA and MCA regions (Supplementary File 2). Out of the 102 individuals with aneurysmal cases included in the study, 33 (24.44%) had aneurysms located in the anterior communicating artery (AcomAC) region, accounting for 33 out of the total 135 aneurysms. An additional 5.9% of the total aneurysms (8 out of 135 aneurysms) were found in the vertebral and basilar arterial regions, as indicated in the Supplementary File 2. A majority of the CAs, 127 out of the total 135 (94% of the total), were in the MCA, ICA, and AComAC regions (Supplementary File 2). Some cases had multiple aneurysms, for example, 2 cases had right ICA and MCA aneurysms, while 10 cases had left ICA and MCA aneurysms (Supplementary File 2).

There were no significant differences between male and female patients affected with CAs in all 1229 cases analysed in those two data sets (Chi-Squared statistic=0.83, p≥0.36) (Table 1). The sex, age of occurrence and location of CAs appear to have remained steady over the past 260 years across all age groups (Table 1 and Supplementary Table 1, and Figure 3). The mode, mean, and median age and SD of patients with ruptured or diagnosed CAs studied from 2011 to 2019 in RAH matched well with the cerebral aneurysmal cases recorded in the past considering the difference in life expectancy between the two time periods studied (1761-1938 and 2011-2019) (Figures 3 and Supplementary Table 1).

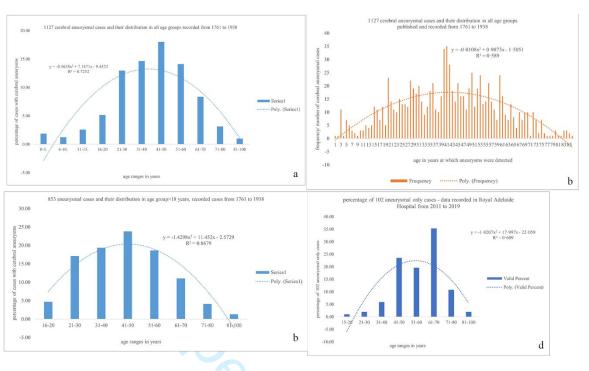


Figure 1- Figures displaying the distribution patterns of cerebral aneurysms in different age groups recorded from 1761 to 1938 and from 2011 to 2019. A polynomial regression lines show the number and distribution of cerebral aneurysm cases across all age groups. a) The distribution of cerebral aneurysmal cases (n=1127) in various age group, recorded from 1761 to 1938. ¹⁴ b) The frequency of cerebral aneurysmal cases and their distribution (n=1127) across all age groups recorded¹⁴ from 1761 to 1938. c) Age (≥18 years) related distribution of individuals affected with cerebral aneurysms over the past 260 years (1761 − 1938) (n=853), recorded¹⁴ from 1761 to 1938, and d) Age (18-100 years) related prevalence (%) of cerebral aneurysms in RAH sample from 2011 to 2019 (n=102). The peak prevalence occurred between 31-60 years (p<0.001). RAH= Royal Adelaide Hospital. RAH= Royal Adelaide Hospital and 14 = McDonald, CA & Korb, M 1939, Intracranial aneurysms, Archives of neurology and psychiatry (Chicago), vol. 42, no. 2, pp. 298-328.

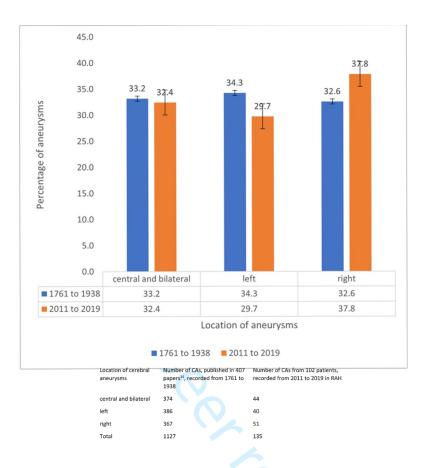


Figure 2- Comparison of the location of cerebral aneurysms between Royal Adelaide Hospital sample (2011 to 2019) (n=135 CAs from 102 patients, orange colour) with those recorded in 407 publications¹⁴ (1761 to 1938) (n=1127 CAs, blue colour). CAs=cerebral aneurysms, 14 = McDonald, CA & Korb, M 1939, Intracranial aneurysms, Archives of neurology and psychiatry (Chicago), vol. 42, no. 2, pp. 298-328.

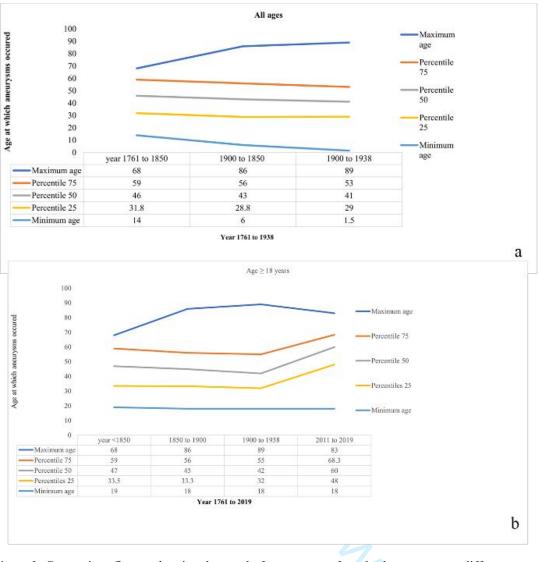


Figure 3: Comparison figures showing the trend of occurrence of cerebral aneurysms at different age group (n=1127) from 1761 to 2019. (a)The values of the 25th, 50th, and 75th percentiles, as well as the minimum and maximum observed all ages of patients with aneurysms, from 1761 to 1938¹⁴; b) The values of the 25th, 50th, and 75th percentiles, as well as the minimum and maximum observed patients with >18 years of age with aneurysms, recorded from 1761 to 1938¹⁴ and 2011 to 2019 in RAH. RAH = Royal Adelaide Hospital, 14 =Data from: McDonald, CA & Korb, M 1939, Intracranial aneurysms, Archives of neurology and psychiatry (Chicago), vol. 42, no. 2, pp. 298-328

Supplementary Figure 1- The prevalence (%) of cerebral aneurysms in relation to age (18-100 years, n=173, cases with aneurysms=102, cases without aneurysm=71), with a median of 62 years, a mean of 60 years, and a standard deviation of 15.75. The peak prevalence occurs between 31-60 years (p<0.001).

Table 1: Prevalence of cerebral aneurysms in males and females: a comparison of the recent hospital-based data recorded in RAH from 2011 to 2019 with the autopsy data published before from 1761 to 1938.

Sex	N=173, cases with or without cerebral aneurysms recorded in RAH from 2011 to 2019.	1127 aneurysm cases (from 1761 to 1938) recorded in 407 publications. ¹⁴	
Sex not defined	0	28	
Female	90	573	
Male	83	526	
Female to male sex ratio	1.08	1.09	

Legend- RAH = royal Adelaide hospital, 14 = McDonald, CA & Korb, M 1939, Intracranial aneurysms, Archives of neurology and psychiatry (Chicago), vol. 42, no. 2, pp. 298-328.

		patients with cerebral aneurysmal aneurysms recorded in RAH from 2011 to 2019	1127 patients 1938	with cerebi	al aneurysr	ns recorded	l in 407 pub	lications - p	oublished fr	om 1761 to
Statistics -		age>18,	age>18	age >=	age >=	age >=	all age,	all age,	all	all age
all cases		2011 to	years, 1761	18 &	18 &	18 &	year	year <	ages,	group, all
with		2019	to 1938	year <	year >=	year >=	<1850	1900 &	year >=	years, >400
cerebral				1850	1850 &	1900		year >=	1900	publications
aneurysms					year <			1850		
					1900					
Age in										
years N	Valid	102	851	41	252	560	42	278	613	935
IN	Missing	0	0	0	0	0	7	14	171	192
Mean age	Wiissing	57.6	44.7	44.3	45.60	44.3	43.6	42.6	41.2	41.7
Median		60.0	43.0	47.0	45.00	42.0	46.0	43.0	41.0	41.0
age		00.0	13.0	17.0	15.00	12.0	10.0	15.0	11.0	11.0
Mode age		48.0	41.0	20.0	40.0	41.0	20.0	40.0	41.0	41.0
Std.		13.1	15.5	15.6	15.6	15.4	16.1	17.5	17.9	17.7
Deviation										
Minimum		18.0	18.0	19.0	18.0	18.0	14.0	6.0	1.5	1.5
age										
Maximum		83.0	89.0	68.00	86.0	89.0	68.0	86.0	89.0	89.0
age					Y /					
Percentiles	25	48.0	32.0	33.50	33.3	32.0	31.8	28.8	29.0	29.0
	50	60.0	43.0	47.00	45.0	42.0	46.0	43.0	41.0	41.0
	75	68.3	56.0	59.00	56.0	55.0	59.0	56.0	53.0	54.0

Legend: 14 = McDonald, CA & Korb, M 1939, Intracranial aneurysms, Archives of neurology and psychiatry (Chicago), vol. 42, no. 2, pp. 298-328.

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Discussion

The age and locations at which CAs occur in the CBAN has not changed over past 260 years (Figures 1, 2 and 3, Table 1 and Supplementary Table 1) despite the life expectancy has increased over time worldwide and the progress in medicine. In the past people had shorter life span on average, and yet the CAs occurred at the same ages as they do now.15 The life expectancy recorded at below 50 years in 1940 and even below 40 years in 1850 was way lower compared to the one recorded above 80 years of age since the year 2000 in Australia. 15 A separate analysis was done for 853 out of the 1127 CAs recorded before 1938 focusing on the age range of 18 to 89 years to align the age group with the currently RAH recorded data from 2011 to 2019, since there were no aneurysmal cases of children (age<18years) in the RAH dataset. In Adelaide there is a separate hospital for children where aneurysmal cases would have been treated, but the authors had no access to these data (Supplementary file 2). Royal Adelaide Hospital is a general hospital, thus individuals of 18 years and less are not admitted. Current study compared the cases of CAs diagnosed by CTA imaging technique (from 2011-2019) with those verified by surgery and autopsy¹⁴, since there were no cerebral angiogram facilities in early years (i.e., before 1938). The cases of aneurysms are commonly diagnosed, when the patients are presented at medical centres after attacks of stroke. 16 Cerebral aneurysms in the past seemed to be ruptured and complicated as early as 18 months of age and as late as 89 years of age with a wide range of age (Supplementary File 1). The findings suggested that the change in lifestyle nor medical practice had no effect at the age/time of formation of CAs in general population. Clinical investigation of lipid profiles in patients commenced after 1950, 17 and they started attributing arterial diseases and aneurysms to the hyperlipidaemia, however, the manifestation of occurrence of aneurysms by age in the past 260 years seems not to be different from the current age of occurrence. Although the lifestyle and the external influences, including medical practice, changed over more than two centuries, aneurysms still occur at approximately the same age. Therefore, aneurysms occur and rupture on their own internal circumstances and are not related to the diet, environmental, and external factors.¹⁸ The most likely internal factor is the severity of the variation on the segments of CBAN that adversely affects the hemodynamics resulting in the formation of aneurysms. 1,19 The condition of the arterial wall should not have changed over the last 260 years and that seems to be less significant than the variation in the components of CBAN. The segmental and communicating arteries play a crucial role in dampening the systolic pressure within the CBAN and reducing the likelihood of aneurysm formation.^{1,19} The severity of arterial variation can have negative effects on the blood flow dynamics through the variant segment of the component of the CBAN. 1,19 The incidence of CAs is about 3.3% in the general population and may not be diagnosed, until they get enlarged as the size of the aneurysm <3mm in diameter can be missed.²⁰ Imaizumi and colleagues found that the prevalence rate of CAs was 4.32% in Japan. 12 The incidence rate of CAs in childhood (age <18 years) has been reported to be 0.5- 4.6%, which is almost as common as the incidence rate observed among adults. 13 Treating CAs cases with a diameter less than 3-mm requires careful consideration, as almost all cases of SAH were caused by ruptured aneurysms, and nearly 50 % cases can be attributed to pre-existing small aneurysms of ≤ 3mm in diameter.²¹ The majority of CAs are detected only when they cause a stroke or other pathological effect (e.g., compression of the optic tract).⁴ Individuals older than 18 years are no longer considered children.^{6,13}

Most of the symptomatic cases of CAs in the paediatric age group were observed in older children (15 + years) ¹³, and only complicated cases of CAs were generally diagnosed and reported. ^{22,23} If the incidence of childhood CAs described (ranges from 0.17 to 4.6%), ²⁴ is corrected for number of years lived, it would be 18.4% of the total aneurysmal cases amongst adults. The adult patients included in CAs studies ideally have an age range of 18-years and above, which can include individuals up to the age of 100 years. ^{12,15} In contrast, the childhood group included in aneurysmal studies typically ranges from birth up to 18-years of age and a few studies have categorized patients who are 18-years or older under the adult group. ^{6,13} When we consider the age range, 0-18 years and 19- 100 years, the incidence of childhood CAs, that should be multiplied by 5 times to correct for the number of years lived, can be comparable to that in adults because the childhood period of life is much shorter than the adulthood. Therefore, the age range of adult group (≥20 years up to 100 years) included in the CAs and stroke studies would be about five times more than the age range of children (i.e., ≤18 years). ^{22,23} That means adults have 5 times more years to develop CAs compared to children. Therefore, the incidence of childhood CAs per year is almost equivalent to adult. ^{21,25} Hens, CAs could develop in early childhood in the presence of a significantly variant component of cerebral arterial anatomy, ^{1,2} and it could take years for them to balloon before

becoming symptomatic and being observed in a tertiary medical center. The overall pattern of location and distribution of childhood CAs was similar to adult as they commonly occurred in ICA, MCA and AcomAC regions.³ Therefore the development of CAs is not age related and found to be prevalent in all age ranges.^{10,12,13,26} Cerebral aneurysms may not always be associated to the advanced age, history of smoking, drinking alcohol but start forming as early as in the childhood in the presence of variant components of cranial blood vessels.²⁷ Smoking, hypertension and increased consumption of alcohol and use of drugs could enhance weakening the vessel wall in the presence of arterial variation and genetic disorder leading to the advancement of aneurysms and its complication.¹³ The mean age at which people were affected by cerebral aneurysms was reported to be 55 to 57 years of age in a study conducted using 1085 aneurysmal cases from 2008 to 2016.²⁸ There are a few reports of CAs published between 1938 and 2011 that could have been compiled for statistical analyses. However, their inclusion into this study, would not have changed its basic conclusions: i.e., large age range and no change through time in the occurrence of CAs.

Transcranial Doppler has been found to be effective in studying brain vessels^{26,29} in infants and can be incorporated as a screening tool to detect variant intracranial vessels that could predispose them to the development of cerebral aneurysms later in life. Ultrasonographic (USG) video screening, involving the placement of the probe in the fontanelles of babies before they close, for variant cerebral arteries, might be introduced as a routine procedure due to its safety.²⁹ Detecting variant components of CBAN using our proposed low-risk cranial USG techniques may help identify at-risk patients early, benefiting them for life. For example, individuals with a diameter ratio greater than 1.4 between the left and right ACA have a 27-fold increased risk of developing cerebral aneurysms in the AcomAC region.¹ The ACA asymmetry can be measured by placing USG probes in a baby's fontanelles, in a simple clinical setup before the fontanelles fuse. Parents of children found to have variations in CBAN could be advised to schedule follow-up brain 'Magnetic Resonance Angiography' scans at specific intervals, such as every 5 years, especially if a more affordable technology for detecting brain aneurysms becomes available. This study was not designed to examine the characteristics of aneurysms, but the focus was on the distribution of aneurysms in different segments of CBAN, trend of occurrence of aneurysms over the past 260-years, and the comparison of cerebral aneurysms in all age ranges.

Limitations:

 The insufficient data on the lack of personal and family history, history of smoking, lipid profile, and blood pressure are limitations of this study. A larger survey and a prospective study could be conducted. A prospective study could involve using ultrasound techniques to identify variations in brain vessels among infants.

Conclusion

Brain arterial aneurysms can develop early in the presence of variant arterial components. Screening children under 24 months using transcranial ultrasonography for variant cerebral arteries may be practical. Those with variations should undergo periodic tests for aneurysms, aiming to prevent haemorrhagic strokes.

Data sharing statement

Additional data are available by emailing Arjun.Burlakoti@unisa.edu.au

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Author contribution statement

Arjun Burlakoti- conceived the idea, collected, and analysed both sets of data, took pictures, recorded videos, contributed to conceptualization, prepared and drafted the manuscript.

 Jaliya Kumaratilake- conceived the idea, contributed to the concept, aided in data interpretation, editing and the revision of the manuscript and approving the article.

Jamie Taylor- conceived the idea, contributed to the concept, aided in data interpretation, editing and the revision of the manuscript and approving the article.

Maciej Henneberg- conceived the idea, masterminded, and helped in statistics, data analysis and interpretation, editing and approving the article.

Competing interests

None declared. All authors have nothing to disclose.

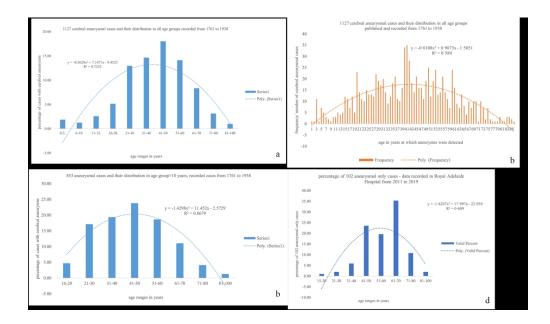
Ethical Approval Statement

The University of Adelaide, Human Research Ethics Board granted permission to access and use data for this research project (Ethics Approval Number: H2014-176).

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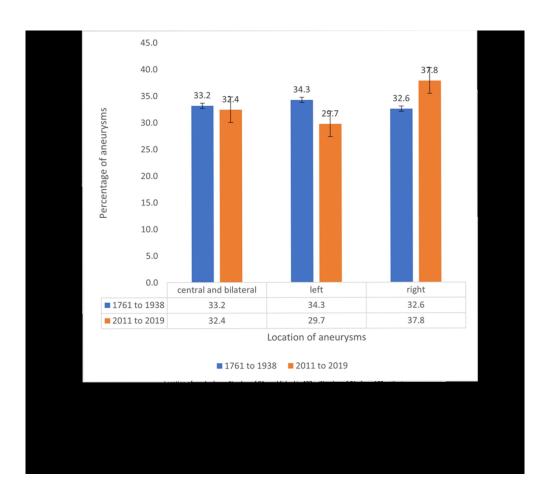
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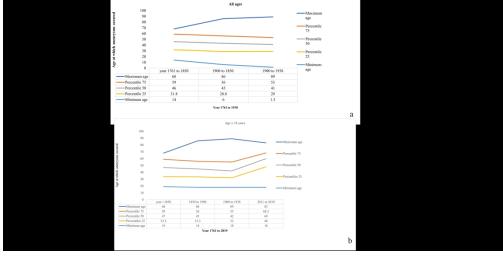
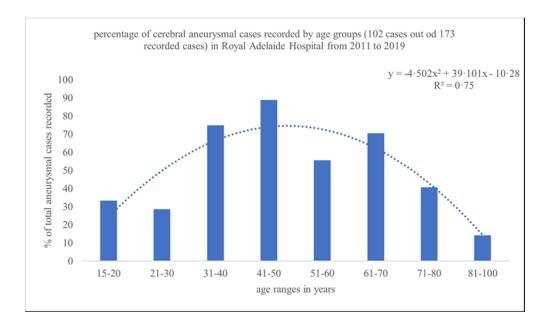


Figure 3: Comparison figures showing the trend of occurrence of cerebral aneurysms at different age groups (n=1127) from 1761 to 2019. (a)The values of the 25th, 50th, and 75th percentiles, as well as the minimum and maximum observed all ages of patients with aneurysms, from 1761 to 1938[14]; b) The values of the 25th, 50th, and 75th percentiles, as well as the minimum and maximum observed patients with >18 years of age with aneurysms, recorded from 1761 to 193814 and 2011 to 2019 in RAH. RAH = Royal Adelaide Hospital, 14 = Data from: McDonald, CA & Korb, M 1939, Intracranial aneurysms, Archives of neurology and psychiatry (Chicago), vol. 42, no. 2, pp. 298-328

220x111mm (330 x 330 DPI)

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135x79mm (330 x 330 DPI)

Table 1: Prevalence of cerebral aneurysms in males and females: a comparison of the recent hospital-based data recorded in RAH from 2011 to 2019 with the autopsy data published before from 1761 to 1938.

Sex	n=173, cases with or without	1127 aneurysm cases (from 1761 to
	cerebral aneurysms recorded in	1938) recorded in 407 publications. 14
	RAH from 2011 to 2019.	

Sex not defined	0	28
Female	90	573
Male	83	526
Female to male sex ratio	1.08	1.09

Legend: RAH = royal Adelaide hospital, 14=McDonald, CA & Korb, M 1939, Intracranial aneurysms, Archives of neurology and psychiatry (Chicago), vol. 42, no. 2, pp. 298-328.

		102	1127 patients	with cerebr	al aneurysr	ns recorded	l in 407 pub	lications - p	oublished fr	om 1761 to
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		with								
		cerebral								
		aneurysmal								
		aneurysms								
		recorded in								
		RAH from								
		2011 to								
		2019								
Statistics -		age>18,	age>18	age >=	age >=	age >=	all age,	all age,	all	all age
all cases		2011 to	years, 1761	18 &	18 &	18 &	year	year <	ages,	group, all
with		2019	to 1938	year <	year >=	year >=	<1850	1900 &	year >=	years, >400
cerebral				1850	1850 &	1900		year >=	1900	publications
aneurysms					year <			1850		
					1900					
Age in										
years										
N	Valid	102	851	41	252	560	42	278	613	935
	Missing	0	0	0	0	0	7	14	171	192
Mean age		57.6	44.7	44.3	45.6	44.3	43.6	42.6	41.2	41.7
Median		60.0	43.0	47.0	45.0	42.0	46.0	43.0	41.0	41.0
age										
Mode age		48.0	41.0	20.0	40.0	41.0	20.0	40.0	41.0	41.0
Std.		13.1	15.5	15.6	15.6	15.4	16.1	17.5	17.9	17.7
Deviation										
Minimum		18.0	18.0	19.0	18.0	18.0	14.0	6.0	1.5	1.5
age										
Maximum		83.0	89.0	68.0	86.0	89.0	68.0	86.0	89.0	89.0
age										
Percentiles	25	48.0	32.0	33.5	33.3	32.0	31.8	28.8	29.0	29.0
	50	60.0	43.0	47.0	45.0	42.0	46.0	43.0	41.0	41.0
	75	68.3	56.0	59.0	56.0	55.0	59.0	56.0	53.0	54.0

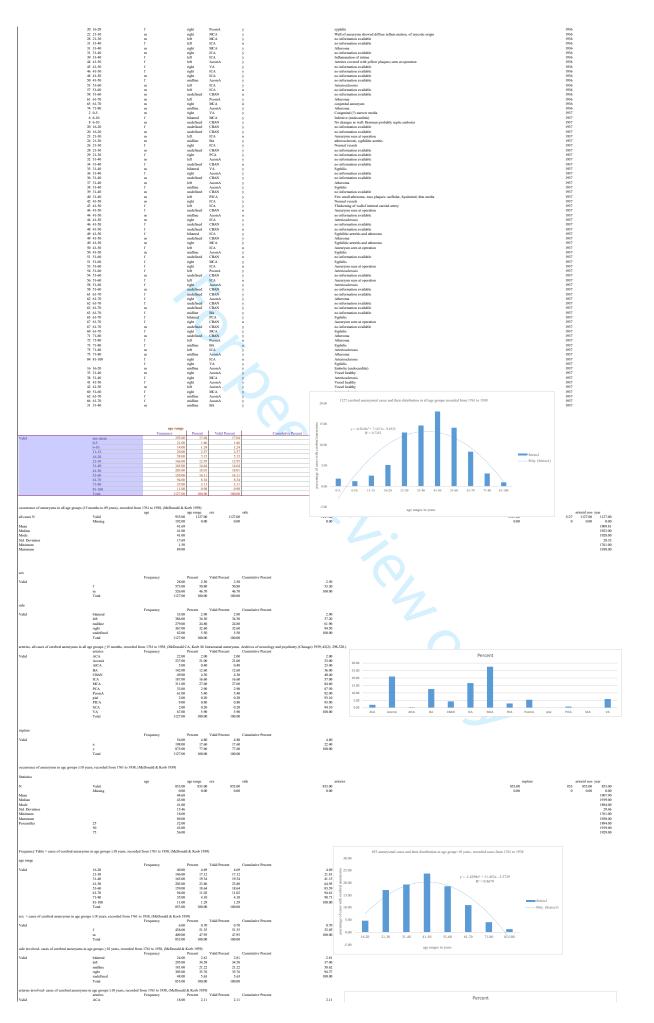
Legend: 14 = McDonald, CA & Korb, M 1939, Intracranial aneurysms, Archives of neurology and psychiatry (Chicago), vol. 42, no. 2, pp. 298-328.

