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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.

Introduction

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 (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 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

individuals aged 30 to 60 years, and this age range has remained relatively unchanged over the past 260 years (Supplementary Table 1, Figures 1, 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 2).

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, $p \geq 0.36$) (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).

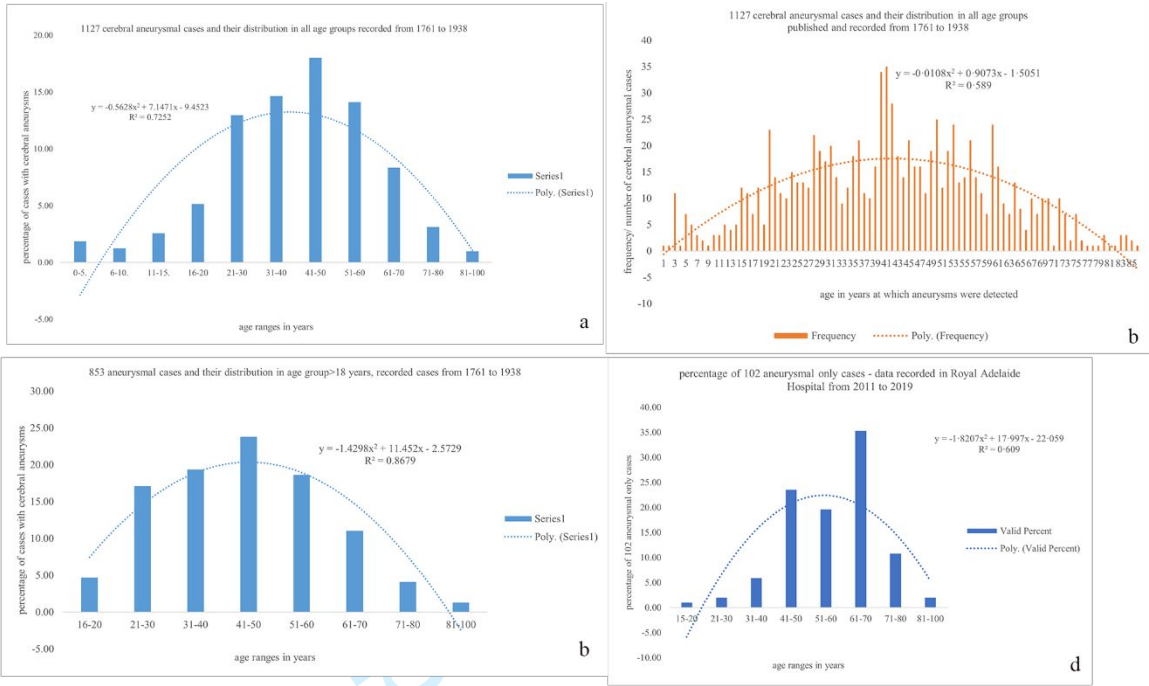


Figure 1- Figures displaying the distribution patterns of cerebral aneurysms in different age groups recorded from 1761 to 1938 and from 2011 to 2019. A polynomial regression lines show the number and distribution of cerebral aneurysm cases across all age groups. a) The distribution of cerebral aneurysmal 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.

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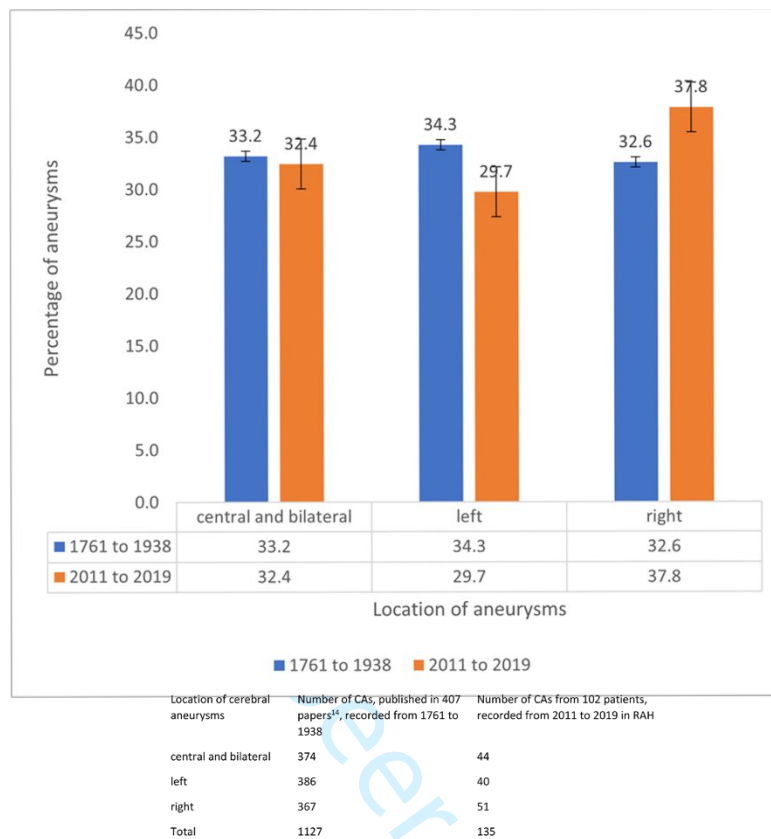