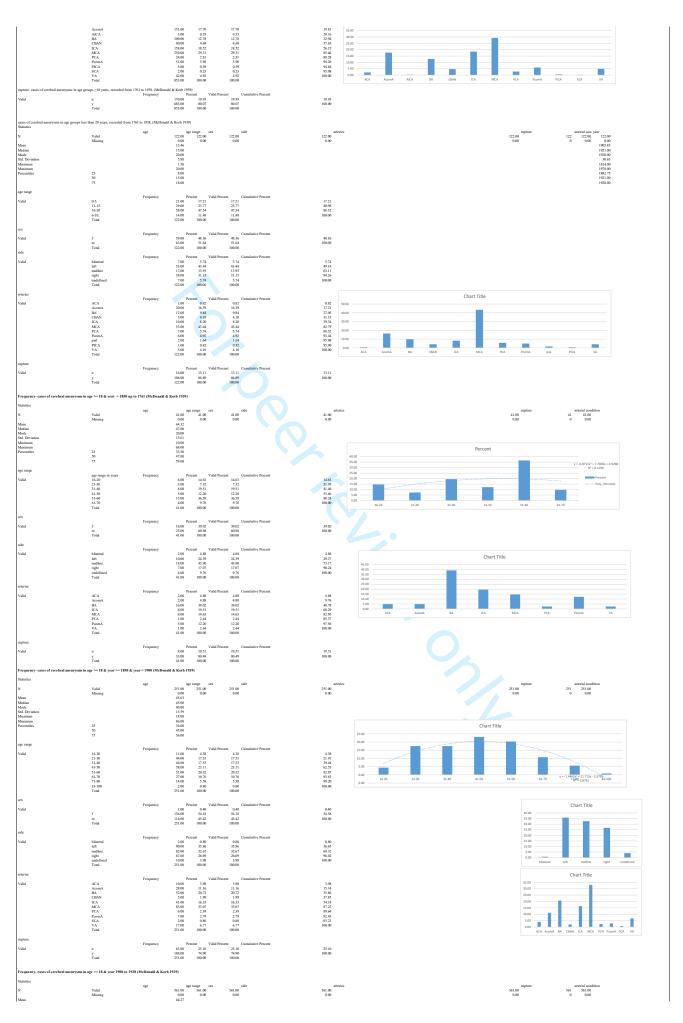
Supplementary file 1: contains type 1 data Manuscript title: The trend of cerebral aneurysms over the past two centuries: N	Need for early screening - An observational study.	
Manuscript title: The trend of cerebral ancuryoms over the past two centuries. A hobrivations is From Possistric communicating artery, ICA—internal carotid AICA—interior inferior cerebellar artery, VA=vertebral artery, CBAN=cerebral age in years 60 51-60	Seed for early screening - An observational study. attery, BA-basiler artery, Acom-amerior communicating artery, M. basal arterial network (artery involved not known), PICA-uposterior in sex, m=male, f=female side affected v arteries involved m biliaterial PoomA	A-middle control attern, JaC variation control attern, TaC-speciation control attern, TaC-speciation control attern, TaC-speciation control attern, TaC-speciation control attern, Manual & Kon 1979 McLoud AC, Kook M. Homestern attenues measures, Auditors of neurology and psychintry (Chicago) 1979-42(2): 28-328.) statis of neurologic repaired-y, not reputer-la- service of neurologic attenues of neurologic atten
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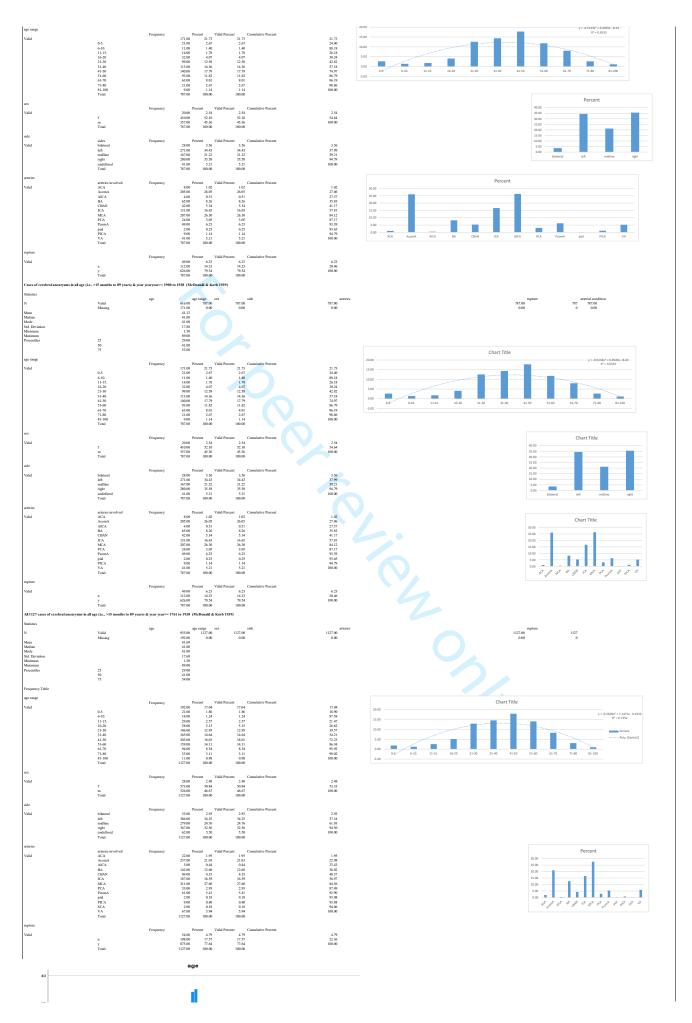
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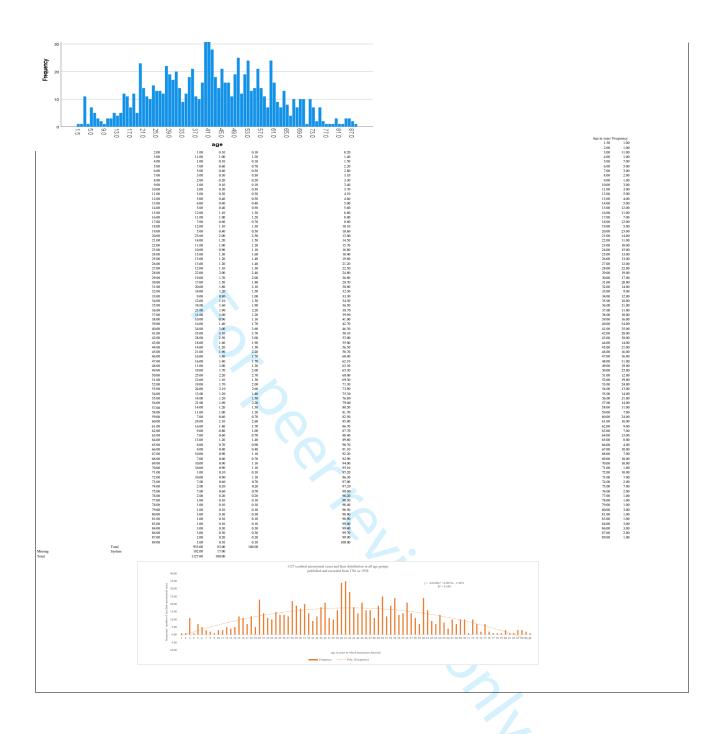
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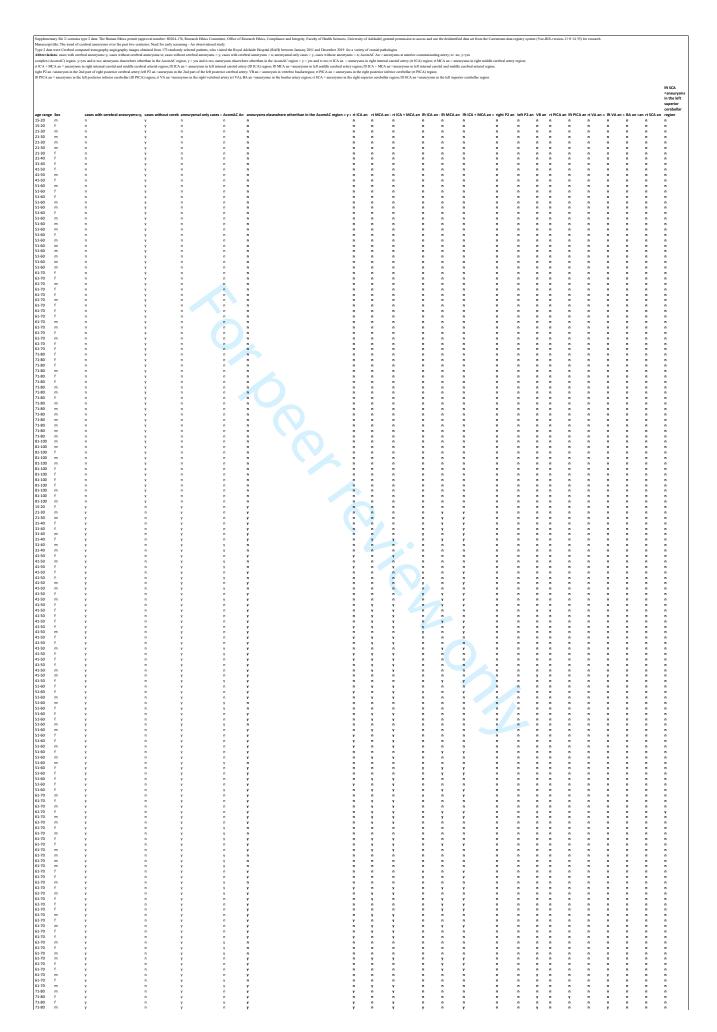


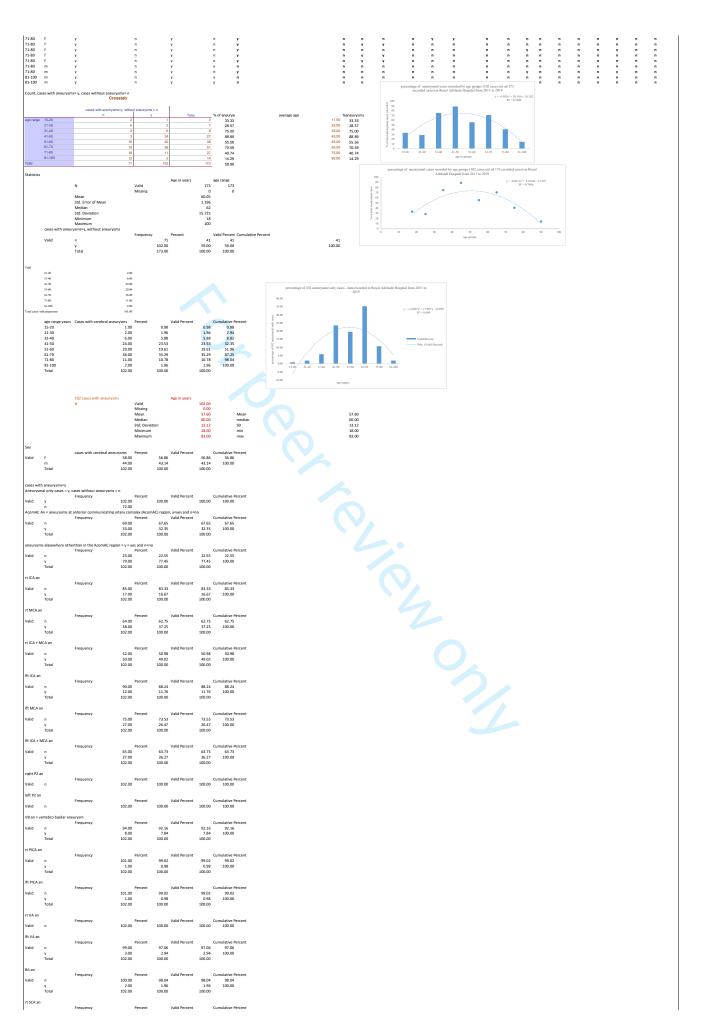












Valid	n		102.00	100.00	100.00	100.00
1						
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age range	- patients with ((n=102) and without aneu				
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	21-30		7.00	4.00	4.00	5.80
	31-40		8	4.6	4.6	10.4
	41-50		27	15.6	15.6	26
	51-60		36	20.8	20.8	46.8
	61-70		51	29.5	29.5	76.3
	71-80		27	15.6	15.6	91.9
	81-100		14	8.1	8.1	100
	Total		173	100	100	
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Valid	f		90	52	52	52
	m		83	48	48	100
	Total		173	100	100	
1						

STROBE Statement—Checklist of items that should be included in reports of cross-sectional studies

23333	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract
		(b) Provide in the abstract an informative and balanced summary of what was done
		and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		1 3 / 2 31 1 31
Study design	4	Present key elements of study design early in the paper
Setting Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment,
Setting	3	exposure, follow-up, and data collection
Dortioinanta	6	
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of
	7	participants
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect
D /	0*	modifiers. Give diagnostic criteria, if applicable
Data sources/	8*	For each variable of interest, give sources of data and details of methods of
measurement		assessment (measurement). Describe comparability of assessment methods if there is
D.		more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable,
		describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding
		(b) Describe any methods used to examine subgroups and interactions
		(c) Explain how missing data were addressed
		(d) If applicable, describe analytical methods taking account of sampling strategy
		(\underline{e}) Describe any sensitivity analyses
Results		
Participants	13*	(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
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and
r		information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and
Walli results	10	their precision (eg, 95% confidence interval). Make clear which confounders were
		adjusted for and why they were included
		(b) Report category boundaries when continuous variables were categorized
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a
Other analyses	17	meaningful time period Peneut other analyses done are analyses of subgroups and interestions and
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and
		sensitivity analyses

Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or
		imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations,
		multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	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

^{*}Give information separately for exposed and unexposed groups.

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.

BMJ Open

The trend of cerebral aneurysms over the past two centuries: Need for early screening - An observational study.

Journal:	BMJ Open
Manuscript ID	bmjopen-2023-081290.R1
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Date Submitted by the Author:	05-Jan-2024
Complete List of Authors:	Burlakoti, Arjun; University of South Australia, Human Anatomy; University of Adelaide, School of Biomedicine, Faculty of Health and Medical Sciences Kumaratilake, Jaliya; The University of Adelaide Adelaide Medical School, School of Biomedicine, Faculty of Health and Medical Sciences Taylor, Jamie; Royal Adelaide Hospital, South Australia Medical Imaging Henneberg, Maciej; The University of Adelaide, School of Biomedicine, Faculty of Health and Medical Sciences; Institute of Evolutionary Medicine, The University of Zurich, Zurich, Switzerland
Primary Subject Heading :	Neurology
Secondary Subject Heading:	Health policy, Pathology, Public health
Keywords:	Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Stroke < NEUROLOGY, Mass Screening, Community child health < PAEDIATRICS

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Abstract

Objective

Cerebral aneurysms (CAs) are linked to variations in the cerebral basal arterial network (CBAN). This study aimed to find the optimal age for screening to detect brain arterial variations and predict aneurysms before rupture.

Design

An observational, quantitative, and retrospective research.

Setting

The study analyzed 1127-cases of CAs published from 1761 to 1938. Additionally, Computed Tomography Angiography images of 173-patients at the Royal Adelaide Hospital (RAH), South Australia between 2011 and 2019 were examined for the presence and the location of aneurysms in CBAN.

Participants

The data were collected from patients at RAH and 407-published sources, including males and females across the entire age range, up to 100 years old.

Outcome measures and results

Data, CAs cases, from 1761 to 1938 included (526-males, 573-females, and 28-unknown sexes). The age of these patients varied from 18 months to 89-years (mean age=42, SD=18). Approximately 11.5% of the CAs occurred in patients less than 20-years old. Among the 1078 aneurysms whose location was reported, 76% were located in the internal carotid (IC), middle cerebral (MC), and anterior communicating artery complex (AcomAC) regions, while the remaining 24% were in the vertebrobasilar (VB) region. Among 173-patients from the RAH aged between 18 and 100 years, (male=83 and female=90, mean age=60, SD=16), 94% of the CAs were found in the IC, MC, and AcomAC regions. The pattern of aneurysm occurrence, as indicated by values at the 25th, 50th, and 75th percentiles, along with the minimum and maximum patient ages, has remained consistent from 1761 to 2019.

Conclusion

The distribution pattern of cerebral aneurysms in relation to sex, age and locations in the CBAN, remained steady over the last 260-years resulting in risk of strokes early in life. Therefore, early screening for CBAN segment variations is advised for stroke prevention if possible.

Key words

Subarachnoid haemorrhage; Childhood Aneurysm; Stroke; Hemodynamics; Cerebral Arteries.

Strengths and limitations of this study:

- To our knowledge, the patterns of distribution and trends of occurrence of cerebral aneurysms have not been systematically studied over the past 260 years.
- The prevalence of cerebral aneurysms in every 50 to 100 years has been investigated for the first time.
- Aneurysms can develop at any age in the presence of variations in cerebral basal arterial network (CBAN). Early detection of variations in CBAN in infant using non-invasive the Doppler ultrasound technique is recommended and continuing screening regularly as needed.
- Reported cases from the tertiary medical centres and 407 papers published over the past 260 years may not represent the general population precisely.
- This investigation is not a continuous study.

Funding

Not applicable, none

Competing interests

None declared. All authors have nothing to disclose.

Introduction

Anatomical variations among components of the cerebral basal arterial network (CBAN) in addition to the trauma, infection, spontaneous dissections, and collagen disorders, have been linked to the formation of cerebral aneurysms (CAs)[1,2,3] and such variations develop during the period of embryonic life.[2] The period taken for the development of CAs may vary among individuals and once formed they may enlarge, compress the surrounding tissues, and rupture leading to subarachnoid haemorrhage (SAH).[3]

Cerebral aneurysms of all sizes have been observed to cause SAH in adults[4] (incidence 6-10/100000), however, they also occur in the age group 0-20 years (incidence rate=1.4-2 per 100000).[5-7] It is not clear that the occurrence of anatomical variation-related aneurysms is limited to any specific age. The management of complicated CAs is costly and the CAs can leave permanent disabilities or even become fatal costing millions of dollars to families and governments.[7-12] The majority of childhood SAH (i.e., incidence 1.4-2 per 100000 children) are caused by the pre-existing cerebral aneurysms.[13] About 5% of the total cerebral aneurysmal cases diagnosed in the clinical setup were in the age group 0 to 19 years and the incidence of childhood SAH is significantly greater in the older age children.[13] The clinical manifestation of aneurysmal cases seen later in life might be the consequence of aneurysms that developed in early childhood. Therefore, this study aims to review cases of CAs using data collected from a tertiary medical center (Royal Adelaide Hospital - South Australia) and published sources to investigate the recent pattern of CAs and how it has changed over the past 260 years. The null hypothesis is that the advancement of medical science did not lead to a reduction in the prevalence of aneurysms by age.

Material and method

Study design, and setting

Two types of data were used in this study.

Type-1 data are composed of 1127 cerebral aneurysmal cases that were published in the 407 papers from 1761 to 1938, as compiled by McDonald and, Korb.[14] These CAs were identified at autopsy and included patients of all ages (average age=41.7 years, mode age=41, median age=41, SD=17.7, age range 1.5 to 89 years) (Supplementary File 1 and Supplementary Table 1).

Type-2 data were Cerebral Computed Tomography Angiography (CTA) images obtained from 173 randomly selected patients, who visited the Royal Adelaide Hospital (RAH), South Australia, between January 2011 and December 2019 for a variety of cranial pathologies; their age ranged from 18 to 100 years, males = 83, female = 90, mean age=60 years, median age=62 years, mode age=61, SD=15.72) with (n=102) or without (n=71) aneurysms (Supplementary Table 1 and Supplementary File 2). These images were anonymised, stored in the Carestream data registry system and the patients have given their consent to use their clinical information for research activities. The consent documents taken from each patient were not provided to the researchers to ensure privacy. The Human Ethics permit (approval number: H2014-176, Research Ethics Committee, Office of Research Ethics, Compliance and Integrity, Faculty of Health Sciences, University of Adelaide) granted permission to access and use the deidentified data set from the Carestream data registry system (Vue-RIS-version-11.0.14.35) for research. Thus, the research materials used in this study comprised 1229 observed cases of CAs that spread across all age groups, spanning a period of approximately 260 years.

Data sources and size

Type-1 data: A range of variables (such as, the year CAs was detected, age, sex, location of the aneurysm) related to 1127 cases of CAs reported in publications from 1761 to 1938,[14] were transferred into an excel data

file, rearranged and subjected to analysis (Supplementary File 1). Type-2 data: The cerebral CTA of 173-patients recorded from 2011 to 2019 in RAH were accessed to study the presence and absence of CAs in different locations of CBAN based on diagnoses made by clinicians. Some cases had multiple aneurysms located in the various segments of CBAN (Supplementary File 2).

The above cases of CAs were grouped into age ranges 0-5, 6-10, 11-15, 16-20, 21-30, 31-40, 41-50, 51-60, 61–70, 71–80, and over 81 years and transferred into the SPSS v. 25 software, for analyses (Supplementary File 1). The observation error has been tested by repeating the observation of the location of CAs in the cerebral CTA images in 20-cases, a month after the first study. There was 100% agreement of repeated observations with those of the first one. The sites of the formation of aneurysms were recorded as the left and right, internal carotid artery (ICA), middle cerebral artery (MCA), anterior cerebral artery (ACA), anterior communicating artery complex (AcomAC), posterior communicating artery (PcomA), posterior cerebral artery (PCA), vertebral artery (VA), basilar artery (BA), posterior inferior cerebellar artery (PICA), anterior inferior cerebellar artery (AICA), superior cerebellar (SCA) and pial arterial regions. In some cases, the areas of location of aneurysms seemed not to have been mentioned and those cases were tabulated under the heading of 'aneurysms located in CBAN (CBAN-an)'. Overall, the locations of nearly 1229 aneurysmal cases from both data sets were broadly divided into four categories: central and bilateral, left and right (Figure 1) before being plotted in the bar charts to study the location and distribution trends of aneurysms in the arterial network over the past 260-years (Figure 2). The aneurysms located in the AcomAC, and basilar arterial regions were classified as the central group of aneurysms. Additionally, in a few cases aneurysms were located simultaneously on left and right sides and those cases were grouped as 'bilateral' (Supplementary File 1 and Supplementary File 2 and Figure 1).

Statistical methods

Data were analysed using Excel and Statistical Package for the Social Sciences (SPSS-IBM, version-25) program (e.g., descriptive, and Chi squared tests). The p values less than 0.05 were considered as statistically significant.

Patient and public involvement

Involving patients was challenging for conducting and planning this research, since researchers were allowed the access only to anonymised raw data recorded in the database. As per the ethics permit (details in the method section), we accessed retrospective anonymized data, precluding patient involvement in research planning and execution. The shared outcome of this study will be informed to the public, families and patients who attend medical centres for various clinical visits, through a series of meetings, seminars, and media releases.

Findings

This study reviewed 1127 aneurysmal cases of patients of all ages from a total of 407 published articles prior to the year 1939. The ages of these patients (male=526, female=573, unknown sex=28) ranged from 18 months to 89 years of age with an average of 41.70 years, mode of 41 years and median of 41 years (SD=17.7) (Supplementary Table 1, Figure 2a, Figure 2b, Figure 2c and Supplementary File 1). The second group of patients with CAs (44 males and 58 females, and n=102) from the RAH (2011 to 2019) with the age range 18-100 years showed that the most common age for diagnosis or complication of CAs ranged from 31-60 years with the calculated mean, median, mode, and standard deviation (SD), 57.60, 60.00, 48.00, and 13.12 years, respectively (Figure 2d and Supplementary-Figure 1). Analysis of both sets of data revealed that the majority of the patients who presented with complicated aneurysms were in their 3rd to 6th decades of life (Supplementary Table 1).

The most important aspect of the two sets of data was the wide age range of occurrence of CAs and the fact that some of the complicated aneurysmal cases appeared at an early age (Figure 2a, Figure 2b, Supplementary File 1). A separate analysis was conducted for 853 out of the 1127 cases of CAs recorded before 1938 (male=409, female=438, unknown sex=6), specifically focusing on the age range of 18 to 89 years to align the age groups with the RAH recorded data from 2011 to 2019 (Supplementary Table 1, Figure 2c and Figure 2d). The similarities of standard deviation (15.45) of those 853 cases (from 1761-1938) and the cases that were recorded from 2011 to 2019 in RAH (13.12 years) validated the comparability of our data and the findings

(Supplementary Table 1). The values of the 25th, 50th, and 75th percentiles, as well as the minimum and maximum observed ages of patients with aneurysms, remained relatively stable from 1761 to 1938 (Figure 3a). Some of these percentile values increased slightly as life expectancy extended from 1761 to the 21st century (Figure 3b). Therefore, the SD, and age distribution of adult patients with ruptured or diagnosed CAs presented in the 2011-2019 dataset were consistent with those cases reported before 1938, indicating persistence of a pattern (Table 1, Figure 2 and 3). Specifically, aneurysms are being frequently diagnosed in individuals aged 30 to 60 years, and this age range has remained relatively unchanged over the past 260 years (Table 1, Figures 2, and 3). Forty nine out of 1127 cases recorded across 407 publications from 1761 to 1938 seemed not to have information about the location of aneurysms in the CBAN, however, 818 out of 1078 identified aneurysms (76%), were in the ICA, MCA and AcomAC regions and rest of them were in the vertebrobasilar region (Supplementary File 1). The location and distribution pattern aneurysms from 102 patients recorded in RAH was consistent with 1078 cases recorded from 1761 to 1938 (Supplementary Files 1 and 2, and Figure 1).

In the type 2 dataset, a total of 135 aneurysms were identified in 102 individuals, with ages ranging from 18 to 83 years, across various components of CBAN (Figure 2d and Supplementary File 2). Among these aneurysms, 38(28.14%) were detected in the right MCA region, while 17(12.6%) were in the right ICA region. In comparison, the left MCA and ICA regions had 27(20%) and 12(8%) aneurysms, respectively, which appeared to be lower in number compared to the right MCA and ICA regions. When considering the distribution of aneurysms based on territory, 55 out of 135 aneurysms (40.74%) in 50 patients were found in the right ICA and MCA territories, whereas 39 out of 135 aneurysms (28.88%) in 37 patients were detected in the left ICA and MCA regions (Supplementary File 2). Out of the 102 individuals with aneurysmal cases included in the study, 33 (24.44%) had aneurysms located in the anterior communicating artery (AcomAC) region, accounting for 33 out of the total 135 aneurysms. An additional 5.9% of the total aneurysms (8 out of 135 aneurysms) were found in the vertebral and basilar arterial regions, as indicated in the Supplementary File 2. A majority of the CAs, 127 out of the total 135 (94% of the total), were in the MCA, ICA, and AComAC regions (Supplementary File 2). Some cases had multiple aneurysms, for example, 2 cases had right ICA and MCA aneurysms, while 10 cases had left ICA and MCA aneurysms (Supplementary File 2).

There were no significant differences between male and female patients affected with CAs in all 1229 cases analysed in those two data sets (Chi-Squared statistic=0.83, p≥0.36) (Table 1). The sex, age of occurrence and location of CAs appear to have remained steady over the past 260 years across all age groups (Table 1 and Supplementary Table 1, and Figure 3). The mode, mean, and median age and SD of patients with ruptured or diagnosed CAs studied from 2011 to 2019 in RAH matched well with the cerebral aneurysmal cases recorded in the past considering the difference in life expectancy between the two time periods studied (1761-1938 and 2011-2019) (Figures 3 and Table 1).

Figure 1- about here

Figure 2 - about here

Figure 3 - about here

Table 1 - Prevalence of cerebral aneurysms in males and females: a comparison of the recent hospital-based data recorded in RAH from 2011 to 2019 with the autopsy data published before from 1761 to 1938.

Sex	N=173, cases with or without cerebral aneurysms recorded in RAH from 2011 to 2019.	1127 aneurysm cases (from 1761 to 1938) recorded in 407 publications.[14]
Sex not defined	0	28
Female	90	573
Male	83	526
Female to male sex ratio	1.08	1.09

Legend- RAH = royal Adelaide hospital, 14 = McDonald, CA & Korb, M 1939, Intracranial aneurysms, Archives of neurology and psychiatry (Chicago), vol. 42, no. 2, pp. 298-328.

Discussion

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The age and locations at which CAs occur in the CBAN has not changed over past 260 years (Figures 1, 2 and 3, Table 1 and Table 1) despite the life expectancy has increased over time worldwide and the progress in medicine. In the past people had shorter life span on average, and yet the CAs occurred at the same ages as they do now.[15] The life expectancy recorded at below 50 years in 1940 and even below 40 years in 1850 was way lower compared to the one recorded above 80 years of age since the year 2000 in Australia.[15] A separate analysis was done for 853 out of the 1127 CAs recorded[14] before 1938 focusing on the age range of 18 to 89 years to align the age group with the currently RAH recorded data from 2011 to 2019, since there were no aneurysmal cases of children (age<18years) in the RAH dataset. In Adelaide there is a separate hospital for children where aneurysmal cases would have been treated, but the authors had no access to these data (Supplementary file 2). Royal Adelaide Hospital is a general hospital, thus individuals of 18 years and less are not admitted. Current study compared the cases of CAs diagnosed by CTA imaging technique (from 2011-2019) with those verified by surgery and autopsy[14], since there were no cerebral angiogram facilities in early years (i.e., before 1938). The cases of aneurysms are commonly diagnosed, when the patients are presented at medical centres after attacks of stroke.[16] Cerebral aneurysms in the past seemed to be ruptured and complicated as early as 18 months of age and as late as 89 years of age with a wide range of age (Supplementary File 1). The findings suggested that the change in lifestyle nor medical practice had no effect at the age/time of formation of CAs in general population. Clinical investigation of lipid profiles in patients commenced after 1950,[17] and they started attributing arterial diseases and aneurysms to the hyperlipidaemia, however, the manifestation of occurrence of aneurysms by age in the past 260 years seems not to be different from the current age of occurrence. Although the lifestyle and the external influences, including medical practice, changed over more than two centuries, aneurysms still occur at approximately the same age. Therefore, aneurysms occur and rupture on their own internal circumstances and are not related to the diet, environmental, and external factors.[18] The most likely internal factor is the severity of the variation on the segments of CBAN that adversely affects the hemodynamics resulting in the formation of aneurysms. [1,19] The condition of the arterial wall should not have changed over the last 260 years and that seems to be less significant than the variation in the components of CBAN. The segmental and communicating arteries play a crucial role in dampening the systolic pressure within the CBAN and reducing the likelihood of aneurysm formation.[1,19] The severity of arterial variation can have negative effects on the blood flow dynamics through the variant segment of the component of the CBAN.[1,19] The incidence of CAs is about 3.3% in the general population and may not be diagnosed, until they get enlarged as the size of the aneurysm <3mm in diameter can be missed.[20] Imaizumi and colleagues found that the prevalence rate of CAs was 4.32% in Japan.[12] The incidence rate of CAs in childhood (age <18 years) has been reported to be 0.5-4.6%, which is almost as common as the incidence rate observed among adults.[13] Treating cases of CAs with a diameter less than 3 mm requires careful consideration, as pre-existing small aneurysms of ≤ 3 mm could rupture, resulting in spontaneous SAH.[21] The majority of CAs are detected only when they cause a stroke or other pathological effect (e.g., compression of the optic tract).[4] Individuals older than 18 years are no longer considered children.[6,13]

Most of the symptomatic cases of CAs in the paediatric age group were observed in older children (15 + years) [13], and only complicated cases of CAs were generally diagnosed and reported.[22,23] If the incidence of childhood CAs described (ranges from 0.17 to 4.6%),[24] is corrected for number of years lived, it would be 18.4% of the total aneurysmal cases amongst adults. The adult patients included in CAs studies ideally have an age range of 18-years and above, which can include individuals up to the age of 100 years.[12,15] In contrast, the childhood group included in aneurysmal studies typically ranges from birth up to 18-years of age and a few studies have categorized patients who are 18-years or older under the adult group.[6,13] When the age range, 0-18 years and 19-100 years is considered, the incidence of childhood CAs, that should be multiplied by 5 times to correct for the number of years lived, can be comparable to that in adults because the childhood period of life is much shorter than the adulthood. Therefore, the age range of adult group (≥20 years up to 100 years) included in the CAs and stroke studies would be about five times more than the age range of children (i.e., ≤18 years).[22,23] That means adults have 5 times more years to develop CAs compared to children. Therefore, the incidence of childhood CAs per year is almost equivalent to adult.[21,25] Hence, CAs could develop in early childhood in the presence of a significantly variant component of cerebral arterial anatomy,[1,2] and it could

take years for them to balloon before becoming symptomatic and being observed in a tertiary medical center. The overall pattern of location and distribution of childhood CAs was similar to adult as they commonly occurred in ICA, MCA and AcomAC regions.[3] Therefore the development of CAs is not age related and found to be prevalent in all age ranges.[10,12,13,26] Cerebral aneurysms may not always be associated to the advanced age, history of smoking, drinking alcohol but start forming as early as in the childhood in the presence of variant components of cranial blood vessels.[27] The mean age at which people were affected by cerebral aneurysms was reported to be 55 to 57 years of age in a study conducted using 1085 aneurysmal cases from 2008 to 2016.[28] There are a few reports of CAs published between 1938 and 2011 that could have been compiled for statistical analyses. However, their inclusion into this study, would not have changed its basic conclusions: i.e., large age range and no change through time in the occurrence of CAs.

Transcranial Doppler has been found to be effective in studying brain vessels [26,29] in infants and can be incorporated as a screening tool to detect variant intracranial vessels that could predispose them to the development of cerebral aneurysms later in life. Ultrasonographic (USG) video screening, involving the placement of the probe in the fontanelles of babies before they close, for variant cerebral arteries, might be introduced as a routine procedure due to its safety. [29] For example, individuals with a diameter ratio greater than 1.4 between the proximal segment of left and right ACA have a 27-fold increased risk of developing cerebral aneurysms in the AcomAC region.[1] The ACA asymmetry can be measured by placing USG probes in a baby's fontanelles, in a simple clinical setup before the fontanelles fuse. Parents of children found to have variations in CBAN could be advised to schedule follow-up brain 'Magnetic Resonance Angiography' scans at specific intervals, such as every 5 years, especially if a more affordable technology for detecting brain aneurysms becomes available. The estimated cost of a single stroke is approximately \$300,000 in Australia.[9] With a haemorrhagic stroke incidence of 10 per 100,000 the total cost amounts to \$45 million per year in a city the size of Adelaide[1], South Australia, which has a population of 1.5 million. Regular screening for individuals with significantly variant brain arteries identified, representing 50% of the population, once every 5 years, and assuming the cost of a single computed tomography angiography or magnetic resonance angiogram is about \$100 each, the total screening cost would be \$1.5 million per year, that means 30 times reduction in cost of strokes. Additionally, the government would receive millions of dollars in return as tax revenue from working individuals who would survive with little to no disability from potential strokes resulting from aneurysms. This study was not designed to examine the characteristics of aneurysms, but the focus was on the distribution of aneurysms in different segments of CBAN, trend of occurrence of aneurysms over the past 260-years, and the comparison of cerebral aneurysms in all age ranges.

Limitations:

The insufficient data on the lack of personal and family history, history of smoking, lipid profile, and blood pressure are limitations of this study. A larger survey and a prospective study could be conducted. A prospective study could involve using ultrasound techniques to identify variations in brain vessels among infants.

Conclusion

Brain arterial aneurysms can develop early in the presence of variant arterial components. Screening children under 24 months using transcranial ultrasonography for variant cerebral arteries may be practical. Those with variations should undergo periodic tests for aneurysms, aiming to prevent haemorrhagic strokes.

Data sharing statement

Additional data are available by emailing Arjun.Burlakoti@unisa.edu.au

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Arjun Burlakoti- conceived the idea, collected, and analysed both sets of data, took pictures, recorded videos, contributed to conceptualization, prepared and drafted the manuscript.

Jaliya Kumaratilake- conceived the idea, contributed to the concept, aided in data interpretation, editing and the revision of the manuscript and approving the article.

Jamie Taylor- conceived the idea, contributed to the concept, aided in data interpretation, editing and the revision of the manuscript and approving the article.

Maciej Henneberg- conceived the idea, masterminded, and helped in statistics, data analysis and interpretation, editing and approving the article.

Ethical Approval Statement

The University of Adelaide, Human Research Ethics Board granted permission to access and use data for this research project (Ethics Approval Number: H2014-176).

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Figure 1 - Comparison of the location of cerebral aneurysms between Royal Adelaide Hospital sample (2011 to 2019) (n=135 CAs from 102 patients, orange colour) with those recorded in 407 publications[14] (1761 to 1938) (n=1127 CAs, blue colour). CAs=cerebral aneurysms, 14 = McDonald, CA & Korb, M 1939, Intracranial aneurysms, Archives of neurology and psychiatry (Chicago), vol. 42, no. 2, pp. 298-328.

Figure 2 - Figures displaying the distribution patterns of cerebral aneurysms in different age groups recorded from 1761 to 1938 and from 2011 to 2019. A polynomial regression lines show the number and distribution of cerebral aneurysm cases across all age groups. a) The distribution of cerebral aneurysmal cases (n=1127) in various age group, recorded from 1761 to 1938.[14] b) The frequency of cerebral aneurysmal cases and their distribution (n=1127) across all age groups recorded¹⁴ from 1761 to 1938. c) Age (≥18 years) related distribution of individuals affected with cerebral aneurysms over the past 260 years (1761 − 1938) (n=853), recorded¹⁴ from 1761 to 1938, and d) Age (18-100 years) related prevalence (%) of cerebral aneurysms in RAH sample from 2011 to 2019 (n=102). The peak prevalence occurred between 31-60 years (p<0.001). RAH= Royal Adelaide Hospital. RAH= Royal Adelaide Hospital and 14 = McDonald, CA & Korb, M 1939, Intracranial aneurysms, Archives of neurology and psychiatry (Chicago), vol. 42, no. 2, pp. 298-328.

Figure 3: Comparison figures showing the trend of occurrence of cerebral aneurysms at different age group (n=1127) from 1761 to 2019. (a)The values of the 25th, 50th, and 75th percentiles, as well as the minimum and maximum observed all ages of patients with aneurysms, from 1761 to 1938[14]; b) The values of the 25th, 50th, and 75th percentiles, as well as the minimum and maximum observed patients with >18 years of age with aneurysms, recorded from 1761 to 1938¹⁴ and 2011 to 2019 in RAH. RAH = Royal Adelaide Hospital, 14 =Data from: McDonald, CA & Korb, M 1939, Intracranial aneurysms, Archives of neurology and psychiatry (Chicago), vol. 42, no. 2, pp. 298-328

Table 1 - Prevalence of cerebral aneurysms in males and females: a comparison of the recent hospital-based data recorded in RAH from 2011 to 2019 with the autopsy data published before from 1761 to 1938.

0	28
90	573
83	526
1.08	1.09
	90 83

Legend- RAH = royal Adelaide hospital, 14 = McDonald, CA & Korb, M 1939, Intracranial aneurysms, Archives of neurology and psychiatry (Chicago), vol. 42, no. 2, pp. 298-328.

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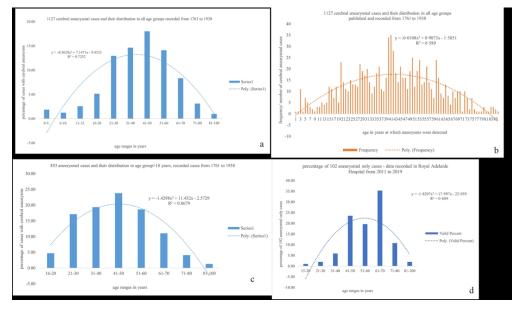


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154x90mm (300 x 300 DPI)

Figure 3: Comparison figures showing the trend of occurrence of cerebral aneurysms at different age groups (n=1127) from 1761 to 2019. (a)The values of the 25th, 50th, and 75th percentiles, as well as the minimum and maximum observed all ages of patients with aneurysms, from 1761 to 1938[14]; b) The values of the 25th, 50th, and 75th percentiles, as well as the minimum and maximum observed patients with >18 years of age with aneurysms, recorded from 1761 to 193814 and 2011 to 2019 in RAH. RAH = Royal Adelaide Hospital, 14 = Data from: McDonald, CA & Korb, M 1939, Intracranial aneurysms, Archives of neurology and psychiatry (Chicago), vol. 42, no. 2, pp. 298-328

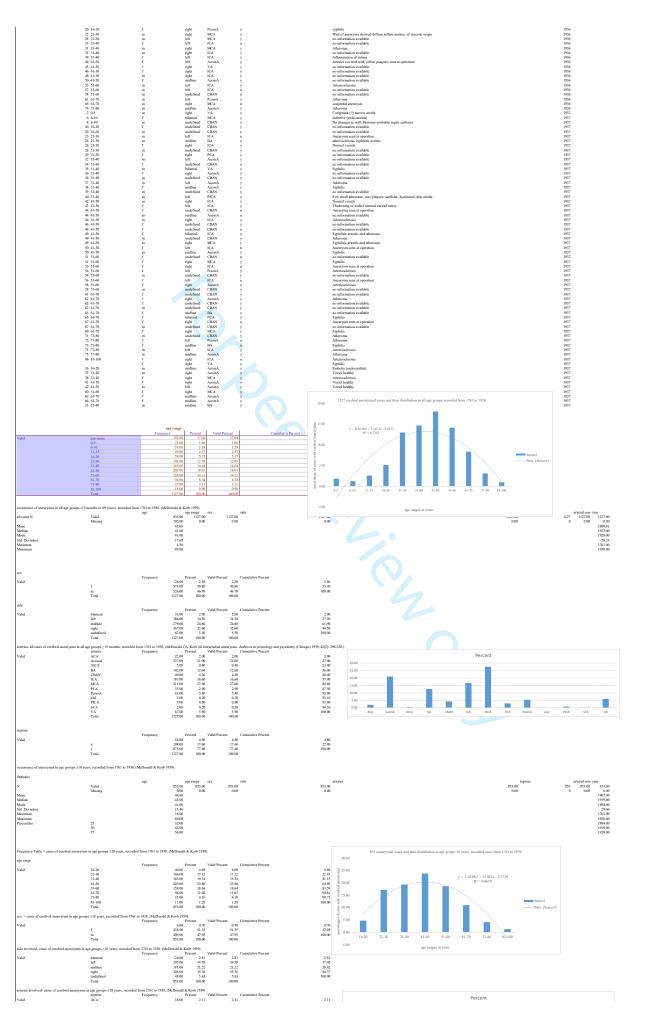
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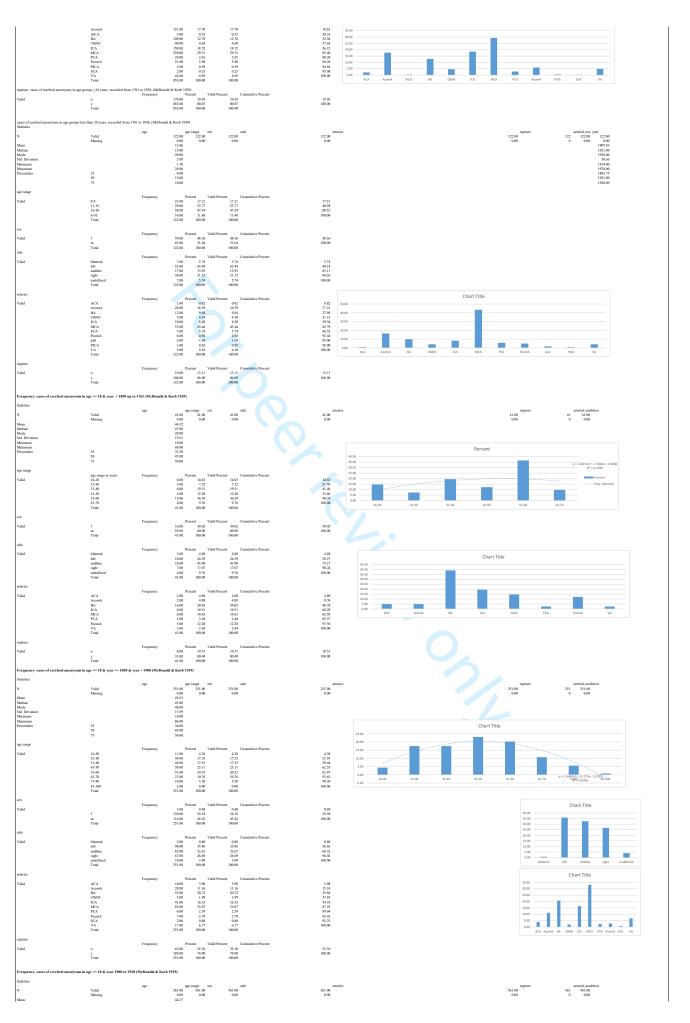
Supplementary file 1: contains type 1 data Manuscript title: The trend of cerebral aneurysms over the past two centuri	ries: Need for early screening - An observational study.			
Abbreviations: PeomA= possterior communicating artery, ICA=internal ca AICA=anterior inferior cerebellar artery, VA=vertebral artery, CBAN=cere age in years 60 51-60	sex, m=male, f=female side affected v arteries involved	CA=middle cerebral artery, ACA=anterior cerebral artery, inferior cerebellar artery. McDonald & Korb 1939=McDon status of aneurysms; ruptured=y, not ruptured=n	PCA-posterior cerebralial artery, SCA-superior cerebellar artery, ald CA, Korb M. Intracranial ancurysms. Archives of neurology and psychiatry (Chicago) 1939; 42(2): 298-328.) arterial condition Vessels rigid, with deposit on inner lining	year of aneurysm detected
52 51-60 64 61-70	m bilateral PoomA f undefined ICA f bilateral ICA	n y n	no information available no information available	1761 1778 1779
20 16-20 20 16-20 57 51-60	f midline BA f midline BA m midline AcomA	y y	no information available no information available Colorous, deposits on routs of vessels	1814 1815 1825
57 51-60 57 51-60	m right ACA m midline AcomA f midline AcomA	y y	Culcarous deposits on costs of vessels Coast of accuryum thick not revaliable no information variables	1825 1825 1825
59 51-60 59 51-60	m midline BA	y y	Middle layer of sac, cartilaginous no information available	1826 1826 1826
19 16-20 39 31-40 45 41-50	m right MCA m left MCA f left PcomA m left MCA	y y y	no informatica available no informatica available no informatica available	1827 1827 1827
35 31-40 21 21-30 24 21-30	m midline BA f midline BA m left VA	n y v	Carotid and vertebral arteries normal Calcarcous deposits on vessels Arteries diseased, in some places cartilaginous	1828 1829 1829
60 51-60 63 61-70 60 51-60	midline BA m right MCA f left MCA m right MCA m right MCA	y Y	Coats of vessels cartilaginous wall this but firm No bone or other appearance of disease	1829 1831 1831 1832
60 51-60 42 41-50 54 51-60	f right ICA	y y	Sae with thin, firm parietes no information available no information available	1832 1833 1833 1834
28 21-30	m midline BA f left ACA left ICA right VA m midline BA	n n	no introduzacio a minocia middle layer thick no information available no information available	1834 1834
68 61-70 20 16-20	f midline BA	n n	Yellow plaques on surface no information available	1834 1835 1836 1837 1837
59 51-60 60 51-60 35 31-40	m midline BA m undefined ICA m right MCA m midline BA	y y y	Middle layer of artery cartilaginous no information available other vessels normal	1837 1837 1839
14 11-15. 20 16-20 49 41-50	f undefined PCA m left ICA	n n	Middle layer of wall thickened no information available Vessels hickened	1839 1842 1842 1842 1844
41 41-50 54 51-60 20 14 20	m midline BA m midline BA f right PoomA	y n	Arteries atheromatous no information available no information available	1844
20 16-20 47 41-50 58 51-60 58 51-60	f right PoomA m midline BA m midline BA m midline BA	y y	no information available ma no information available	1846 1846 1846 1846 1847
62 61-70 34 31-40	f right PoomA	y y	no information available no information available	1846 1847
35 31-40 52 51-60	m left ICA f left ICA m midline BA	y y n	no information available halthy arteries no information available	1847 1848 1848
33 31-40 35 31-40 39 31-40	m midline BA m midline BA f undefined ICA	y y	no information available Other arteries healthy No calcareous deposit in cerebral vessels	1849 1849 1849 1849
18 16-20 30 21-30 70 61-70	m undefined VA f left PcomA	n y	Calcareous deposit in wall of sac No fatty afteromatous changes in arteries Other vessels without changes	1849 1850 1850 1850
70 61-70 20 16-20 21 21-30		n n	no information available no information available	1850 1851
35 31-40 38 31-40	f undefined PCA f midline AcomA m left MCA midline BA	n y n	no information available no information available no information available	1851 1851 1851 1851
45 41-50 65 61-70	m midline BA m undefined ICA m midline BA	n n	no information available no information available no information available	1851 1851 1851 1851 1851 1851
53 51-60	m midline BA f undefined MCA	n y y	no information available no information available no information available	1851 1851 1855
56 51-60 57 51-60 70 61-70	m right PCA	y n	no information available Vessels very afteromatous no information available	1855 1855 1855 1855
35 31-40 40 3140	m left MCA m midline BA	y n	Arteries not afheromatous no information available Manual within but houlder	1855 1855 1856
52 51-60 47 41-50	f right ICA f left ICA	y y	Middle coat thickened no information available	1856 1857 1858
54 51-60 56 51-60 60 51-60	m midline BA m right SCA f midline AcomA	n y	Verstehal arteries thickened Afteroma Vessels thickened and rigid	1858 1858 1858
17 16-20 30 21-30 34 31-40 35 31-40	f left MCA f left MCA m midline BA	y y y	Embolie no information available Hoalthy vessels	1859 1859 1859 1859
35 31-40 43 41-50 58 51-60	f left ACA f midline BA m left MCA	y y	Healthy vessels Atheroma Atheroma	1859 1859 1859 1860
16 16-20 24 21-30 47 41-50	m left ICA f midline BA	n y	no information available embolic Plates in coats of aneurysm	1860 1860 1860
24 21-30 14 11-15. 42 41-50	m right MCA m left MCA	y y	Walls of sac calcareous Walls of sack thick and atheromatous no disease of other vessels Vessels otherwise healthy	1860 1860 1861 1862
48 41-50 56 51-60	m midline BA f midline BA m midline BA m left MCA	n n	no information available Afteroma	1862 1862 1862
68 61-70 80 71-80 28 21-30 37 31-40	f midline AcomA m midline BA	n y	Wall of see hard and cretaceous healthy vessels Healthy vessels	1862 1862 1862 1864 1864
16 16 20	m midline BA undefined AICA m left ICA	y n	Other vessels slightly afteromatous Afteroma Vessels healthy	
24 21-30 39 31-40 43 41-50	m left MCA m midline BA f left ICA	y y	Vessels healthy Soft arteries No afteroma Walls afteromatous	1865 1865 1865 1865
46 41-50 49 41-50	f left ACA f midline AcomA	n y	Vessels very atheromatous Other arteries healthy	1865 1865 1865
51 51-60 53 51-60 59 51-60	f midline BA m left MCA f right MCA m left ACA	y y	Arteris not discussed Walls not afferorations no information a wailable no information a wailable	1865 1865 1865 1865
21 21-30 61 61-70 27 21-30	f left MCA f left VA	y y y	No disease of vessels no information available	1865 1866 1867
27 21-30 29 21-30 78 71-80 13 11-15.	f left MCA f right MCA	y y y	Arteries thickened no information available No atheroma	1867 1867 1867 1868 1868
13 11-15. 24 21-30 34 31-40	m right MCA f left ICA f left MCA	y y	No afteroma Reas of arteries healthy no information available Walls of amonysymatheromatous; vessels at base not discused	1868 1868 1868
36 31-40 40 31-40 40 31-40	f midline BA m left ACA	y y	Old endocarditis; questionable embolic origin Small atheromatous patches on wall Vessels normal	1868 1868 1868 1868 1868
50 41-50 53 51-60 56 51-60	f left MCA	n y	vesses normal Thick and opaque, but not materially diseased Slightly atheromatous Arteries selectroic, with atheromatous plates	1868 1868 1868
56 51-60 59 51-60 60 51-60	m left MCA f midline BA	n y	Vessels very atheromatous Atheroma	
60 51-60 14 11-15. 19 16-20	f right MCA m left ICA m left VA	y y y	Vessels very atheromatous Other vessels healthy no information available	1868 1868 1869 1869
28 21-30 41 41-50 48 41-50	m left MCA f right MCA f left MCA	y y y	no information available no information available Afteroma	1369 1369 1369
56 51-60 61 61-70	m right ICA f midline BA	y n y	Several patches ofdegeneration onbusilar artery Vessels atheromatous Embolio ecotision (endocarditis)	1869 1869 1869 1870
13 11-15. 15 11-15. 17 16-20	f right MCA m right MCA m right MCA f left ACA	y y y	Other vessels healthy; embolic origin of ancurysm Embolic origin Vessels healthy	1870 1870 1870 1870
20 16-20 26 21-30 26 21-30	m right MCA f left MCA m milline BA	y n	Embolic origin Vessel plagged by yellow fibrin (vegetations on aortic valves) Romainine vessels healthy	1870 1870 1870
26 21-30 26 21-30 35 31-40 37 31-40	f right MCA m undefined PCA	y n	Komaning vessels healthy Sybhilite lesions no information available Colkaneous degeneration of coats of vessel no information available Sidgit afferonations grades Sidgit afferonation grades	1870 1870
49 41-50 50 41-50	m midline BA f left PCA	y y	Syphilite besses so suffermines newables sold administration	1170 1170 1170 1170 1170 1170 1170 1170
60 51-60 67 61-70 54 51-60	m right VA m midline AcomA	y y y	Vessels diseased Afteroma Afteromatous	1870 1870 1871
29 21-30 45 41-50	m midline BA m left VA	y n y	Arteries at base highly Atheromatous Other arteries at base anheromatous Slight afferentious changes	1871 1872 1872
61 61-70 20 16-20 20 16-20 24 21-30	f midline BA f right PcomA	y y y	Vessels atheromatous Embolic Embolic eschnoidis Embolic eschnoidis	1872 1873 1873 1873
27 21-30 40 31-40		y y y		1873 1873 1873 1873
68 61-70	m million DA	n n	Embolic Wals mick; other vessels healthy Vessels hickened	1873 1874
24 21-30 33 31-40 40 31-40	m undefined ICA m left ICA f right ICA	n n	v Color multicant validable Marked attended to the color of the color	1874 1875 1875 1875
43 41-50 45 41-50 45 41-50	f right ICA m right MCA m midline AcomA m left MCA	y y y	no information available Arteries slightly atheromatous Vessels normal	1875 1875 1875
46 41-50 53 51-60 56 51-60	m bilateral ICA f left ICA m left VA	n y n	Intimal arteriosclerosis Walls thick and atheromatous no information available	1875 1875 1875
60 51-60 69 61-70 34 31-40	f undefined SCA f midline AcomA	y n v	Interes artification and vessels Vessels atheromatous no information available	1875 1875 1875 1875 1875 1876
34 31-40 41 41-50	m left MCA	y y	no information available Rest of arteries free of atheroma	1876 1876 1876 1876
50 41-50 63 61-70 16 16-20	f right MCA f right ICA m midline BA	y y y	Aderoma no information available no information available	1876 1876 1877 1877
18 16-20 20 16-20 22 21-30	f right MCA m midline AcomA f left ICA	n y n	no information available No other disease of vessels Vessels healthy, probably embolie	1877 1877 1877
40 31-40	f right MCA m left MCA	y y y	Healthy vessels Vessels at base healthy Arteries tortunous andomall in caliber; deposits of calcureous degeneration no information available	1877 1877 1877 1877 1877 1877
42 41-50 53 51-60 12 11-15. 30 21-30	m right MCA f midline BA m right PCA m left ICA f right MCA	n y n	Embolic (endocarditis) Thickening of vessels , with symbilitic infil tration of small cells	1877 1878 1878 1878
30 21-30 47 41-50 50 41-50	m right PCA m left ICA f right MCA m right ACA f left MCA m left MCA m left MCA m left VA	y n		1878 1878
50 41-50 72 71-80 20 16-20 36 31-40	m right ACA f left MCA m left MCA m left VA	y y y	Al atteries and aneuryum white and opaque;microscopic syphilitic changes of Heubner Vesicle atheromatous Not atheromatous Thickened walks: endarteritis	1878 1878 1880 1880
39 31-40 40 31-40 44 41-50	m right MCA f midline AcomA m midline BA	y y y	no information available Afteroma no information available	1880 1880 1880
55 51-60 57 51-60 75 71-80	heft MCA m midline BA f midline BA	n y n	To introduction automators Self and aftercomatous Aftercomatous vessels at base Attercomatous Attercomatous	1880 1880 1880
12 11-15. 40 31-40 44 41-50	m left MCA f left PcomA	y y	Verificontinuous Wall of sae atheroma tous; other vessels healthy Healthy vessels no information available	1881 1881
50 41-50 73 71-80	m midline BA f midline AcomA f night ICA f right PcomA	y n	no information available no information available Very atheromatous Wall thickened	1880 1880 1881 1881 1881 1881 1881 1881
80 71-80 16 16-20 17 16-20	f right PcomA m midline BA m midline AcomA	n y y	no information available Healthy	1881 1882 1883
40 31-40 61 61-70	m midline BA f undefined ICA m left VA	n y n	Afteroma no information available Fatty degeneration of intima	1882 1883 1883 1883 1884
29 21-30 40 31-40 21 21-30	m undefined CBAN f left MCA	y y n	e may to egociamo do a minima Enfebrilo Afterorma Calcarecous clot in sac	1884 1885 1885 1886
40 31-40 21 21-30 22 21-30	m left MCA f left ICA f left ICA	y n	Canacrous dost in sac Syphilife Walls hard, no atheromatous degeneration	1885 1886 1886

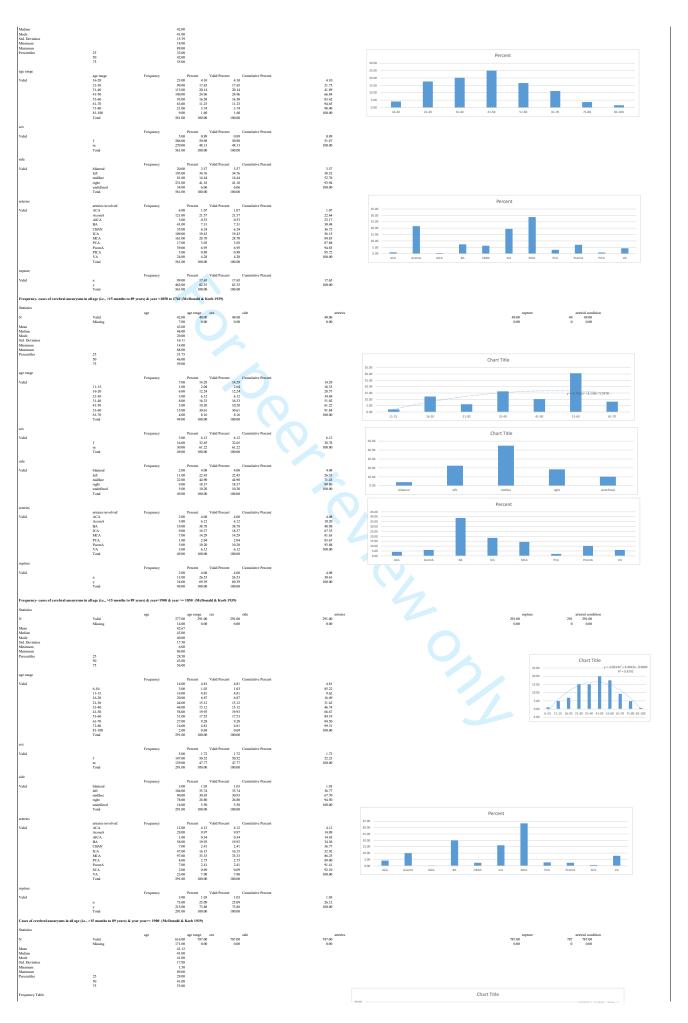
		ad Miles		Cal Tr	
27 21-30 20 16-20 30 21-30 30 21-30	f m	midline BA left MCA right VA right MCA	y n y y	Syphilite Embolic Embolic (endocarditis) Embolic (endocarditis)	1886 1887 1887
31 31-40 36 31-40 40 31-40	m m	right ICA midline BA	n y	Laterian (Cateconarium) no information available No embolism or atheroma No embolism or atheroma No embolism or atheroma	1887 1887 1887
43 41-50 49 41-50 60 51-60	f f	right PCA	y y	Activists fire of atheroma Embolic (endocarditis) no informatica available	1887 1887 1887
60 31-60		left VA undefined VA	y n	Arteriosclerosis Arteriosclerosis	1887 1887
53 51-60 26 21-30	f m		y n	Arteriosclerosis no information available Septic endocarditis	1887 1888 1889
43 41-50 51 51-60 56 51-60	m m f	midline AcomA midline AcomA	n y y	no information avuilable Atteriese free of atheroma Atterioselevosis	1889 1889 1889
6 6-10. 15 11-15. 15 11-15.	m m	right VA right PCA right MCA	y n	Sopic embolus endocarditis Sopic embolus endocarditis	1890 1890 1890
15 11-15. 15 11-15. 15 11-15.	t t	bilateral ICA right MCA	n y y	Septic embolus endocanditis Septic embolus endocanditis Septic embolus endocanditis	1890 1890 1890
16 16-20 17 16-20 18 16-20	f m m	right MCA left ICA right MCA	y n	Septic embolas Septic embolas endocarditis Septic embolas	1890 1890 1890
25 21-30 25 21-30 25 21-30	m f	left MCA	n n y	Septie embolas endocantisis Septie embolas endocantisis Afacroma Septie embolas endocantisis	1890 1890 1890
25 21-30 25 21-30 31 31-40	f m m	right MCA right MCA right MCA left MCA	y y y	Septic embolus endocarditis Septic embolus	1890 1890 1890
35 31-40 35 31-40 45 41-50	f m f	left MCA left MCA	n y y	Septic embolas endocaedids Afteroma Afteroma	1890 1890 1890
45 41-50 50 41-50 56 51-60 66 61-70	m m m	left MCA left MCA right ICA right ICA	y y n	Adecoma Septic embolus Adecoma Adecoma	1890 1890 1890 1890
60 51-60 35 31-40 47 41-50	f m m	midline BA midline BA left MCA	n y	Afteroma Other vessels healthy	1891 1892 1893
7 6-10. 10 6-10. 14 11-15.	m f	midline BA left VA left VA midline BA	y y	No afteroma no information a valiable no information a valiable no information a valiable	1894 1894 1894
25 21-30 26 21-30 26 21-30 28 21-30	m f	midline BA right ICA right ICA left MCA	y y	no information available no information available Soft attrics no information available	1894 1894 1894
28 21-30 28 21-30 29 21-30	m f m	left MCA midline AcomA left MCA	y y	no information available no information available no information available no information available	1894 1894 1894
30 21-30 31 31-40 32 31-40	f m	right MCA midline AcomA left MCA	y y	no information available no information available no information available	1894 1894 1894
32 31-40 32 31-40 36 31-40	r m r	midline BA midline BA midline PcomA	y y y	no information available no information available no information available	1894 1894 1894
36 31-40 40 31-40 40 31-40	m f m	left ACA midline BA midline AcomA	y y y	no information available no information available no information available	1894 1894 1894
41 41-50 42 41-50 42 41-50	m f m	right VA left ICA left MCA	y y y	no information available no information available no information available	1894 1894 1894
42 41-50 43 41-50 43 41-50 43 41-50	m f m	midline BA right ICA left VA left MCA	y y y	no infermation available no infermation available no infermation available no infermation available infermation available	1894 1894 1894 1894
43 41-50 43 41-50 43 41-50 44 41-50	m m f	right MCA undefined CBAN	y y y	no information available no information available no information available no information available information available	1894 1894 1894 1894
44 41-50 45 41-50 45 41-50 45 41-50	f f	midline AcomA left MCA midline AcomA left ICA	y y	no information available no information available	1894 1894 1894 1894
45 41-50 46 41-50 46 41-50 46 41-50	m f m	midline BA right MCA	y y	no information available no information available no information available	1894 1894 1894 1894
46 41-50 48 41-50 48 41-50 49 41-50	m f	right MCA right ICA right ICA left VA	y y y	no information available no information available no information available	1894 1894 1894 1894
49 41-50 49 41-50 50 41-50 50 41-50	f f	midline PcomA right MCA	y y y	no information available no information available no information available	1894 1894
50 41-50 51 51-60 52 51-60 53 51-60	m f	left MCA right MCA left MCA left MCA	y y y	no information available	1894 1894 1894 1894
53 51-60 54 51-60 54 51-60	f	midline AcomA midline AcomA right MCA	y y	no internation available no information available no information available no information available information available	1894 1894 1894
55 51-60	f m	right ICA	y y	no information available	1894
55 51-60 56 51-60 56 51-60 57 51-60 57 51-60	f f	midline BA left MCA right MCA right ACA midline AcomA	y y y	an information available no information available no information available no information available no information available	1894 1894 1894
	r r		y y y	no information available no information available no information available	1894 1894 1894
60 51-60 60 51-60 60 51-60 61 61-70	t t	left ACA left ACA left MCA midline BA	y y	no information available no information available no information available	1894 1894 1894
61 61-70 61 61-70 62 61-70 63 61-70 63 61-70	m f	midline BA right ICA midline AcomA left ACA	y y y	no information available no information available no information available no information available on information available	1894 1894 1894 1894 1894
64 61-70 64 61-70	f f	midline AcomA left ICA midline AcomA	y y y	no information available no information available	1894 1894
65 61-70 67 61-70 67 61-70	f f	left ICA left ICA right ICA left ICA	y y y	no information available no information available no information available	1894 1894 1894
69 61-70 70 61-70 72 71-80 72 71-80	f f f	right ICA	y y y	no information available no information available no information available	1894 1894 1894
73 71-80 73 71-80	f f f	right ICA left MCA right VA right VA	y y y	no information available no information available no information available	1894 1894 1894
73 71-80 73 71-80 79 71-80	f f	midline AcomA	y y y	no information available no information available no information available	1894 1894 1894
80 71-80 81 81-100 86 81-100	f f m	right ACA left MCA midline AcomA	y y y	no information available	1894 1894 1894
21 21-30 29 21-30	i m	midline CBAN right ICA midline BA	y y y	no information available other vessels healthy no information available	1894 1895 1895
40 31-40 40 31-40 47 41-50	r f f	midline BA right MCA	y n y	Wall of ancurymn had two patches of atheroma no information available no information available	1895 1897 1897
50 41-50 53 51-60 69 61-70	m f	left MCA left MCA bilateral ICA midline BA	y y n	no information available no information available no information available no information available	1897 1897 1897
28 21-30 54 51-60 70 61-70 29 21-30	m m f	midline BA right MCA midline BA	n y n	no information available	1898 1898 1898 1899
68 61-70 10 6-10. 11 11-15.	m m	left VA left pial right pial left MCA	n y y	Engagine selection with afternomators plaques (Variousla determinants Embelie (nedecentitis) Embeli	1900 1901 1901
27 21-30 28 21-30 32 31-40	f m f	midline BA right MCA	y y y	normal vosacis no information available Embolie (endocarditis)	1901 1901 1901
50 41-50 76 71-80 29 21-30	f f	right MCA right PcomA	y y y	Adecoma A factoria no information available normal rosseds	1901 1901 1902
34 31-40 45 41-50 22 21-30	m f	left ICA	y y y	Syphila Wall of left internal curotid arresy thickened healthy Line of athreoma at point of ancuryum	1902 1902 1903
39 31-40 64 61-70 27 21-30	f m	right ICA right MCA right PcomA midline AcomA	y y	Line to a surrouna in point of metaryoni Syphilia Wallis of other arteries healthy as information available.	1903 1903 1904
40 31-40 65 61-70 70 61-70	f f	right ICA right ACA midline BA biliteral ICA	y n	read to control article beauty to information available Addressma Addressma	1904 1904 1904
86 81-100 87 81-100 40 31-40	m f m	right ICA midline BA	n n	no information available Adressma Syphilis Marked selenosis	1904 1904 1905
42 41-50 50 41-50 51 51-60	m f	right VA right VA midline BA	y n y n	Localized syphilitic periarteritis of ancuryom no information available Syphilis	1905 1905 1905 1905
6 6-10. 28 21-30 69 61-70	m f m f	left MCA midline BA bilateral VA	y y n	Mycotic (staphylococcic endocarditis) no information avvailable Arteriosclerosis	1906 1906 1906
14 11-15. 40 31 40		bilateral ICA left BA left MCA	y n y	no information available no information available Vessels normal	1906 1907 1907
48 41-50 50 41-50 51 51-60	m f f m	left ICA left MCA midline AcomA	n y y	no afteroma Arteries healthy no information available	1907 1907 1907
55 51-60 61 61-70 63 61 70	f f f	bilateral MCA left ICA	y y n	no information available no information available no information available	1907 1907
65 61-70 68 61-70 84 81-100	f m f	left VA midline BA	y n	Basilar artery tortuous and diseased no information available	1907 1907
29 21 30	m	left AcomA	n n y	no information available no information available no information available frequence f	1907 1907 1908
65 61-70 30 21-30 27 21-30	enn enn enn	right MCA left ACA midline BA	n y y	Irregular, cartilegi mous thickening of arteries at base Advecoma Thickening: spylis linic endurerisis obliterans Other arteries normal	1908 1909 1910
44 41-50 57 51-60 64 61-70	f m m	right MCA bilateral VA	y n y	Arteriosclerosis no informativa available Arteriosclerosis	1910 1910
25 21-30 36 31-40 37 31-40	t t	left VA right AICA left PCA	n y n	Thick and hard Thickening of vessels Aneuryon congenital	1910 1911 1911
42 41-50 42 41-50	m f m	right ICA right ICA left VA	n y y	no information available no information available Roth overheld attrict hickened	1911 1911 1911
53 51-60 62 61-70 21 21-30	m f m	left MCA left ICA milline BA	y y	Syphilis no information available Healthy vessels	1911 1911 1911
21 21-30 22 21-30 25 21-30 31 31-40	m f	right ACA right MCA right AICA undefined CBAN	y y	Ascuryona congenital Embolic (endescutilis) Ascuryona congenital On arterioselerosis	1912 1912 1912 1912
32 31-40 36 31-40 37 31 40	m f f	left MCA	y y y	Ancuryum congenital Walls healthy (probably embolic) Embolic (endocaudiis)	1912 1912
37 31-40 38 31-40	r m f	left MCA midline AcomA	y y y	Aneurysm congenital Aneurysm congenital	1912 1912
40 31-40 42 41-50	m f m	left MCA left ICA	y y y	Aseroyma congenital Embolic (endscardiis) Aseroyma congenital Embolic (endscardiis)	1912 1912
42 41-50 44 41-50 48 41-50	m m f	left VA right MCA left MCA	y y y	Vessels somewhathickened; "congenital" (") Arteriosclerosis Aneurymn congenital	1912 1912 1912
51 51-60	ţ	left ACA	у	Syphilific endurteritis of cerebral arteries	1912

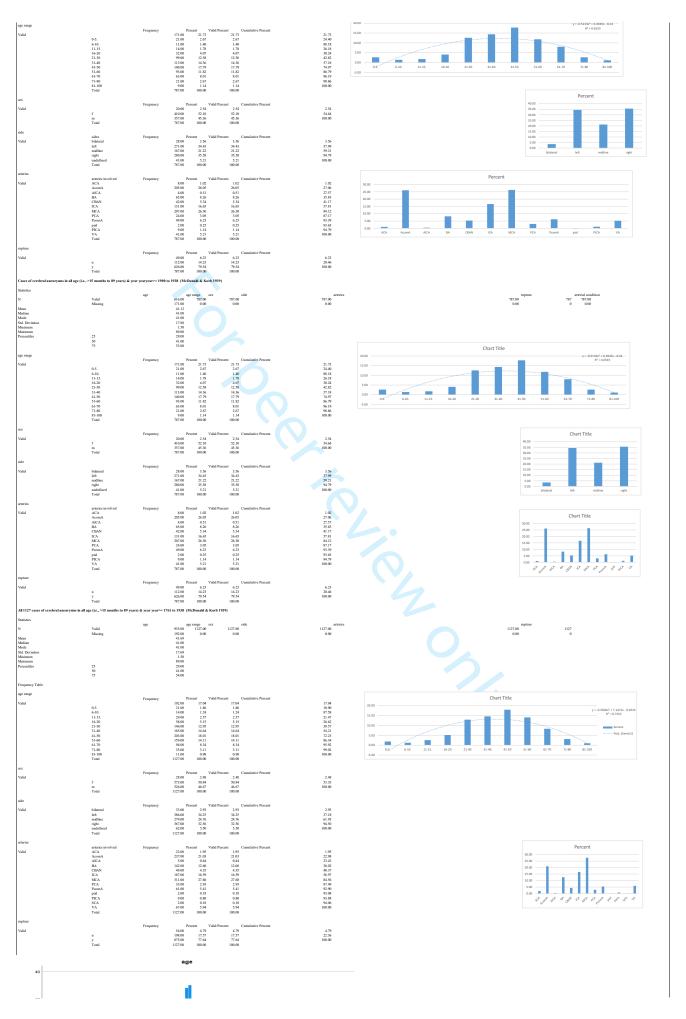
52 51-60		right MCA	у	Syphilitic coduteritis oblitarum of cerebral vessels	1912
55 51-60 56 51-60 56 51-60 57 51-60	m f f	left ICA midline BA left PICA right MCA	n y y y	no information available Ancuryone congenited Ancuryone congenited Anterior and the confidence of the	1912 1912 1912 1912
63 61-70 6 6-10. 12 11-15. 18 16-20	f f m	right MCA right PICA left MCA left PCA	y y y	Activoscierosis Activoscieros Activosciero	1912 1913 1913 1913
30 21-30 31 31-40 33 31-40 36 31-40	f f m	right PcomA right VA undefined CBAN right PCA	y n y	Syphilis no information available	1913 1913 1913
36 31-40 37 31-40 40 31-40 41 41-50 42 41-50	m f m	right PCA right VA left ACA left BCA left MCA	n y n	Syphilis, gammatous arterlisi Endarteriis Accesyon congesiuli no information available Small schoolscop luques	1913 1913 1913 1913 1913
42 41-50 42 41-50 56 51-60 58 51-60 72 71-80	m m f	right AICA undefined CBAN right MCA	y y y y	Soft vessels Small grayish white flecks on vessels Only slight thickening	1913 1913 1913
72 71-80 57 51-60	m f m	right MCA right MCA right ICA midline BA	y y y	Arterioschrosis Marked arterioschrosis Afteroma no information available	1913 1913 1913 1914
40 31-40 50 41-50 7 6-10.	f m m f	right VA left AcomA left PICA right MCA left ICA	y y y	proliferative endocardinis embolism (endocardinis) no information available embolis	1915 1915 1915 1916
15 11-15. 16 16-20 16 16-20 19 16-20 22 21-30	f f m m	left ICA right MCA left MCA left PoomA right MCA	y y y y	umbolic umbolic umbolic embolic healthy artry	1916 1916 1916 1916 1916
22 21-30 22 21-30 22 21-30 28 21-30	m m m	left AcomA right MCA left ICA	n y y	embolic conjonital aneusysm conjonital aneusysm conjonital aneusysm	1916 1916 1916 1916
31 31-40 36 31-40 36 31-40 36 31-40	m f m	right MCA left PoomA left ICA	y y y	embolic slight arterial degeneration Afteroma embolic	1916 1916 1916 1916
40 31-40 40 31-40 41 41-50	f m m	right PcomA right ICA	y y n	no information available healthy array no africorum embolic	1916 1916 1916
41 41-50 42 41-50 44 41-50 46 41-50 47 41-50	m f f	right ACA left PICA left AcomA right AcomA right ICA	y y y	no adriroma no información available atrivial degeneration no información available	1916 1916 1916 1916 1916
48 41-50 48 41-50 49 41-50 49 41-50	m f f m	right MCA right MCA left AcomA left AcomA	n y y	no information available activation deposits Atherona no information available no information available	1916 1916 1916 1916
50 41-50 51 51-60 53 51-60 53 51-60		right AcoumA right MCA right MCA left AcoumA	y y n	no information available. Afterorum no information available Attriconations available Attriconationsis.	1916 1916 1916 1916
55 51-60 58 51-60	m f f	right AcomA right ICA	y y y	no information avuilable consjonala ineuryum embolici Afteroma	1916 1916
60 51-60 67 61-70 70 61-70 72 71-80 75 71-80	m f f m	right MCA left MCA left ICA left ICA undefined CBAN	y n y	embolic no information available artical degeneration no information available	1916 1916 1916 1916 1916
86 81-100	m	right MCA left ACA midline BA undefined CBAN	n n	no information available embolic embolic embolic	1916 1916 1916 1916
	m	left MCA left ACA right MCA	y y	no information available embolic embolic embolic	1916 1916 1916
12 11-15. 32 31-40 47 41-50 52 51-60	f m f	right AcomA bilineral ICA left VA right ICA midline BA	y y y	vescel healthy no information available vescel soft no information available vescel soft no information available	1917 1917 1917 1917
53 51-60 21 21-30 26 21-30 53 51-60	m f f	right MCA right ICA left MCA	y y y	Arteion-levois a middle consideration and the consideration and th	1917 1918 1918 1918
54 51-60 87 81-100 2 0-5. 18 16-20 27 21-30	f m m	left PCA right MCA left MCA bilisteral MCA bilisteral MCA	y y y	not uncorrelation revaluates Focal reaso of intimal indicating Vescels soft and thin No trace of specialities are described as decrease in dante fibers in media of vessels No trace of specialities are deviced revolutionally a docrease in dante fibers in media of vessels	1918 1918 1919 1919
28 21-30 35 31-40 36 31 40	m m f	right VA right MCA	y y y	Slight infinant thickening of other vessels atherosclerosis	1919 1919
39 31-40 42 41-50 45 41-50 53 51-60 53 51-60	: 	right PoomA left AcomA left MCA left MCA midline BA left PoomA	y y y	Scarrered posthos of intimat thick enting Arteriood levelsis afteriood levelsis afteriood levelsis afteriood levelsis	1919 1919 1919 1919 1919
55 51-60 56 51-60 68 61-70	m m f	left PcomA midline BA right PcomA left AcomA right MCA	y y y	Scattered purches of intimal inducening Vescula induced with plaques Scattered plaques	1919 1919 1919 1919
28 21-30 29 21-30 36 31-40	m f	midline AcomA midline AcomA midline AcomA midline AcomA midline BA	y y y y	Suatered unbearing Suatered unbearing Suatered without so information available to information available to information available to information available	1919 1920 1920 1920
37 31-40 30 41-50 55 51-60 56 51-60	f f m	midline AcomA midline AcomA midline AcomA midline AcomA right AcomA	y y y	no unformation variables into information variables Schrossi of cerebral arrives no information variables	1920 1920 1920 1920 1920
67 61-70 9 6-10. 13 11-15. 20 16-20	f m m	midline AcomA left PCA midline AcomA undefined CBAN	y y y	no information sevaluble no information sevaluble néroted enhouse, other vessels normal no information available no information available	1920 1921 1921 1921
27 21-30 37 31-40 37 31-40 39 31-40	f f m	midline AcomA left AcomA left AcomA undefined CBAN	y n y	did microttanion synamose Admonia Admonia Medial seleptisis and Ibed, intensi thickening Adstroicelessisis Attroicelessisis	1921 1921 1921 1921
44 41-50 44 41-50 46 41-50	m m f	left AcomA left AcomA	y y y	Infected embolus; slight intimat thickening of other vessels Other vessels normal	1921 1921
46 41-50 50 41-50 52 51-60 61 61-70 61 61-70	m f	left AcounA right VA left AcounA bilaceral VA midline AcounA bilaceral MCA	y n y n	Ancorom Afteromation available an information available Ancoromation available an information available an information available Ancoromation and available Ancoromation and available Ancoromation and available Ancoromation	1921 1921 1921 1921 1921 1921
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46 41-50 50 41-50 54 51-60 16 16-20	f m	midline BA right ICA left VA	y n y n	emotions (casocierinis) no information variable Arteriosclevois Mossic emotion Mossic emotion	1922 1922 1922 1922 1923
18 16-20 22 21-30 22 21-30	f m	left AcomA right MCA left PICA	y y y y	Mycotic embolism	1923 1923 1923
24 21-30 25 21-30 29 21-30 29 21-30	m m m	right MCA undefined CBAN left MCA left MCA	y y y	Embolic (endocareditis) no information available Embolic (endocareditis) Embolic (endocareditis) Embolic (endocareditis)	1923 1923 1923 1923
31 31-40 33 31-40 36 31-40 36 31-40	m f m	right MCA left MCA left ICA right ICA midline AcomA	y n y y	Embolic (endocanditis) Mycotic embolism no inferentica avvalible no inferentica avvalible	1923 1923 1923 1923
42 41-50 43 41-50 45 41-50 45 41-50	t t t	right MCA undefined CBAN	y y n y	Embolic (endocanditis) Arteriosciencis no information avvailable Arteriosciencis	1923 1923 1923 1923
49 41-50 50 41-50 52 51-60 52 51-60	m f f	midline AcomA left ICA right ICA midline AcomA right ICA	y n n y	no information available Arterioscleosis no information available Arterioscleosis no information available Arterioscleosisis	1923 1923 1923 1923
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70 61-70 70 61-70 70 61-70 74 71-80 75 71-80	f f m f	left MCA right PCA left AcomA left PcomA	y y n	Arteriosclerosis Arteriosclerosis Arteriosclerosis Arteriosclerosis Arteriosclerosis	1923 1923 1923 1923
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29 21-30 29 21-30 30 21-30	f m m	right ICA right ICA midline BA left AcomA	y y n	Healthy vessels healthy vessels Gummatous arteritis	1924 1924 1924
41 41-50 41 41-50 43 41-50 47 41-50 49 41-50	f f f	left ICA left AcomA right ICA midline BA	y y y	Enforcentisis or arteriorischemois Internal selection (sendocardinis) no information available no information available	1924 1924 1924 1924
49 41-50 60 51-60	=======================================	right AcomA	y y y	Arteriosclerosis no informerion available Afteroma no informerion available	1924 1924 1924 1924 1924 1924
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	f f f	left ICA left ICA left AcomA left AcomA left PcomA left PcomA		no information available	1924 1924 1924 1924 1924
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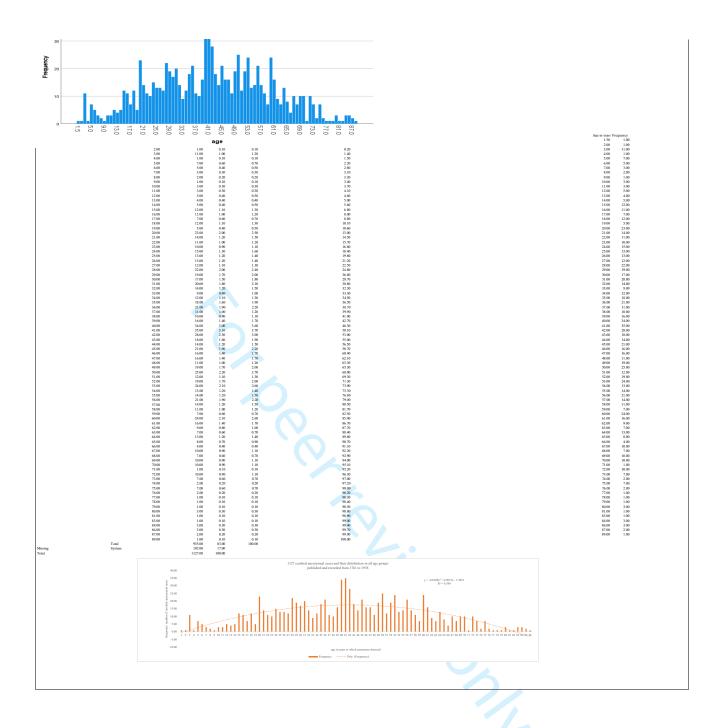
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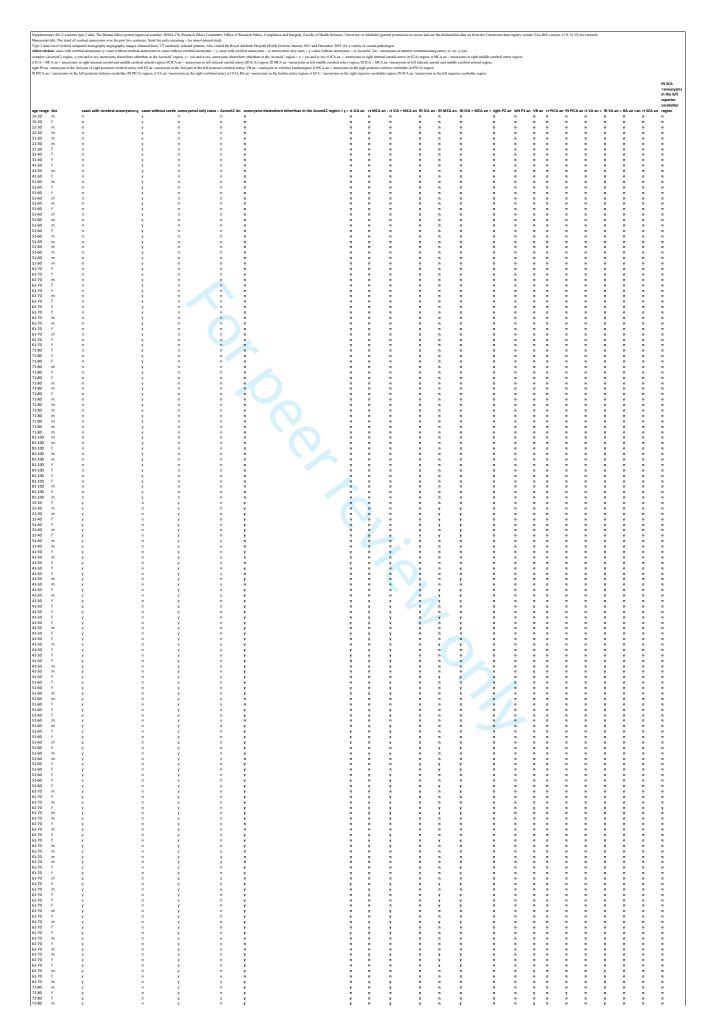


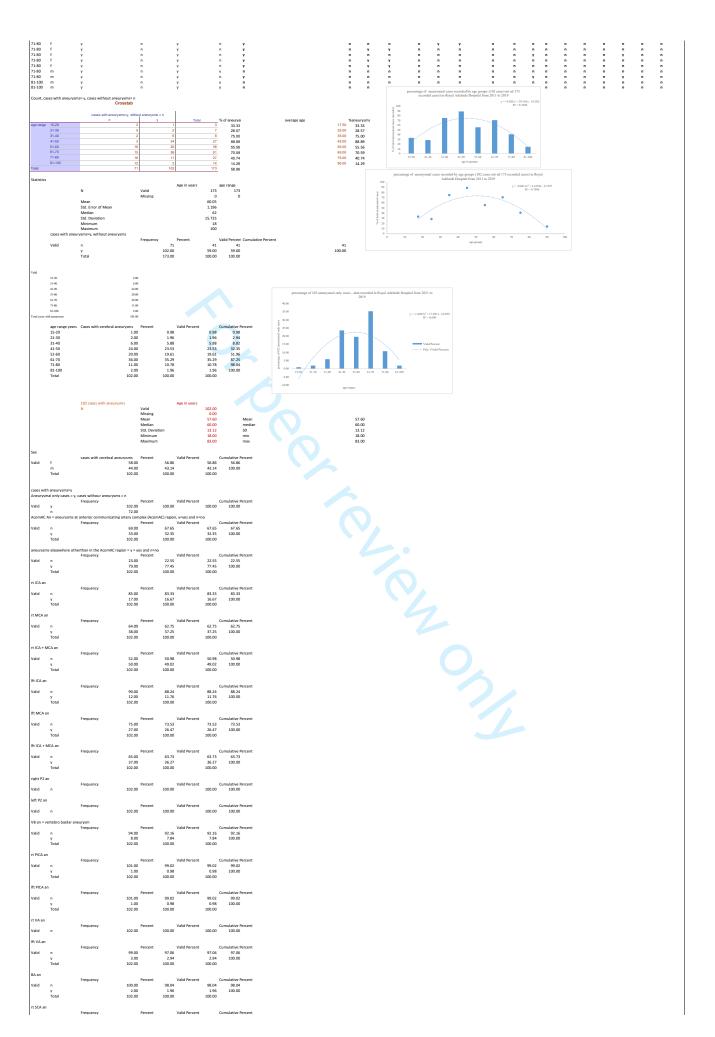




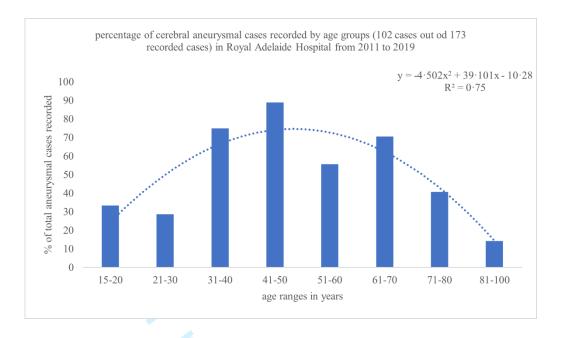








ralid	n		102.00	100.00		100.00	100.00	
ft SCA a	n							
		Frequency	F	Percent	Valid Percent		Cumulative Percent	
falid	n		101.00	99.02		99.02	99.02	
	v		1.00	0.98		0.98	100.00	
	Total		102.00	100.00		100.00		
		h (n=102) and without a	(71)	landered in the street				
ge rang	e- patients wit	Frequency			Valid Percent		Cumulative Percent	
falid	15-20		3.00	1.70		1.70	1.70	
	21-30		7.00	4.00		4.00	5.80	
	31-40		8	4.6		4.6	10.4	
	41-50		27	15.6		15.6	26	
	51-60		36	20.8		20.8	46.8	
	61-70		51	29.5		29.5	76.3	
	71-80		27	15.6		15.6	91.9	
	81-100		14	8.1		8.1	100	
	Total		173	100		100		
ex			F	Percent	Valid Percent		Cumulative Percent	
		Frequency				52		
ex falid	f	Frequency	90	52			52	
	f m Total	Frequency	90 83 173	52 48 100		48 100	100	



Supplementary Figure 1- The prevalence (%) of cerebral aneurysms observed over a broad age range (18-100 years, n=173, cases with aneurysms=102, cases without aneurysm=71), with a median of 62 years, a mean of 60 years, and a standard deviation of 15.75, is shown in the chart. The peak prevalence occurs between 31-60 years (p<0.001).

Supplementary Table 1: Statistical parameters of distributions of aneurysmal cases reported from 1761-1938,[14] and recorded in RAH from 2011 to 2019.

		102	1127 patients with cerebral aneurysms recorded in 407 publications - published from 1761 to							
		patients	1938							
		with								
		cerebral								
		aneurysmal								
		aneurysms								
		recorded in								
		RAH from								
		2011 to								
		2019								
Statistics -		age>18,	age>18	age >=	age >=	age >=	all age,	all age,	all	all age
all cases		2011 to	years, 1761	18 &	18 &	18 &	year	year <	ages,	group, all
with		2019	to 1938	year <	year >=	year >=	<1850	1900 &	year >=	years, >400
cerebral				1850	1850 &	1900		year >=	1900	publications
aneurysms					year <			1850		
1900										
Age in										
years										
N	Valid	102	851	41	252	560	42	278	613	935
	Missing	0	0	0	0	0	7	14	171	192
Mean age		57.6	44.7	44.3	45.6	44.3	43.6	42.6	41.2	41.7
Median		60.0	43.0	47.0	45.0	42.0	46.0	43.0	41.0	41.0
age										
Mode age		48.0	41.0	20.0	40.0	41.0	20.0	40.0	41.0	41.0
Std.		13.1	15.5	15.6	15.6	15.4	16.1	17.5	17.9	17.7
Deviation										
Minimum		18.0	18.0	19.0	18.0	18.0	14.0	6.0	1.5	1.5
age										
Maximum		83.0	89.0	68.0	86.0	89.0	68.0	86.0	89.0	89.0
age										
Percentiles	25	48.0	32.0	33.5	33.3	32.0	31.8	28.8	29.0	29.0
	50	60.0	43.0	47.0	45.0	42.0	46.0	43.0	41.0	41.0
	75	68.3	56.0	59.0	56.0	55.0	59.0	56.0	53.0	54.0

Legend: 14 = McDonald, CA & Korb, M 1939, Intracranial aneurysms, Archives of neurology and psychiatry (Chicago), vol. 42, no. 2, pp. 298-328.

STROBE Statement—Checklist of items that should be included in reports of cross-sectional studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract
		(b) Provide in the abstract an informative and balanced summary of what was done
		and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment,
2		exposure, follow-up, and data collection
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of
1		participants
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect
		modifiers. Give diagnostic criteria, if applicable
Data sources/	8*	For each variable of interest, give sources of data and details of methods of
measurement		assessment (measurement). Describe comparability of assessment methods if there is
		more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable,
		describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding
		(b) Describe any methods used to examine subgroups and interactions
		(c) Explain how missing data were addressed
		(d) If applicable, describe analytical methods taking account of sampling strategy
		(\underline{e}) Describe any sensitivity analyses
Results		
Participants	13*	(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
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and
		information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and
		their precision (eg, 95% confidence interval). Make clear which confounders were
		adjusted for and why they were included
		(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

Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or
		imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations,
		multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	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

^{*}Give information separately for exposed and unexposed groups.

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.

BMJ Open

The trend of cerebral aneurysms over the past two centuries: Need for early screening - An observational study.

Journal:	BMJ Open
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Date Submitted by the Author:	08-Feb-2024
Complete List of Authors:	Burlakoti, Arjun; University of South Australia, Human Anatomy; University of Adelaide, School of Biomedicine, Faculty of Health and Medical Sciences Kumaratilake, Jaliya; The University of Adelaide Adelaide Medical School, School of Biomedicine, Faculty of Health and Medical Sciences Taylor, Jamie; Royal Adelaide Hospital, South Australia Medical Imaging Henneberg, Maciej; The University of Adelaide, School of Biomedicine, Faculty of Health and Medical Sciences; Institute of Evolutionary Medicine, The University of Zurich, Zurich, Switzerland
Primary Subject Heading :	Neurology
Secondary Subject Heading:	Health policy, Pathology, Public health
Keywords:	Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Stroke < NEUROLOGY, Mass Screening, Community child health < PAEDIATRICS

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1 2		
3	1	The trend of cerebral aneurysms over the past two centuries: Need for early screening - An
4 5	2	observational study
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35	Abstract

- 36 Objective
- 37 Cerebral aneurysms (CAs) are linked to variations in the cerebral basal arterial network (CBAN). This study
- aimed to find the optimal age for screening to detect brain arterial variations and predict aneurysms before
- 39 rupture.
- 40 Design
- 41 An observational, quantitative, and retrospective research.
- 42 Setting
- The study analyzed 1127-cases of CAs published from 1761 to 1938. Additionally, Computed Tomography
- 44 Angiography images of 173-patients at the Royal Adelaide Hospital (RAH), South Australia between 2011 and
- 45 2019 were examined for the presence and the location of aneurysms in CBAN.
 - **Participants**
- The data were collected from patients at RAH and 407-published sources, including males and females across
- the entire age range, up to 100 years old.
- 49 Outcome measures and results
- Data, CAs cases, from 1761 to 1938 included (526-males, 573-females, and 28-unknown sexes). The age of
- 51 these patients varied from 18 months to 89-years (mean age=42, SD=18). Approximately 11.5% of the CAs
- occurred in patients less than 20-years old. Among the 1078 aneurysms whose location was reported, 76% were
- located in the internal carotid (IC), middle cerebral (MC), and anterior communicating artery complex
- 54 (AcomAC) regions, while the remaining 24% were in the vertebrobasilar (VB) region. Among 173-patients
- from the RAH aged between 18 and 100 years, (male=83 and female=90, mean age=60, SD=16), 94% of the
- CAs were found in the IC, MC, and AcomAC regions. The pattern of aneurysm occurrence, as indicated by
- values at the 25th, 50th, and 75th percentiles, along with the minimum and maximum patient ages, has remained
- 58 consistent from 1761 to 2019.
- 59 Conclusion
- The distribution pattern of cerebral aneurysms in relation to sex, age and locations in the CBAN, remained
- steady over the last 260-years resulting in risk of strokes early in life. Therefore, early screening for CBAN
- segment variations is advised for stroke prevention if possible.
- 63 Key words
- 64 Subarachnoid haemorrhage; Childhood Aneurysm; Stroke; Hemodynamics; Cerebral Arteries.
- 65 Strengths and limitations of this study:
 - To our knowledge, the patterns of distribution and trends of occurrence of cerebral aneurysms have not been systematically studied over the past 260 years.
 - Aneurysms can develop at any age in the presence of variations in cerebral basal arterial network (CBAN). Early detection of variations in CBAN in infant using non-invasive the Doppler ultrasound technique is recommended and continuing screening regularly as needed.
 - Reported cases from the tertiary medical centres and 407 papers published over the past 260 years may not represent the general population precisely.
 - This investigation is not a continuous study.
- 75 Funding

/6	Not app	licabl	le, non	ıe

Competing interests

None declared. All authors have nothing to disclose.

Introduction

Anatomical variations among components of the cerebral basal arterial network (CBAN) in addition to the trauma, infection, spontaneous dissections, and collagen disorders, have been linked to the formation of cerebral aneurysms (CAs)[1,2,3] and such variations develop during the period of embryonic life.[2] The period taken for the development of CAs may vary among individuals and once formed they may enlarge, compress the surrounding tissues, and rupture leading to subarachnoid haemorrhage (SAH).[3]

Cerebral aneurysms of all sizes have been observed to cause SAH in adults[4] (incidence 6-10/100000), however, they also occur in the age group 0-20 years (incidence rate=1.4-2 per 100000).[5-7] It is not clear that the occurrence of anatomical variation-related aneurysms is limited to any specific age. The management of complicated CAs is costly and the CAs can leave permanent disabilities or even become fatal costing millions of dollars to families and governments.[7-12] The majority of childhood SAH (i.e., incidence 1.4-2 per 100000 children) are caused by the pre-existing cerebral aneurysms.[13] About 5% of the total cerebral aneurysmal cases diagnosed in the clinical setup were in the age group 0 to 19 years and the incidence of childhood SAH is significantly greater in the older age children.[13] The clinical manifestation of aneurysmal cases seen later in life might be the consequence of aneurysms that developed in early childhood. Therefore, this study aims to review cases of CAs using data collected from a tertiary medical center (Royal Adelaide Hospital - South Australia) and published sources to investigate the recent pattern of CAs and how it has changed over the past 260 years. The null hypothesis is that the advancement of medical science did not lead to a reduction in the prevalence of aneurysms by age.

Material and method

Study design, and setting

- Two types of data were used in this study.
- Type-1 data are composed of 1127 cerebral aneurysmal cases that were published in the 407 papers from 1761
- to 1938, as compiled by McDonald and, Korb.[14] These CAs were identified at autopsy and included patients
- of all ages (average age=41.7 years, mode age=41, median age=41, SD=17.7, age range 1.5 to 89 years)
- 105 (Supplementary File 1 and Supplementary File 2).
- Type-2 data were Cerebral Computed Tomography Angiography (CTA) images obtained from 173 randomly
- selected patients, who visited the Royal Adelaide Hospital (RAH), South Australia, between January 2011 and
- December 2019 for a variety of cranial pathologies; their age ranged from 18 to 100 years, males = 83, female =
- 90, mean age=60 years, median age=62 years, mode age=61, SD=15.72) with (n=102) or without (n=71)
- aneurysms (Supplementary File 2 and Supplementary File 3). These images were anonymised, stored in the
- 111 Carestream data registry system and the patients have given their consent to use their clinical information for
- research activities. The consent documents taken from each patient were not provided to the researchers to
- ensure privacy. The Human Ethics permit (approval number: H2014-176, Research Ethics Committee, Office of
- Research Ethics, Compliance and Integrity, Faculty of Health Sciences, University of Adelaide) granted
- permission to access and use the deidentified data set from the Carestream data registry system (Vue-RIS-
- version-11.0.14.35) for research. Thus, the research materials used in this study comprised 1229 observed cases
- of CAs that spread across all age groups, spanning a period of approximately 260 years.

Data sources and size

- Type-1 data: A range of variables (such as, the year CAs was detected, age, sex, location of the aneurysm)
- related to 1127 cases of CAs reported in publications from 1761 to 1938,[14] were transferred into an excel data

- file, rearranged and subjected to analysis (Supplementary File 1). Type-2 data: The cerebral CTA of 173-
- patients recorded from 2011 to 2019 in RAH were accessed to study the presence and absence of CAs in
- different locations of CBAN based on diagnoses made by clinicians. Some cases had multiple aneurysms
- located in the various segments of CBAN (Supplementary File 3).
- The above cases of CAs were grouped into age ranges 0-5, 6-10, 11-15, 16-20, 21-30, 31-40, 41-50, 51-60,
- 61-70, 71-80, and over 81 years and transferred into the SPSS v. 25 software, for analyses (Supplementary File
- 1). The observation error has been tested by repeating the observation of the location of CAs in the cerebral
- CTA images in 20-cases, a month after the first study. There was 100% agreement of repeated observations with
- those of the first one. The sites of the formation of aneurysms were recorded as the left and right, internal
- carotid artery (ICA), middle cerebral artery (MCA), anterior cerebral artery (ACA), anterior communicating
- artery complex (AcomAC), posterior communicating artery (PcomA), posterior cerebral artery (PCA), vertebral
- artery (VA), basilar artery (BA), posterior inferior cerebellar artery (PICA), anterior inferior cerebellar artery
- (AICA), superior cerebellar (SCA) and pial arterial regions. In some cases, the areas of location of aneurysms
- seemed not to have been mentioned and those cases were tabulated under the heading of 'aneurysms located in
- CBAN (CBAN-an)'. Overall, the locations of nearly 1229 aneurysmal cases from both data sets were broadly
- divided into four categories: central and bilateral, left and right (Figure 1) before being plotted in the bar charts
- to study the location and distribution trends of aneurysms in the arterial network over the past 260-years (Figure
- 2). The aneurysms located in the AcomAC, and basilar arterial regions were classified as the central group of
- aneurysms. Additionally, in a few cases aneurysms were located simultaneously on left and right sides and those
- cases were grouped as 'bilateral' (Supplementary File 1 and Supplementary File 3 and Figure 1).

Statistical methods

- Data were analysed using Excel and Statistical Package for the Social Sciences (SPSS-IBM, version-25)
- program (e.g., descriptive, and Chi squared tests). The p values less than 0.05 were considered as statistically
- significant.

Patient and public involvement

- Involving patients was challenging for conducting and planning this research, since researchers were allowed
- the access only to anonymised raw data recorded in the database. As per the ethics permit (details in the method
- section), we accessed retrospective anonymized data, precluding patient involvement in research planning and
- execution. The shared outcome of this study will be informed to the public, families and patients who attend
- medical centres for various clinical visits, through a series of meetings, seminars, and media releases.

Findings

- This study reviewed 1127 aneurysmal cases of patients of all ages from a total of 407 published articles prior to
- the year 1939. The ages of these patients (male=526, female=573, unknown sex=28) ranged from 18 months to
- 89 years of age with an average of 41.70 years, mode of 41 years and median of 41 years (SD=17.7)
- (Supplementary File 2, Figure 2a, Figure 2b, Figure 2c and Supplementary File 1). The second group of patients
- with CAs (44 males and 58 females, and n=102) from the RAH (2011 to 2019) with the age range 18-100 years
- showed that the most common age for diagnosis or complication of CAs ranged from 31-60 years with the
- calculated mean, median, mode, and standard deviation (SD), 57.60, 60.00, 48.00, and 13.12 years, respectively
- (Figure 2d and Supplementary File 4). Analysis of both sets of data revealed that the majority of the patients
- who presented with complicated aneurysms were in their 3rd to 6th decades of life (Supplementary File2).
- The most important aspect of the two sets of data was the wide age range of occurrence of CAs and the fact that
- some of the complicated aneurysmal cases appeared at an early age (Figure 2a, Figure 2b, Supplementary File
- 1). A separate analysis was conducted for 853 out of the 1127 cases of CAs recorded before 1938 (male=409,
- female=438, unknown sex=6), specifically focusing on the age range of 18 to 89 years to align the age groups
- with the RAH recorded data from 2011 to 2019 (Supplementary File 2, Figure 2c and Figure 2d). The
- similarities of standard deviation (15.45) of those 853 cases (from 1761-1938) and the cases that were recorded
- from 2011 to 2019 in RAH (13.12 years) validated the comparability of our data and the findings
- (Supplementary File 2). The values of the 25th, 50th, and 75th percentiles, as well as the minimum and

maximum observed ages of patients with aneurysms, remained relatively stable from 1761 to 1938 (Figure 3a). Some of these percentile values increased slightly as life expectancy extended from 1761 to the 21st century (Figure 3b). Therefore, the SD, and age distribution of adult patients with ruptured or diagnosed CAs presented in the 2011-2019 dataset were consistent with those cases reported before 1938, indicating persistence of a pattern (Table 1, Figure 2 and 3). Specifically, aneurysms are being frequently diagnosed in individuals aged 30 to 60 years, and this age range has remained relatively unchanged over the past 260 years (Table 1, Figures 2, and 3). Forty nine out of 1127 cases recorded across 407 publications from 1761 to 1938 seemed not to have information about the location of aneurysms in the CBAN, however, 818 out of 1078 identified aneurysms (76%), were in the ICA, MCA and AcomAC regions and rest of them were in the vertebrobasilar region (Supplementary File 1). The location and distribution pattern aneurysms from 102 patients recorded in RAH was consistent with 1078 cases recorded from 1761 to 1938 (Supplementary File 1, Supplementary File 2, and Supplementary File 3).

In the type 2 dataset, a total of 135 aneurysms were identified in 102 individuals, with ages ranging from 18 to 83 years, across various components of CBAN (Figure 2d and Supplementary File 3). Among these aneurysms, 38(28.14%) were detected in the right MCA region, while 17(12.6%) were in the right ICA region. In comparison, the left MCA and ICA regions had 27(20%) and 12(8%) aneurysms, respectively, which appeared to be lower in number compared to the right MCA and ICA regions. When considering the distribution of aneurysms based on territory, 55 out of 135 aneurysms (40.74%) in 50 patients were found in the right ICA and MCA territories, whereas 39 out of 135 aneurysms (28.88%) in 37 patients were detected in the left ICA and MCA regions (Supplementary File 3). Out of the 102 individuals with aneurysmal cases included in the study, 33 (24.44%) had aneurysms located in the anterior communicating artery (AcomAC) region, accounting for 33 out of the total 135 aneurysms. An additional 5.9% of the total aneurysms (8 out of 135 aneurysms) were found in the vertebral and basilar arterial regions, as indicated in the Supplementary File 3. A majority of the CAs, 127 out of the total 135 (94% of the total), were in the MCA, ICA, and AComAC regions (Supplementary File 3). Some cases had multiple aneurysms, for example, 2 cases had right ICA and MCA aneurysms, while 10 cases had left ICA and MCA aneurysms (Supplementary File 3).

There were no significant differences between male and female patients affected with CAs in all 1229 cases analysed in those two data sets (Chi-Squared statistic=0.83, p≥0.36) (Table 1). The sex, age of occurrence and location of CAs appear to have remained steady over the past 260 years across all age groups (Table 1 and Supplementary File 2, and Figure 3). The mode, mean, and median age and SD of patients with ruptured or diagnosed CAs studied from 2011 to 2019 in RAH matched well with the cerebral aneurysmal cases recorded in the past considering the difference in life expectancy between the two time periods studied (1761-1938 and 2011-2019) (Figures 3 and Table 1).

Figure 1- about here

4 Figure 2 - about here

Figure 3 - about here

Table 1 - Prevalence of cerebral aneurysms in males and females: a comparison of the recent hospital-based data recorded in RAH from 2011 to 2019 with the autopsy data published before from 1761 to 1938.

Sex	N=173, cases with or without cerebral	1127 aneurysm cases (from 1761 to 1938)
	aneurysms recorded in RAH from 2011	recorded in 407 publications.[14]
	to 2019.	
	10 2019.	
Sex not defined	0	28
Female	90	573
Male	83	526
Female to male sex ratio	1.08	1.09
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Legend- RAH = royal Adelaide hospital, 14 = McDonald, CA & Korb, M 1939, Intracranial aneurysms, Archives of neurology and psychiatry (Chicago), vol. 42, no. 2, pp. 298-328.

Discussion

The age and locations at which CAs occur in the CBAN has not changed over past 260 years (Figures 1, 2 and 3, Table 1 and Table 1) despite the life expectancy has increased over time worldwide and the progress in medicine. In the past people had shorter life span on average, and yet the CAs occurred at the same ages as they do now.[15] The life expectancy recorded at below 50 years in 1940 and even below 40 years in 1850 was way lower compared to the one recorded above 80 years of age since the year 2000 in Australia.[15] A separate analysis was done for 853 out of the 1127 CAs recorded [14] before 1938 focusing on the age range of 18 to 89 years to align the age group with the currently RAH recorded data from 2011 to 2019, since there were no aneurysmal cases of children (age<18years) in the RAH dataset. In Adelaide there is a separate hospital for children where aneurysmal cases would have been treated, but the authors had no access to these data (Supplementary File 3). Royal Adelaide Hospital is a general hospital, thus individuals of 18 years and less are not admitted. Current study compared the cases of CAs diagnosed by CTA imaging technique (from 2011-2019) with those verified by surgery and autopsy[14], since there were no cerebral angiogram facilities in early years (i.e., before 1938). The cases of aneurysms are commonly diagnosed, when the patients are presented at medical centres after attacks of stroke. [16] Cerebral aneurysms in the past seemed to be ruptured and complicated as early as 18 months of age and as late as 89 years of age with a wide range of age (Supplementary File 1). The findings suggested that the change in lifestyle nor medical practice had no effect at the age/time of formation of CAs in general population. Clinical investigation of lipid profiles in patients commenced after 1950,[17] and they started attributing arterial diseases and aneurysms to the hyperlipidaemia, however, the manifestation of occurrence of aneurysms by age in the past 260 years seems not to be different from the current age of occurrence. Although the lifestyle and the external influences, including medical practice, changed over more than two centuries, aneurysms still occur at approximately the same age. Therefore, aneurysms occur and rupture on their own internal circumstances and are not related to the diet, environmental, and external factors.[18] The most likely internal factor is the severity of the variation on the segments of CBAN that adversely affects the hemodynamics resulting in the formation of aneurysms.[1,19] The condition of the arterial wall should not have changed over the last 260 years and that seems to be less significant than the variation in the components of CBAN. The segmental and communicating arteries play a crucial role in dampening the systolic pressure within the CBAN and reducing the likelihood of aneurysm formation.[1,19] The severity of arterial variation can have negative effects on the blood flow dynamics through the variant segment of the component of the CBAN.[1,19] The incidence of CAs is about 3.3% in the general population and may not be diagnosed, until they get enlarged as the size of the aneurysm <3mm in diameter can be missed.[20] Imaizumi and colleagues found that the prevalence rate of CAs was 4.32% in Japan.[12] The incidence rate of CAs in childhood (age <18 years) has been reported to be 0.5-4.6%, which is almost as common as the incidence rate observed among adults.[13] Treating cases of CAs with a diameter less than 3 mm requires careful consideration, as pre-existing small aneurysms of ≤ 3 mm could rupture, resulting in spontaneous SAH.[21] The majority of CAs are detected only when they cause a stroke or other pathological effect (e.g., compression of the optic tract).[4] Individuals older than 18 years are no longer considered children.[6,13]

Most of the symptomatic cases of CAs in the paediatric age group were observed in older children (15 + years) [13], and only complicated cases of CAs were generally diagnosed and reported. [22,23] If the incidence of childhood CAs described (ranges from 0.17 to 4.6%), [24] is corrected for number of years lived, it would be 18.4% of the total aneurysmal cases amongst adults. The adult patients included in CAs studies ideally have an age range of 18-years and above, which can include individuals up to the age of 100 years. [12,15] In contrast, the childhood group included in aneurysmal studies typically ranges from birth up to 18-years of age and a few studies have categorized patients who are 18-years or older under the adult group. [6,13] When the age range, 0-18 years and 19-100 years is considered, the incidence of childhood CAs, that should be multiplied by 5 times to correct for the number of years lived, can be comparable to that in adults because the childhood period of life is much shorter than the adulthood. Therefore, the age range of adult group (≥20 years up to 100 years) included in the CAs and stroke studies would be about five times more than the age range of children (i.e., ≤18 years).[22,23] That means adults have 5 times more years to develop CAs compared to children. Therefore, the incidence of childhood CAs per year is almost equivalent to adult. [21,25] Hence, CAs could develop in early

childhood in the presence of a significantly variant component of cerebral arterial anatomy,[1,2] and it could take years for them to balloon before becoming symptomatic and being observed in a tertiary medical center. The overall pattern of location and distribution of childhood CAs was similar to adult as they commonly occurred in ICA, MCA and AcomAC regions.[3] Therefore the development of CAs is not age related and found to be prevalent in all age ranges.[10,12,13,26] Cerebral aneurysms may not always be associated to the advanced age, history of smoking, drinking alcohol but start forming as early as in the childhood in the presence of variant components of cranial blood vessels.[27] The mean age at which people were affected by cerebral aneurysms was reported to be 55 to 57 years of age in a study conducted using 1085 aneurysmal cases from 2008 to 2016.[28] There are a few reports of CAs published between 1938 and 2011 that could have been compiled for statistical analyses. However, their inclusion into this study, would not have changed its basic conclusions: i.e., large age range and no change through time in the occurrence of CAs.

Ultrasonographic video screening by placing the probe in the fontanelles of babies before they close has been found to be safe and effective in studying brain vessels[26,29] and can be incorporated as a screening tool to detect variations in intracranial vessels that could predispose to the development of cerebral aneurysms later in life. One illustration of such possibility is that individuals with the left and right ACA proximal segment diameter ratio greater than 1.4 have a 27-fold increased risk of developing cerebral aneurysms in the AcomAC region.[1] Parents of children found to have variations in CBAN could be advised to schedule follow-up screening periodically, especially if a more affordable and convenient technology for detecting brain aneurysms becomes available. The current screening recommendation is based on the congenital variations of segments of CBAN, but such variations could occur later on life in cases of pathology like atherosclerosis and could cause aneurysms. Future studies to test the association of presence of anatomical variations in CBAN in infancy and future risk of both unruptured and ruptured intracranial aneurysms in adulthood are recommended.

The estimated cost of a single stroke is approximately \$300,000 in Australia.[9] With a haemorrhagic stroke incidence of 10 per 100,000 the total cost amounts to \$45 million per year in a city the size of Adelaide[1], South Australia, which has a population of 1.5 million. Regular screening for individuals with significantly variant brain arteries identified, representing 50% of the population, once every 5 years, and assuming the cost of a single computed tomography angiography or magnetic resonance angiogram is about \$100 each, the total screening cost would be \$1.5 million per year, that means 30 times reduction in cost of strokes. Additionally, the government would receive millions of dollars in return as tax revenue from working individuals who would survive with little to no disability from potential strokes resulting from aneurysms. This study was not designed to examine the characteristics of aneurysms, but the focus was on the distribution of aneurysms in different segments of CBAN, trend of occurrence of aneurysms over the past 260-years, and the comparison of cerebral aneurysms in all age ranges.

Limitations:

The insufficient data on the lack of personal and family history, history of smoking, lipid profile, and blood pressure are limitations of this study. A larger survey and a prospective study could be conducted. A prospective study could involve using ultrasound techniques to identify variations in brain vessels among infants.

Conclusion

Brain arterial aneurysms can develop early in the presence of variant arterial components. Screening children under 24 months using transcranial ultrasonography for variant cerebral arteries may be practical. Those with variations should undergo periodic tests for aneurysms, aiming to prevent some haemorrhagic strokes if an affordable and convenient technology for detecting brain aneurysms becomes available.

331 Data sharing statement

Additional data are available by emailing Arjun.Burlakoti@unisa.edu.au

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334 None

 335 ORCID iD

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- 337 Author contribution statement
- Arjun Burlakoti- conceived the idea, collected, and analysed both sets of data, took pictures, recorded videos,
- contributed to conceptualization, prepared and drafted the manuscript.
- Jaliya Kumaratilake- conceived the idea, contributed to the concept, aided in data interpretation, editing and the
- revision of the manuscript and approving the article.
- Jamie Taylor- conceived the idea, contributed to the concept, aided in data interpretation, editing and the
- revision of the manuscript and approving the article.
- Maciej Henneberg- conceived the idea, masterminded, and helped in statistics, data analysis and interpretation,
- editing and approving the article.
- 346 Ethical Approval Statement
- The University of Adelaide, Human Research Ethics Board granted permission to access and use data for this
- research project (Ethics Approval Number: H2014-176).
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12	419	Figure 1 - Comparison of the location of cerebral aneurysms between Royal Adelaide Hospital sample (2011 to
13	420	2019) (n=135 CAs from 102 patients, orange colour) with those recorded in 407 publications[14] (1761 to 1938)
14	421	(n=1127 CAs, blue colour). CAs=cerebral aneurysms, 14 = McDonald, CA & Korb, M 1939, Intracranial
15	422	aneurysms, Archives of neurology and psychiatry (Chicago), vol. 42, no. 2, pp. 298-328.
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17 18	423	
19	424	Figure 2 - Figures displaying the distribution patterns of cerebral aneurysms in different age groups recorded
20	425	from 1761 to 1938 and from 2011 to 2019. A polynomial regression lines show the number and distribution of
21	426	cerebral aneurysm cases across all age groups. a) The distribution of cerebral aneurysmal cases (n=1127) in
22	427	various age group, recorded from 1761 to 1938.[14] b) The frequency of cerebral aneurysmal cases and their
23	428	distribution (n=1127) across all age groups recorded from 1761 to 1938. c) Age (≥18 years) related
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25	429	distribution of individuals affected with cerebral aneurysms over the past 260 years (1761 – 1938) (n=853),
26	430	recorded ¹⁴ from 1761 to 1938, and d) Age (18-100 years) related prevalence (%) of cerebral aneurysms in RAH
27	431	sample from 2011 to 2019 (n=102). The peak prevalence occurred between 31-60 years (p<0.001). RAH= Royal
28	432	Adelaide Hospital. RAH= Royal Adelaide Hospital and 14 = McDonald, CA & Korb, M 1939, Intracranial
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34	436	Figure 3: Comparison figures showing the trend of occurrence of cerebral aneurysms at different age group
35	437	(n=1127) from 1761 to 2019. (a) The values of the 25th, 50th, and 75th percentiles, as well as the minimum and
36	438	maximum observed all ages of patients with aneurysms, from 1761 to 1938[14]; b) The values of the 25th, 50th,
37	439	and 75th percentiles, as well as the minimum and maximum observed patients with >18 years of age with
38	440	aneurysms, recorded from 1761 to 1938 ¹⁴ and 2011 to 2019 in RAH. RAH = Royal Adelaide Hospital, 14 = Data
39	441	from: McDonald, CA & Korb, M 1939, Intracranial aneurysms, Archives of neurology and psychiatry
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Table 1 - Prevalence of cerebral aneurysms in males and females: a comparison of the recent hospital-based data recorded in RAH from 2011 to 2019 with the autopsy data published before from 1761 to 1938.

Sex	N=173, cases with or without cerebral aneurysms recorded in RAH from 2011 to 2019.	1127 aneurysm cases (from 1761 to 1938) recorded in 407 publications.[14]
Sex not defined	0	28
Female	90	573
Male	83	526
Female to male sex ratio	1.08	1.09

Legend- RAH = royal Adelaide hospital, 14 = McDonald, CA & Korb, M 1939, Intracranial aneurysms, Archives of neurology and psychiatry (Chicago), vol. 42, no. 2, pp. 298-328.

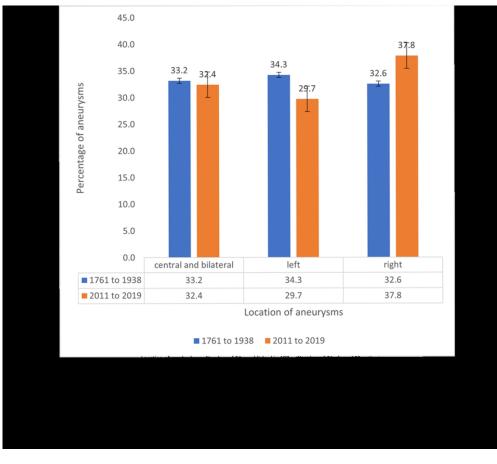


Figure 1 - Comparison of the location of cerebral aneurysms between Royal Adelaide Hospital sample (2011 to 2019) (n=135 CAs from 102 patients, orange colour) with those recorded in 407 publications[14] (1761 to 1938) (n=1127 CAs, blue colour). CAs=cerebral aneurysms, 14 = McDonald, CA & Korb, M 1939, Intracranial aneurysms, Archives of neurology and psychiatry (Chicago), vol. 42, no. 2,

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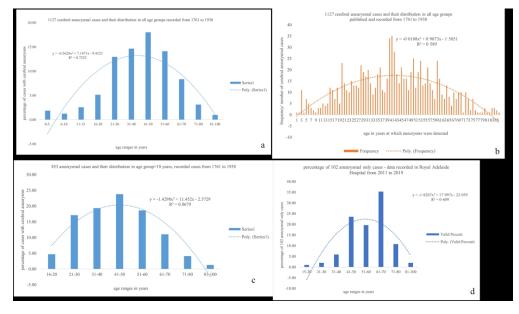


Figure 2 - Figures displaying the distribution patterns of cerebral aneurysms in different age groups recorded from 1761 to 1938 and from 2011 to 2019. A polynomial regression lines show the number and distribution of cerebral aneurysm cases across all age groups. a) The distribution of cerebral aneurysmal cases (n=1127) in various age group, recorded from 1761 to 1938.[14] b) The frequency of cerebral aneurysmal cases and their distribution (n=1127) across all age groups recorded14 from 1761 to 1938. c) Age (≥18 years) related distribution of individuals affected with cerebral aneurysms over the past 260 years (1761 − 1938) (n=853), recorded14 from 1761 to 1938, and d) Age (18-100 years) related prevalence (%) of cerebral aneurysms in RAH sample from 2011 to 2019 (n=102). The peak prevalence occurred between 31-60 years (p<0.001). RAH= Royal Adelaide Hospital. RAH= Royal Adelaide Hospital and 14 = McDonald, CA & Korb, M 1939, Intracranial aneurysms, Archives of neurology and psychiatry (Chicago), vol. 42, no. 2, pp. 298-328.

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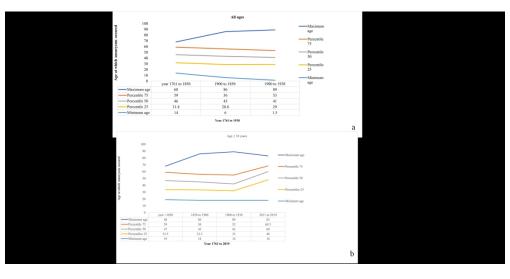


Figure 3: Comparison figures showing the trend of occurrence of cerebral aneurysms at different age groups (n=1127) from 1761 to 2019. (a)The values of the 25th, 50th, and 75th percentiles, as well as the minimum and maximum observed all ages of patients with aneurysms, from 1761 to 1938[14]; b) The values of the 25th, 50th, and 75th percentiles, as well as the minimum and maximum observed patients with >18 years of age with aneurysms, recorded from 1761 to 193814 and 2011 to 2019 in RAH. RAH = Royal Adelaide Hospital, 14 = Data from: McDonald, CA & Korb, M 1939, Intracranial aneurysms, Archives of neurology and psychiatry (Chicago), vol. 42, no. 2, pp. 298-328

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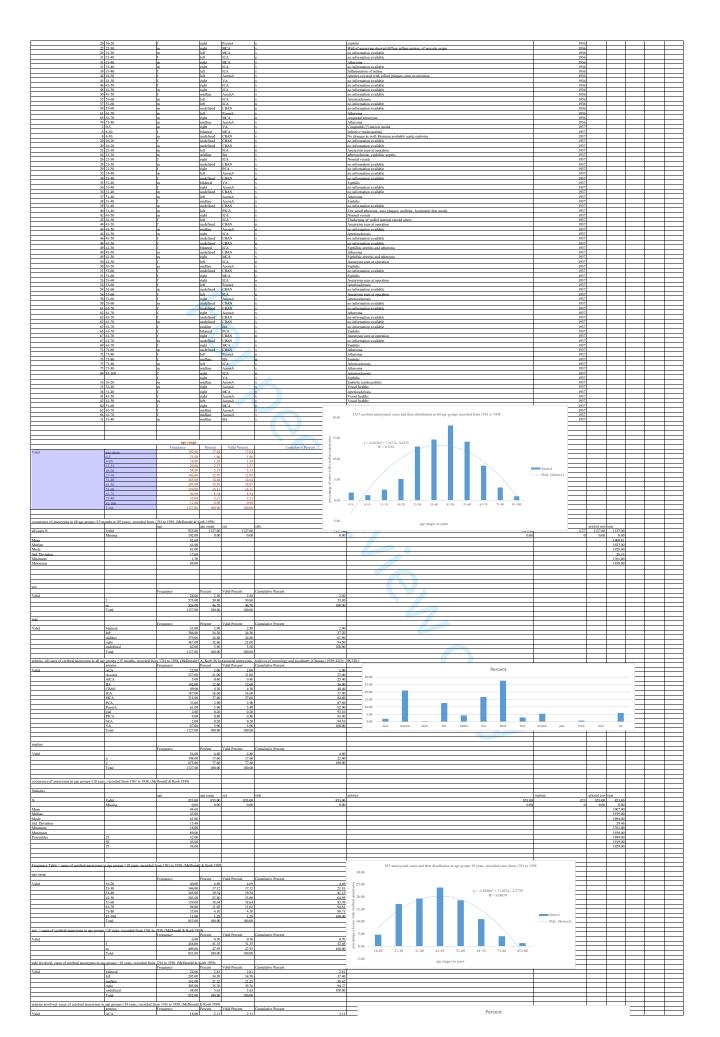
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62 61-70 34 31-40 35 31-40	f m	right PcomA left PcomA left ICA	y v	no information available no information available no information available	1846 1847 1847				=
52 51-60 33 31-40	f m	left ICA midline BA midline BA	y n	habity arteries no information available no information available	1848 1849 1849				
35 31-40 33 31-40	m f	midline BA undefined ICA	y y	Other arteries healthy No calcareous deposit in cerebral vessels	1845 1845				
18 16-20 30 21-30	m f	undefined VA left PcomA midline BA	n y	Calcarcous deposit in wall of sac No. fatty afteromatous changes in atteries Other vessels without changes	1849 1850 1850				=
39 21-30 70 61-70 20 16-20 21 21-30	r r	left ICA undefined PCA	n n	Outer vessels wearder the vessels vessels of the vessels vesse	1850				H
35 31-40 38 31-40	m m	midline AcomA left MCA midline BA	y n	no information available no information available	1851 1851 1851		╧	╧	\blacksquare
45 41-50 65 61-70	m m	midline BA undefined ICA	n n	no information available no information available	1851 1851 1851				\blacksquare
	r	midline BA midline BA undefined MCA	n y	no information available no information available no information available	1851 1851		₽		Ħ
53 51-60 56 51-60 57 51-60	f m	midline BA right PCA right MCA	y y	no information available no information available Vessels ver abbreomatous	1855 1855 1855	H	+=		柙
70 61-70	f m	midline BA left MCA	n y	no information available Arteries not atheromatous	1855 1855		1		\blacksquare
35 31-40 40 31-40 52 51-60	f r	midline BA left PCA right ICA	n y	no information available Vessels this part healthy Middle coat thickened	1856 1850 1857		\pm		=
\$2 \$1.60 47 \$1.50 \$4 \$1.60	r m	left ICA midline BA right SCA	y n	no information available Vertebral arteries thickened	1858 1859 1859				Ħ
56 51-60 60 51-60 17 16-20	ſ	midline AcomA left MCA	y y	Atheroma Vessels thickened and rigid Finholic	1858 1859				\blacksquare
30 21-30 34 31-40 35 31-40	m f	left MCA midline BA left ACA	y y	no information available Healthy vessels Healthy vessels	1855 1855 1855		ᆂ	<u> </u>	
43 41-50 58 51-60 16 16-20	f m	midline BA left MCA	y y	Atheroma Atheroma in information available	1855 1855 1860				\blacksquare
24 21-30 47 41-50	m f	midline BA midline BA	y n	embolic Plates in coats of aneurysm	1860 1860				
24 21-30 14 11-15. 42 41-50	m m	right MCA left MCA midline BA	y y	Walls of sac calcureous Walls of sack thick and atherematous no disease of other vessels Vessels otherwise healthy	1861 1862 1862				
48 41-50 56 51-60	r m	midline BA midline BA	n n	reside (outer as mission of the control of the cont	1862 1862				
68 61-70 80 71-80 28 21-30	r m	left MCA midline AcomA midline BA	n v		1862 1862 1864				=
28 21-30 37 31-40	m.	undefined AICA	ý	Healthy vessels Online vessels slightly afteromatous Afteroma	1864 1864				
16 16-20 24 21-30 39 31-40	m m	left ICA left MCA midline BA	y y	Vessels healthy Soft arteries No afteroma	1865 1865 1865				=
43 41-50 46 41-50	r r	left ICA left ACA	y n	Walls atheromatous Vessels very atheromatous	1865 1865				
49 41-50 51 51-60 53 51-60	f m	midline AcomA midline BA left MCA	y y	Other attries healthy Attries not diseased Walls not atheronatous	1865 1865 1865				
59 51-60 21 21-30	f m	right MCA left ACA left MCA	y y	no information available	1865 1865 1866				=
61 61-70 27 21-30	f f	left VA left ICA	y y	No disease of specific so information withhole so information withhole Antress thicknead	1866 1867				-
29 21-30 78 71-80 13 11-15.	f m	left MCA right MCA right MCA	y y y	no information available No afteriorna No afterioris healthy	1867 1867 1868				=
24 21-30 34 31-40 36 31-40	r r	left ICA left MCA midline BA	y n	no information available Walls of ancursantileromatous vessels at base not diseased Old endocardisis ouestionable embole orinin	1868 1868 1868				
40 31-40 40 31-40	m m	left ACA left MCA	y y	Small atheromatous patches on wall Vessels normal	1869 1869				
50 41-50 53 51-60 56 51-60	r r	left MCA left PcomA right MCA	n y n	Thick and opeque, but not materially diseased Slightly atheromations Arteries selected, with atheromations plates	1868 1868 1868				=
\$6 \$1.60 \$9 \$1.60	m f	midline BA	y y	Vessels very atheromatous Atheroma	1868 1868				
60 51-60 14 11-15. 19 16-20	f m m	inght MCA left ICA left VA	y v	Vessels very atheromatous Other ressels healthy as information a validable	1869 1865 1865				=
28 21-30 41 41-50 48 41-50	m f	left MCA right MCA left MCA	y y	no information available no information available Africoma	1865 1865 1865				
56 51-60 61 61-70	m f	right ICA midline BA	y n	Several patches ofdegeneration onbasilar artery Vessels atheromatous	1865 1865				
12 11-15. 13 11-15. 15 11 15	f m	right MCA right MCA right MCA	y y	Embolic occlusion (endocarditis) Other vessels healthy; embolic origin of ancurysm Embolic origin	1870 1870				
15 11-15. 17 16-20 20 16-20	ſ	right ACA	y y	Embolic origin Vesuck healthy Embolic origin Vesuck origin Vesuck origin Vesuck plauged by vellow fibrin (vegetations on nortic valves)	1870 1870 1870				=
26 21-30 26 21-30 26 21-30	m f	left MCA midline BA right MCA	n v	Vessel phaged by vellour fibria (vegetations on aortic valves) Romaining vessels healthy Stybilitie besions on information available	1870 1870 1870		╧	╧	\blacksquare
26 21-30 35 31-40 37 31-40 49 41-50	m	right MCA undefined PCA midline BA midline BA	n y	Calcareous degeneration of coats of vessel	1876 1870 1870 1870				丰
50 41-50 60 51-60	r	left PCA	y y	no information available Slight atheromations patches Vessels diseased	1870				=
67 61-70 54 51-60	m f	right VA midline AcomA left MCA	y y	Afteroma Afteromatous Arteries at base highly Afteromatous	1870 1871 1871				+1
29 21-30 45 41-50 61 41-70	m m	midline BA left VA	y y	Other arteries at base atheromatous Slight atheromatous changes	1872 1872				\blacksquare
61 61-70 20 16-20 20 16-20 24 21-30	f m	midline BA right PcomA undefined CBAN undefined CBAN	y y	Vessels atheromatous Embolic Embolic	1872 1873 1873				\blacksquare
	m m	undefined CBAN	y y	Embolic arachnoidiós Perforated embolized wall of small arach noid artery Embolic	1873 1873 1873				=
40 33-40 68 61-70	m m	midline AcomA	0.00	W alis hick : other vessels healthy Vessels thickened so information available	1873 1874				\blacksquare
24 21-30 33 31-40 40 31-40	m f	miline BA undefined ICA left ICA right ICA	n n	Marked arteriosclerosis Walls of sac partly calcified	1875 1875 1875				\blacksquare
43 41-50 45 41-50 45 41-50	en en	right MCA midline AcomA left MCA	y y y	no information available Arteries slightly afteromatous Vessels normal	1875 1875 1875				=
46 41-50 53 51-60	m f	bilateral ICA left ICA	n y	Intimai arteriosclerosis Walls thick and atheromatous	1875 1875				\blacksquare
56 51-60 60 51-60 69 61-70	f f	left VA undefined SCA midline AcomA	y n	no information available Intense atheroma of vessels Vessels atheromatous	1875 1875 1875			1	\blacksquare
34 31-40 34 31-40	f m	right MCA	y y	no information available no information available	1876 1876				\blacksquare
41 41-50 50 41-50 63 61-70	r r	right MCA right ICA	y y	Rest of atteries free of atheroma Ahdrooma no information available	1876 1876 1876				=
16 16-20 18 16-20	m f m	midline BA right MCA midline AcomA	n y	no information available No other disease of vessels	1877 1877 1877				± 1
20 16-20 22 21-30 40 31-40	f f	midline AcomA left ICA right MCA	n y	Vesiels healthy, probably embotic Healthy vesiels	1877				Ħ
40 31-40 42 41-50 53 51-60	m f	left MCA right MCA midline BA	y n	Vessels at base healthy Arteries tortuous andsmall in caliber; deposits of calcareous degeneration iso information available	1877 1877 1877				=
12 11-15. 30 21-30 47 41-50	m m	right PCA left ICA right MCA	y n v	Embolic (endocarditis) Thickening of vessels, with syphilitic infil tration of small cells Very atheromatous	1878 1878 1879	H	=		Ħ
50 41 50	r	right ACA left MCA	n y	All arteries and ancurysm white and opaque:microscopic syphilitic changes of Heubner Vessels atheromatous	1878 1878		₽		=
20. 31-20 72. 71-30 20. 16-20 36. 31-40 39. 31-40	m m		y y	Not afteromatous Thickened wallic endarteritis no information available	1880 1880 1880				
39 31-40 40 31-40 44 41-50 55 51-60	f m	right MCA midline AcomA midline BA	y y	Afteroma no information available	1880 1880 1880		1		
57 51-60 75 71-80	m f	left MCA midline BA midline BA	y n	SSIF and atheromatous Afteromatous vesich at base Anticomatous Anticomatous	1880 1880		\pm		=
12 11-15. 40 31-40 44 41-50	m f	left MCA left PoomA midline BA	y y	Wall of sac atherona tous; other vessels healthy Healthy vessels no information available	1881 1881 1881				Ħ
50 41-50 73 71-80	r r	midline AcomA right ICA	y n	no information available Very atheromatous	1881				\blacksquare
80 71-80 16 16-20 17 16-20	m m	right PcomA midline BA midline AcomA	n y y	Wall thickned no information available Healthy	1881 1882 1883				\pm
40 31-40 61 61-70	m f	midline BA undefined ICA	y n	Afteroma no information available	1883 1883				otan
	r	left VA undefined CBAN left MCA	y y	Fatt depotential of a fatter than the fatter t	1884 1884 1885		ŧ		=
29 21-30 40 31-40 21 21-30 22 21-30	m r	left MCA left MCA left ICA	n V	Calcarcous clot in sac Syphilisic Walls hard: no atheromatous degeneration	1885 1886 1886				± 1
					1880				

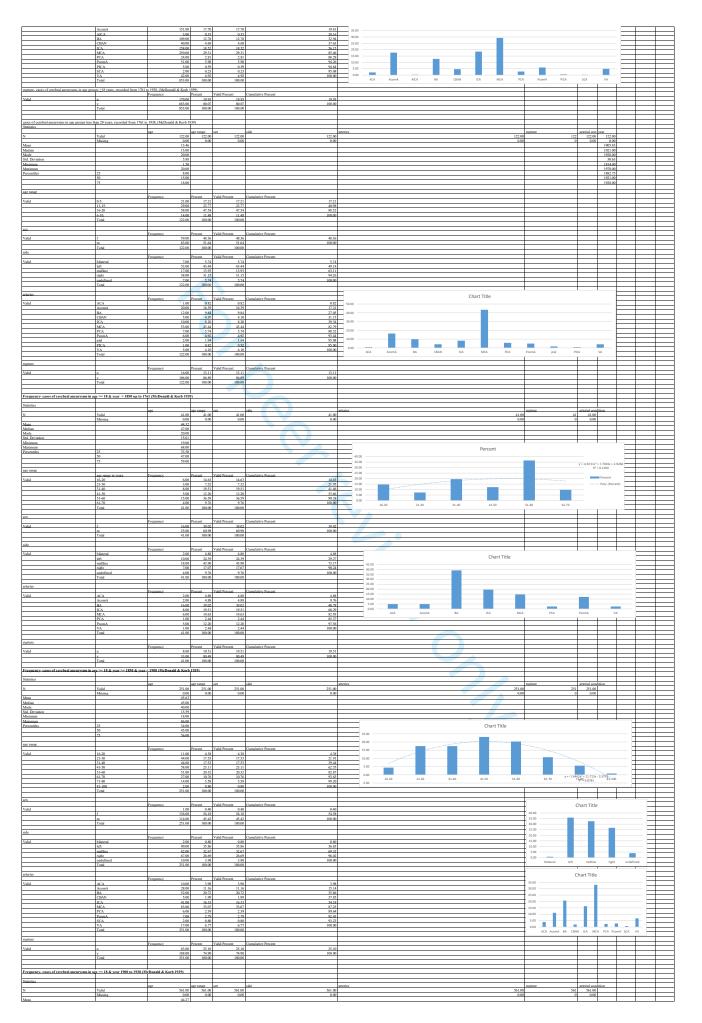
20	21-30	m midline	BA	Tue .	Syphilitic	1	886			
	16-20 21-30	f left right	MCA VA	y v	Symmole Embolic (endocarditis)	1	887 887	-		
30	21-30	m right m right	MCA ICA	y n	Embolic (endocarditis) ass information available No embolism or atherous		887 887 887			
40	31-40 31-40	m midline f right	BA MCA	y y	No embolism or atheroma	1	887			
49	41-50 41-50	f right f undefined	PCA CBAN	n V	Arteries free of atheroma Embolic (endocarditis)	li li	887 887			
60	51-60	f left left undefined	MCA VA	n n	no information available Atteriosclerosis Atteriosclerosis	1	887 887 887			
- C	\$1-60	undefined	VA VA			1	887 888	=	=	
26	21-30 41-50	f midline m midline m midline	BA AcomA		no information available Septic endocarditis no information available	1:	889 889	—	=	
51	51-60 51-60	m midline f midline	AcomA AcomA	y y	Arteries free of atheroma Arteriosclerosis	11	889 889			
6	6-10. 11-15.	m right m right	VA PCA	y n	Septic embolus Septic embolus endocarditis	1	890 890			
15 15	11-15. 11-15.	m right m	MCA MCA	n n	Septic embolus endocarditis Septic embolus endocarditis	1	890 890			
15 15	11-15. 11-15. 16-20	f bilateral right	MCA MCA	y y	Septic embolus endocarditis Septic embolus endocarditis	1	890 890 890			
		f right m left	ICA	y n	Septic embolus Septic embolus endocarditis	1	890			
18 25	16-20 21-30	m right	MCA MCA	y n	Septic embolus Septic embolus endocarditis	li li	890 890			
25 25	21-30 21-30 21-30	m left f	MCA MCA MCA	y v	Septic embolus endocarditis Atheroma Septic embolus endocarditis		890 890 890	<u> </u>	=	
25	21-30 21-30 31-40	f right m right	MCA MCA	y y	Septic embolus endocarditis Septic embolus endocarditis Septic embolus	1	890 890	<u> </u>	=	
35	31-40 31-40	f left m left	MCA MCA		Septic embolus endocarditis Afteroma	1	890 890			
45	41-50 41-50	f left	MCA MCA	y	resociotas Afecroma Afecroma	1	890 890	—	=	
50	41-50 51-60	m left	MCA ICA	y n	Americana Septic embolis Afteroma	1:	890 890	—	=	
60	61-70 51-60	m right f midling	ICA BA	n n	Afteroma	II II	890 891			
47	31-40 41-50	m midline m left	BA MCA	y n	Other vessels healthy No atheroma	11	892 893			
7 10	6-10. 6-10.	m midline f left	BA VA	y y	no information available no information available	11	894 894			
25	11-15. 21-30	m left m midline	VA BA	y y	no information available	li li	894 894			
26 26	21-30 21-30 21-30	f right m right	ICA ICA MCA	y y	Soft arteries no information available	li li	894 894			
		f left m midline	AcomA	y y	no information available no information available		894 894			
29 30	21-30 21-30 21-30 31-40	f left f right m midline	MCA MCA AcomA	y y	no information available no information available no information available	I I	894 894 894			
32	31-40 31-40 31-40	f left midline	MCA	y	no information available no information available		894 894	=		
32	31-40 31-40	m midline	BA BA	y y	no information available	1	894	=		
36	31-40 31-40 31-40	f midline m left f midline	ACA BA	y v	no information available no information available no information available	I I	894 894 894	—	=	
40	31-40 31-40 41-50	m midline m right	AcomA VA	y v	no morrantes available no information available no information available	1:	894 894	E^-		
42	41-50 41-50 41-50	f left m left	ICA MCA	y y	no information available no information available	13	894 894	E		
42 43	41-50 41-50	m midline right	BA ICA	y y	no information available	1	894 894	E		E
43 43	41-50 41-50	m left m left	VA MCA	y y	no information available no information available	1	894 894			E
43 43	41-50 41-50	m right m undefined	MCA CBAN	y y	no information available no information available	11	894 894			
45	41-50 41-50	f midline f left	AcomA MCA	y y	no information available no information available	1:	894 894	Ħ	Ħ	$= \mathbb{F}$
45 45	41-50 41-50 41-50	f midline m left	AcomA ICA	y y	no information available no information available	1	894 894			
46	41-50	f midline m right	BA MCA MCA	y	no information available no information available no information available		894 894	<u> </u>	=	=
48	41-50 41-50	m right	ICA	y y	no information available	I I	894 894			
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50	41-30 41-30 41-30	f right	MCA MCA	y y	no information a valiable no information available	1:	894 894	—		
51 52	51-60 51-60	m left f right f left	MCA MCA	y y	no information available no information available	1	894 894	—	\blacksquare	\vdash
53	51-60 51-60	f left f midline	MCA AcomA	y y	no information available no information available	1:	894 894			
54	51-60 51-60	f midline m right	AcomA MCA	y y	no information available no information available	13	894 894	—	=	
55	51-60 51-60	f right m left	ICA VA	y y	no information available no information available	1:	894 894			
56	51-60 51-60	m midline f left	BA MCA	y y	no information available no information available	1	894 894			
56 57	51-60 51-60	f right f	MCA ACA	y y	no information available no information available no information available	1	894 894			
60	51-60 51-60	f midline f left	AcomA VA	y y	no information available	1:	894 894			
60	51-60 51-60 51-60	f left f	ACA ACA	y y	no information available no information available	1	894 894 894			
61	61-70	f left f midline	MCA BA	y	no information available no information available	13	894			
62	61-70 61-70 61-70	m right f midline f left	AcomA ACA	y	no information available no information available no information available		894 894 894	=		
63	61-70 61-70 61-70	f midline	AcomA ICA	y y	no information available no information available	1	894 894			
64	61-70	f midline	AcomA	y	no information available no information available	1	894 894			===
67	61-70	f left right	ICA ICA	y v	no information available	1	894 894	—	=	
69	61-70 61-70	f left right	ICA ICA	y v	no information a vanishbe no information available	1	894 894	—	=	
72	71-80 71-80	f left f right	VA ICA	y y	no information available no information available	1	894 894			
73	71-80 71-80	f left f right	MCA VA	y y	no information available no information available	1:	894 894			
73	71-80 71-80	f right f midling	VA AcomA	y y	no information available no information available	1	894 894			
80	71-80 71-80	f midline f right	BA ACA	y y	no information available no information available	1	894 894			
81 86	81-100 81-100	f left m midline	AcomA	y	no information available no information available	II II	894 894			
	21-30	f midline m right	CBAN ICA	y	no information available other vessels healthy	1	894 895			
34	21-30 31-40	m midline f left	BA ICA	y y	no information available Wall of ancuryam had two patches of atheroma	11	895 895	=	=	
	31-40 41-50 41-50	f right	MCA MCA	y	no information available no information available no information available		897 897			===
53	51-60 61-70	m left	MCA ICA	y n	no information available no information available		897 897	—	=	
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	51-60 61-70 21-30	f right	MCA	y	no information available	li li	898 898	ݪ		
68 10	61-70 6-10.	m midline	BA	n	Extensive sclerosis with atheromatous plaques Syphilitie	1	898 898 898 898	E		
27	11-15.	m left m left	VA pial	n n y	Extensive acleronis with athenomatous plaques Syphilitie Vessels athenomatous Embolic (endocarditis)	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	898 898 898 899 900			
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222 269 279 289 289 299 241 252 252 252 252 252 252 252 252 252 25	21-30 31-40 41-59 71-80 21-30 31-40 41-59 21-30 31-40 41-59 21-30 31-40 61-70 21-30 31-40		VA piid piid MCA BA MCA MCA MCA MCA MCA MCA MCA MCA MCA MC		Executive activates with attenuations places Solidish Sol	11 12 12 12 12 12 12 12 12 12 12 12 12 1	898 898 898 899 990 900 900 901 901 901 901 901 901 9			
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33 33 33 33 34 34 34 34 34 34 34 34 34 3	21-36 31-46 41-50 41-50 41-50 31-40 31-40 31-40 31-40 31-40 41-50 31-40 41-50	March March	YA		Executive actions with determination players Fractions: Fraction		\$398. \$398. \$398. \$399. \$399. \$399. \$390. \$390. \$390. \$300. \$3			
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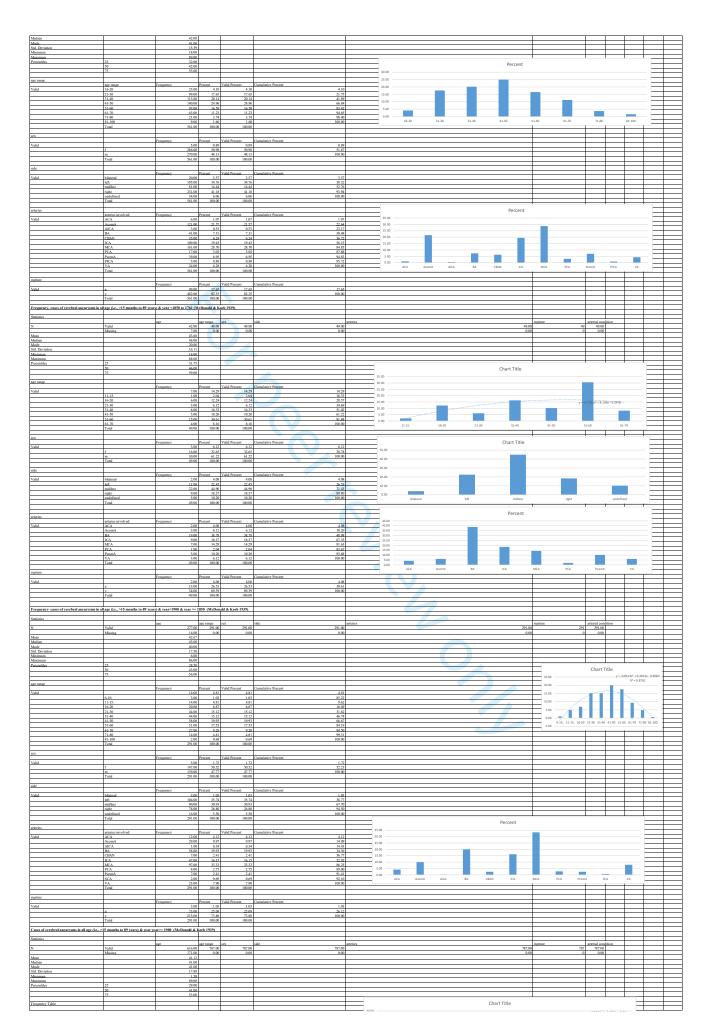
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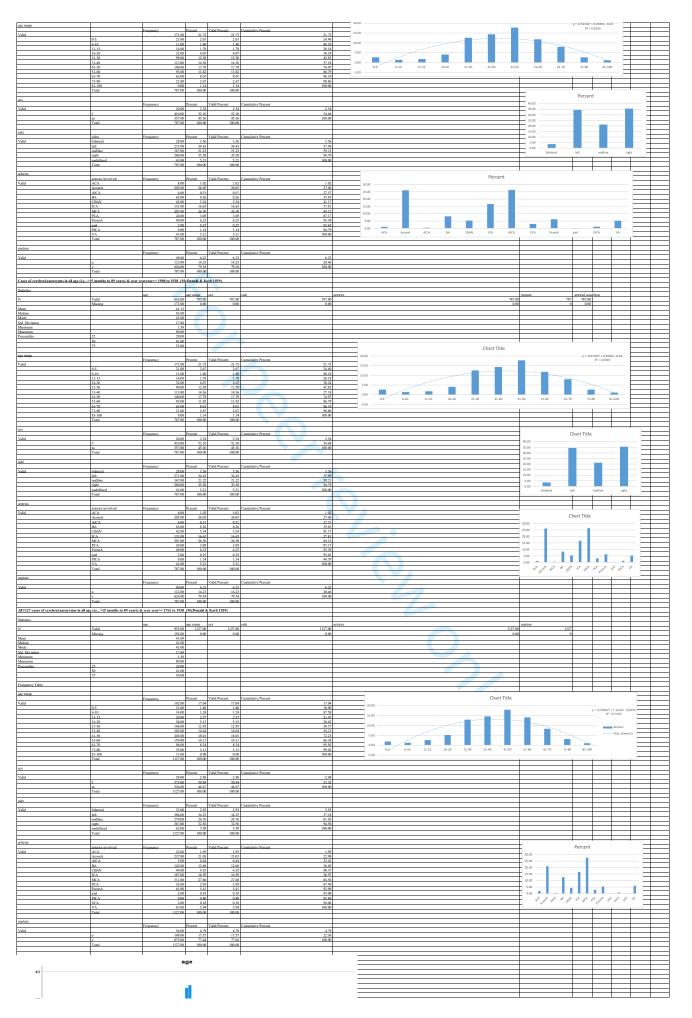
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31	31-40 31-40	f f	left left left	AcomA AcomA	y no information available y no information available y in information available	1928 1928				
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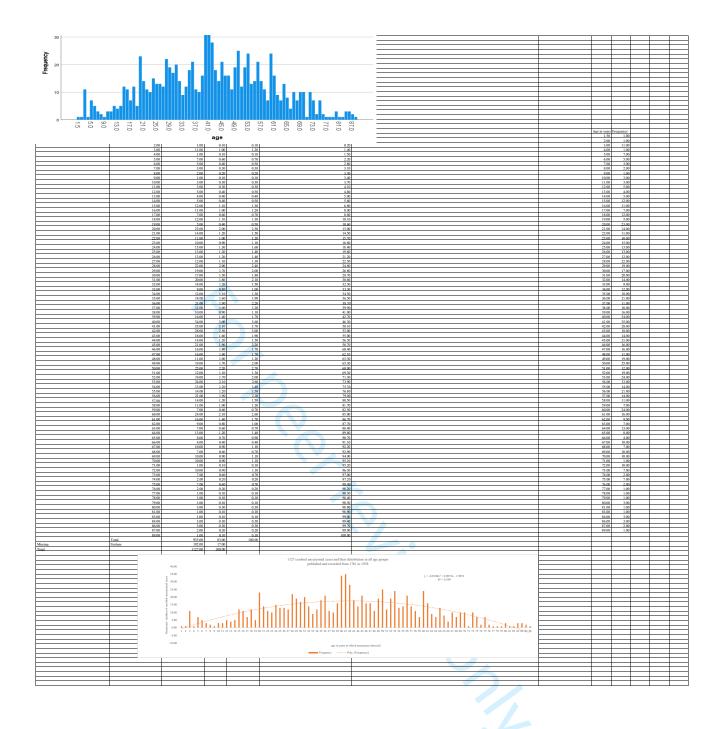
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30	21-30	m f	undefined right	CBAN PoomA	y y	no information available No other pathologic changes	1	928 929				
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47	31-40 41-50 51-60	r r	left right left	ICA PoomA ICA	y v		1	929 929				=
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77	71-80 11-15.	m r	midline left	BA MCA	y y	Afteroma Congenital ancurysm	- 1	930 931				
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31	21-30 31-40 31-40	f m	right right	PcomA MCA	y y	no information available	1	931				
33 34	31-40 31-40 31-40	r m	bilateral	AcomA PCA	y y	Congenital ancuryom Calcarcous deposits	1 1	931 931 931				
40	31-40	m f		ICA ICA	y y	Arterioselerosis Congenital aneurysm	1	931				
40	31-40 41-50 41-50	f r	left left right	AcomA MCA	y y	no information available Slight evidence of arteriosclerosis Atteriosclerosis Atteriosclerosis	1	931 931 931				
46	41-50 41-50 41-50	f f	left	PoomA ICA	y y	Artenisoelerosis Few yellow plaques on basilar artery Artenisoelerosis	1	931 931				=
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66	61-70 61-70	r r	right right	PcomA MCA	y y	Some thickening of Ibid. intima, probably of infectious origin Arterioselerosis	1	931 931				
66 70	61-70 61-70 71-80	m m	midline left midline	BA ICA	y y	Arteriosclerosis Arteriosclerosis Arteriosclerosis	1	931 931 931				
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24 25	21-30 21-30	m f	midline right	BA PcomA	y y	Mycotic No other abnormalities of vessels	1	932 932				
29	21-30 21-30	m	right	MCA PoomA	y y	Congenital aneuryim no information available		932 932				
30	21-30 21-30 31-40	r r	left bilateral	PCA MCA	n y	Arteriosclerosis Congenital aneuvam Diffuse decenerative chances in all three coats	1	932 932 932				
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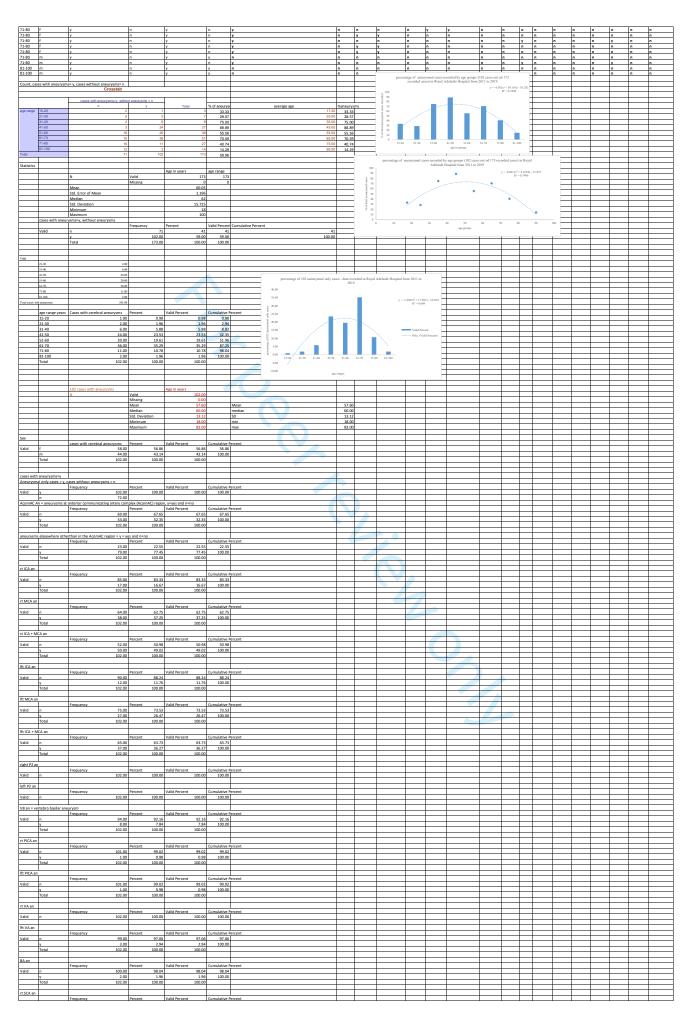
 Supplementary File 2: Statistical parameters of distributions of aneurysmal cases reported from 1761-1938 ¹⁴ and recorded in RAH from 2011 to 2019

1/61-1938	3, ^{±4} and re		RAH from 2							
		102	1127 patients	with cereb	ral aneurysi	ns recorded	l in 407 pub	lications - p	published fr	om 1761 to
		patients	1938							
		with								
		cerebral								
		aneurysmal								
		aneurysms								
		recorded in								
		RAH from								
		2011 to								
		2019								
Statistics -		age>18,	age>18	age >=	age >=	age >=	all age,	all age,	all	all age
all cases		2011 to	years, 1761	18 &	18 &	18 &	year	year <	ages,	group, all
with		2019	to 1938	year <	year >=	year >=	<1850	1900 &	year >=	years, >400
cerebral			()	1850	1850 &	1900		year >=	1900	publications
aneurysms			C		year <			1850		
			· ·		1900					
Age in										
years					Y ,					
N	Valid	102	851	41	252	560	42	278	613	935
	Missing	0	0	0	0	0	7	14	171	192
Mean age		57.6	44.7	44.3	45.6	44.3	43.6	42.6	41.2	41.7
Median		60.0	43.0	47.0	45.0	42.0	46.0	43.0	41.0	41.0
age										
Mode age		48.0	41.0	20.0	40.0	41.0	20.0	40.0	41.0	41.0
Std.		13.1	15.5	15.6	15.6	15.4	16.1	17.5	17.9	17.7
Deviation										
Minimum		18.0	18.0	19.0	18.0	18.0	14.0	6.0	1.5	1.5
age										
Maximum		83.0	89.0	68.0	86.0	89.0	68.0	86.0	89.0	89.0
age										
Percentiles	25	48.0	32.0	33.5	33.3	32.0	31.8	28.8	29.0	29.0
	50	60.0	43.0	47.0	45.0	42.0	46.0	43.0	41.0	41.0
	75	68.3	56.0	59.0	56.0	55.0	59.0	56.0	53.0	54.0

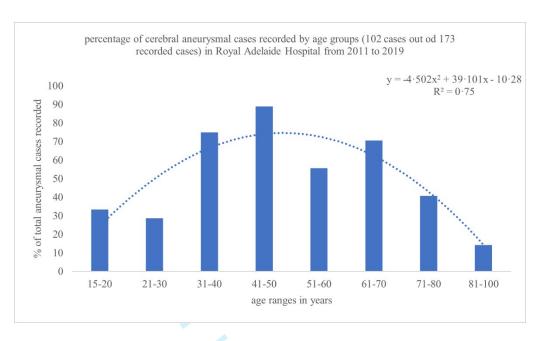
Legend: 14 = McDonald, CA & Korb, M 1939, Intracranial aneurysms, Archives of neurology and psychiatry

(Chicago), vol. 42, no. 2, pp. 298-328.

applementa	ry file 3: contains ty	type 2 data: The Human Ethics permit (ap perebral aneurysms over the past two cents	proval number: H2014-1 tries: Need for early sere	76, Research Ethics Commit ening - An observational stu	tee, Office of Ro	search Ethics, Compliance and Integrity, Faculty of Health Sciences, U	niversity of /	Adelaide) granti	ad permission to acce	ess and use t	he deidentified	data set from the Care	estream data re	gistry system	(Vue-R	IS-version-11	-0-14-35) for	research	_	H		_
ype 2 data bbreviatio	were Cerebral comp us: cases with cereb	puted tomography angiography images of bral aneurysms=y, cases without cerebral	stained from 173 randon aneurysms=n; cases with	nly selected patients, who vis hout cerebral aneurysms = y,	ited the Royal A cases with cerel	delaide Hospital (RAH) between January 2011 and December 2019 for real aneurysms = n ; aneurysmal only cases = y , cases withour aneurysm	a variety of is = n; Acom	cranial patholo AC An = aneur	gies rysms at anterior com	nmunicating	artery; n= no, y	r-yei										
ICA + MC	A an = ancurysms i	in right internal carotid and middle cereb	ral arterial region; lft ICA	A an = aneurysms in left inter	nal carotid arter	re otherthan in the AcomAC region = $y = yes$ and $n=no$; rt ICA an = ar y (Ift ICA) region; Ift MCA an =ancurysms in left middle cerebral artery y; VB an = ancurysm in vertebro basilarregion; rt PICA an = ancurysm	region; lft I	CA + MCA an	=aneurysms in left in	nternal caroti	d and middle o	rsms in right middle c crebral arterial region:	erebral artery	region;					<u> </u>			
PICA an	aneurysms in the l	left posterior inferior cerebellar (Ift PICA) region; rt VA an =aneu	arysms in the right vertebral	artery (rt VA); B	A an =ancurysms in the basilar artery region; rt SCA = ancurysms in th	e right super	ior cerebellar re	sgion; Ift SCA an =an	neurysms in	the left superior	r cerebellar region							\equiv			1
																			l			Ift SCA =aneurysm: in the left
																			ı			superior cerebellar
ge range 5-20	Sex m	cases with cerebral aneurysms=y,	cases without cereb	aneurysmal only cases :	AcomAC An		n	rt MCA an :	rt ICA + MCA an	lft ICA an :	lft MCA an	lft ICA + MCA an = n	right P2 an	n	n	rt PICA an	n	n	ift VA an =	= BA an =an n	rt SCA an	
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1-70 1-70 1-70	f f	n n	y y	n n	n n		n n	n n	n n	n n	n n	n n	n n		n n	n n	n n	n n	n n	n n	n n	n n
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1-100 1-100	m f	n n	y y	n n	n n	n n	n n	n n	n n	n n	n n	n n	n n	n n	n n	n n	n	n n	n n	n n	n n	n n
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1-50 1-50	f m	y y	n n	y y	y n	n Y	n n	n n	n n	n Y	n n	n y	n n	n n	n n	n n	n n	n n	n n	n n	n n	n n
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1-50 1-50 1-50	m f	y y	n n	y y	n n		n v	n v	n v	y n	n n	y y	n n	n n	n n	n n	n n	n n	n n	n n	n n	n n
1-50 1-50	f m	y y	n n	y y	n Y		n n	y n	y n	n n	n Y	n Y	n n		n n	n n	n n	n n	n n	n n	n n	n n
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1-60 1-60 1-60	f f	y y	n n	y y	y n_		n n	n y	n Y	n n_	n n	n n	n n		n n	n n	n n	n n	n n	n n	n n	n n
1-60 1-60	f m	у	n n	y y	n y	n	n	y n	y n	n n	n n	n n	n n	n	n n	n n	n n	n n	n n	n n	n n	n n
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1-60 1-60	m m	y	n n	y y	n Y	n	n n	y n	y n	n n	n n	n n	n n	n	n	n n	n n	n n	n n	n	n n	n n
1-60 1-60 1-60	f f	y	n n	y y	n n	y	n	n n y	n n	n n	y y n	y n	n n	n	n n	n n	n n	n n	n	n n	n	n n
1-60 1-60	f f	y y	n n	y y	n y	y y	y n	n Y	Y Y	n n	n y	n y	n n	n n	n n	n n		n n		n n	n n	n n
1-70 1-70	m f		n n	y y	n n			n Y	n Y	y n	n n	y n	n n		n n	n n	n n	n n	n n	n n	n n	n n
1-70 1-70 1-70	m f m	y y	n n	y y	n n		n n	y y y	y y	n n	n Y	n Y	n n	n n	n Y n	n n	n n	n n	n n	n n	n n	n y
1-70 1-70 1-70		v	n n	y y	n y	Ÿ		y y n	y y n	n n	n n	n n		n		n n					n n	n n
1-70 1-70	m f	У	n n	y y	y y	n Y	n n	n y	n Y	n n	n n	n n	n n	n n	n n	n n	n n	n n	n n	n n	n n	n n
1-70 1-70	f m	y y	n n	y y	n n	у	n n	y y	y y	n n	n -	y n	n n	n	n n	n n	n n	n n	n n	n n	n n	n n
1-70 1-70 1-70	m m	y	n n	y y	y y	n		n n	n n		n n	n n		n	n n	n n	n n	n n	n n		n n	n n
1-70 1-70	f f	У	n n	y y	n n	у	n	n n	n .		n n	y y	n n	n	n	n n	n n	n n			n n	n n
1-70 1-70	m f	y y	n n	y y	y y		n Y	n n	n Y	n n	n Y	n Y	n n		n n	n n	n n	n n	n n	n n	n n	n n
1-70 1-70 1-70	m f		n n	y y	n n	y y	n n	y y	n n	n n	n Y	n Y	n n	n n	n n	n n	n n	n n	n n	n n	n n	n n
1-70 1-70	f m	y y	n n	y y	n n	y y	n n	n n y	n .	n n	y y n	y n	n n	n n	n n	n n	n n	n n	n n	n n	n n	n n
1-70 1-70	f m	y y	n n	y y	n n	y y	y n	n Y	Y	n n	n Y	n Y	n n	n n	n n	n n		n n	n n	n n	n n	n n
1-70 1-70	f m		n n	y y	n n		n Y	n n	y y	n n	n n	n n	n n		n n	n n	n n	n n	n n		n n	n n
1-70	f m	y y	n n	y y	y y		n n	n n	n n	n n	n n	n n	n n	n n	n n	n n	n n	n n	n n	n n	n n	n n
	m f	У	n n	y y	n n	y y	n n	y n	y n	n n	y y	y y	n n	n n	n n	n n	n n	n n	n n	n	n n	n n
1-70		Iv.	in .	У	n		n	n	n	n	Y	у	n	n	n	n	n	n	n	n	n	n
1-70 1-70 1-70 1-70 1-70	f m	У	n	y	n	Y	n	n	n	n n	n	n n	n	n	y	n	n	n	v	n	n	n
1-70 1-70 1-70 1-70 1-70	f m f m	y y	n n	y y y	n y y n	n Y	n n	n y n	n y y	n n	n n n	n n n	n n	n n	n n	n n n	n n n	n n	n n	n n	n n n	n n n
1-70 1-70 1-70 1-70	f m m f	y y y y	n n	y y y y y	n y y n n	n Y Y Y	n n y n	n Y	n y y	n n n n	n n	n n n n	n n n	n n n	n n	n n n	n n n y	n n	n n n	n n n	n n	n n n



Valid	n	102.00	100.00	100.00	100.00											
Ift SCA an															L	
					Cumulative R										L	
Valid	n	101.00	99.02		99.02										Ь—	
	v	1.00	0.98	0.98	100.00											
	Total	102.00	100.00	100.00												
															Ь—	
age range	patients with (n=	102) and without aneurysms (n=71)														
		Frequency		Valid Percent	Cumulative 8	Percent									<u> </u>	
	15-20	3.00	1.70	1.70	1.70										<u> </u>	
	21-30	7.00	4.00	4.00	5.80										<u> </u>	
	31-40	8	4.6	4.6	10.4										<u> </u>	
	41-50	27	15.6	15.6	26										<u> </u>	
	51-60	36	20.8	20.8	46.8										<u> </u>	
	61-70	51	29.5	29.5	76.3										<u> </u>	
	71-80	27	15.6	15.6	91.9										<u> </u>	
	81-100	14	8.1	8.1	100										<u> </u>	
	Total	173	100	100											—	
															—	
Sex															<u> </u>	
		Frequency	Percent	Valid Percent	Cumulative F	Percent									—	
Valid	f	90	52	52	52										⊢—	
	m	83	48	48	100										⊢—	—
	Total	173	100	100											⊢—	
															⊢—	
															⊢—	
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<u> </u>	l													L	ь	



Supplementary File 4: The prevalence (%) of cerebral aneurysms observed over a broad age range (18-100 years, n=173, cases with aneurysms=102, cases without aneurysm=71), with a median of 62 years, a mean of 60 years, and a standard deviation of 15.75, is shown in the chart. The peak prevalence occurs between 31-60 years (p<0.001).

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract
		(indicated- line number 2 in the main document)
		(b) Provide in the abstract an informative and balanced summary of what was done
		and what was found (done, lines from 35 to 62)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
		(done, lines 81 to 95)
Objectives	3	State specific objectives, including any prespecified hypotheses (done, lines 94 to 98)
Methods		
Study design	4	Present key elements of study design early in the paper (line 101)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment,
20mg	J	exposure, follow-up, and data collection (not applicable)
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of
Tarticipants	O	participants (not applicable)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect
variables	,	modifiers. Give diagnostic criteria, if applicable (lines 125 to 140)
Data saurass/	8*	
Data sources/	8"	For each variable of interest, give sources of data and details of methods of
measurement		assessment (measurement). Describe comparability of assessment methods if there is
		more than one group (lines 102 to 117)
Bias	9	Describe any efforts to address potential sources of bias (the first author studied type
		2 data himself and as such biases were eliminated, The Human Ethics permit
		(approval number: H2014-176, lines 112 to 116)
Study size	10	Explain how the study size was arrived at (we used two sources of data, lines 102,
		103, 106 and 109, we had no influence upon changing sample sizes)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable,
		describe which groupings were chosen and why (lines 142 to 144, lines 135 to 140)
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding
		(lines 142 to 144)
		(b) Describe any methods used to examine subgroups and interactions (not
		applicable)
		(c) Explain how missing data were addressed (not applicable)
		(d) If applicable, describe analytical methods taking account of sampling strategy
		(not applicable)
		(e) Describe any sensitivity analyses (not applicable)
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially
1	-	eligible, examined for eligibility, confirmed eligible, included in the study,
		completing follow-up, and analysed (type 1 data already published, type two data
		participants, lines 106 to 117)
		(b) Give reasons for non-participation at each stage (not applicable)
		(c) Consider use of a flow diagram (not applicable)
Description 1-4	1 1 4	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and
		information on exposures and potential confounders (see table 1, line 213 to 218, and
		supplementary file 1 and supplementary File 2, and supplementary File 3)

		(b) Indicate number of participants with missing data for each variable of interest (not applicable)
Outcome data	15*	Report numbers of outcome events or summary measures (lines 151 to 201)
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and
		their precision (eg, 95% confidence interval). Make clear which confounders were
		adjusted for and why they were included (not applicable)
		(b) Report category boundaries when continuous variables were categorized (see the
		supplementary File 1, supplementary File 2 and supplementary File 3)
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a
		meaningful time period (not applicable)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and
		sensitivity analyses (not applicable)
Discussion		
Key results	18	Summarise key results with reference to study objectives (lines 239 to 241)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or
		imprecision. Discuss both direction and magnitude of any potential bias (lines 322 to
		324)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations,
		multiplicity of analyses, results from similar studies, and other relevant evidence (rest
		of the discussion, lines 246 to 298)
Generalisability	21	Discuss the generalisability (external validity) of the study results (line numbers 310
		to 317)
Other information		
Funding	22	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 (not applicable)

^{*}Give information separately for exposed and unexposed groups.

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.