Figure 2- Comparison of the location of cerebral aneurysms between Royal Adelaide Hospital sample (2011 to 2019) (n=135 CAs from 102 patients, orange colour) with those recorded in 407 publications¹⁴ (1761 to 1938) (n=1127 CAs, blue colour). CAs=cerebral aneurysms, 14 = McDonald, CA & Korb, M 1939, Intracranial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

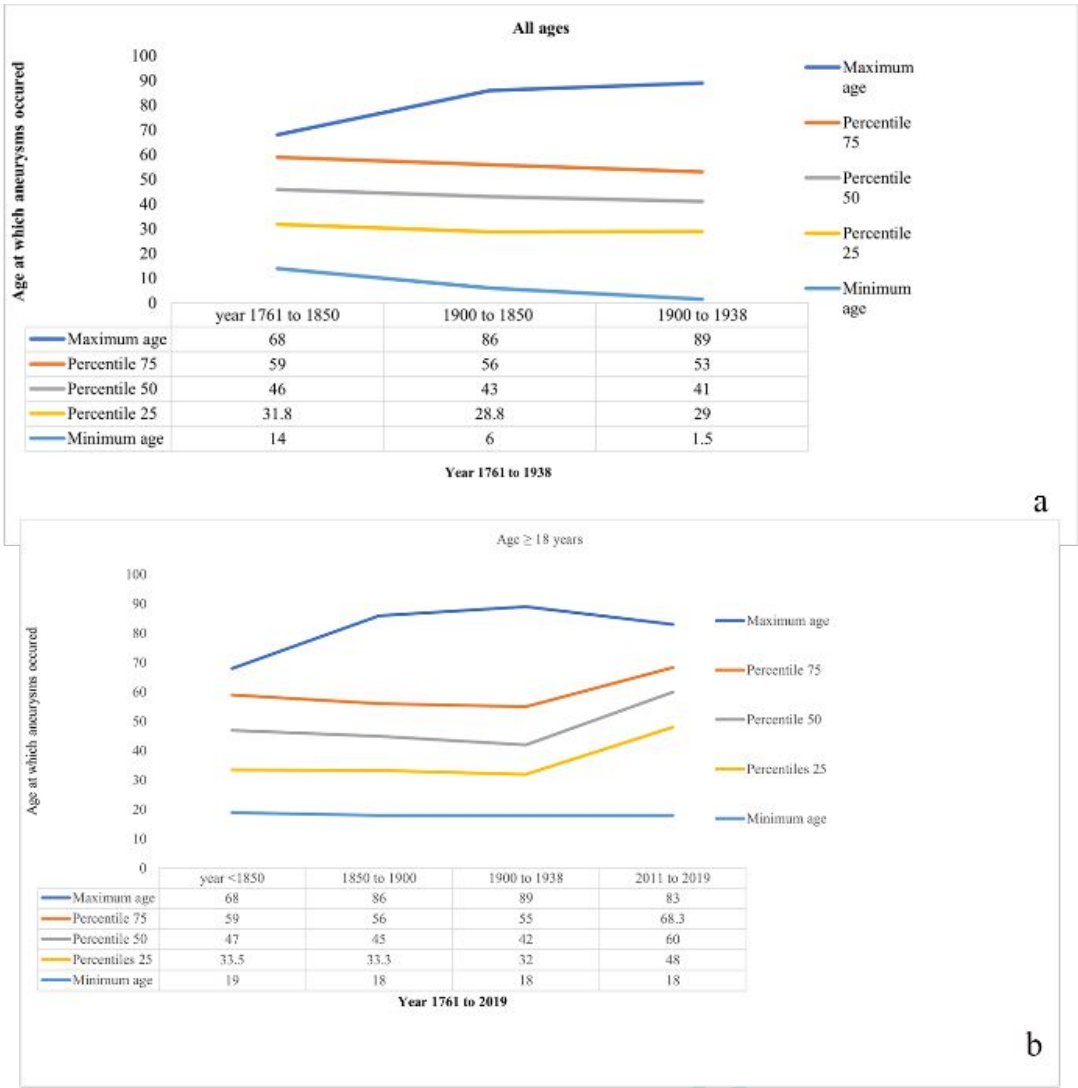
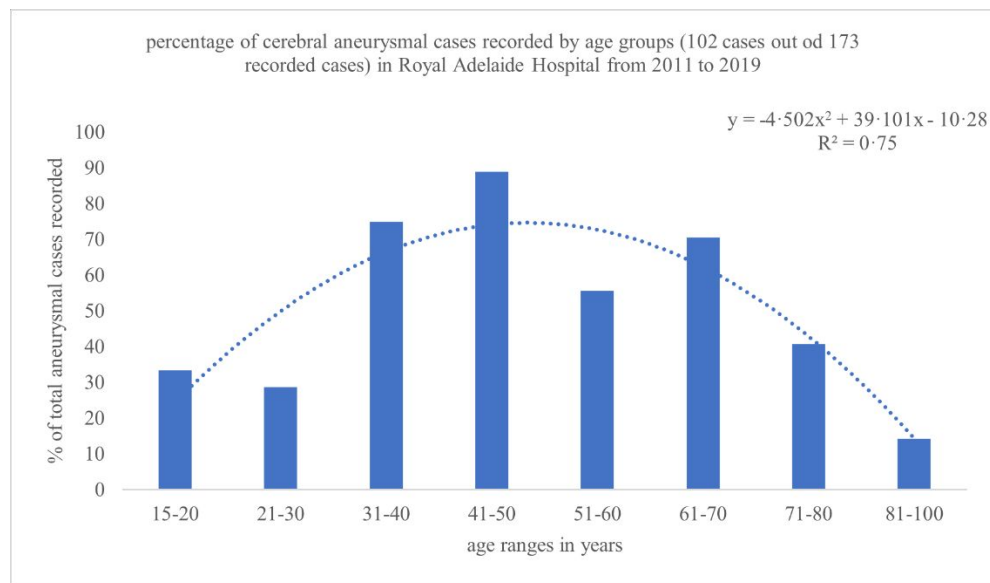


Figure 3: Comparison figures showing the trend of occurrence of cerebral aneurysms at different age group (n=1127) from 1761 to 2019. (a)The values of the 25th, 50th, and 75th percentiles, as well as the minimum and maximum observed all ages of patients with aneurysms, from 1761 to 1938¹⁴; b) The values 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

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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.

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

		102 patients with cerebral aneurysms recorded in RAH from 2011 to 2019	1127 patients with cerebral aneurysms recorded in 407 publications - published from 1761 to 1938							
Statistics - all cases with cerebral aneurysms		age>18, 2011 to 2019	age>18 years, 1761 to 1938	age >= 18 & year < 1850	age >= 18 & year >= 1850 & year < 1900	age >= 18 & year >= 1900	all age, year < 1850	all age, year < 1900 & year >= 1850	all ages, year >= 1900	all age group, all years, >400 publications
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	45.60	44.3	43.6	42.6	41.2	41.7
Median age		60.0	43.0	47.0	45.00	42.0	46.0	43.0	41.0	41.0
Mode age		48.0	41.0	20.0	40.0	41.0	20.0	40.0	41.0	41.0
Std. Deviation		13.1	15.5	15.6	15.6	15.4	16.1	17.5	17.9	17.7
Minimum age		18.0	18.0	19.0	18.0	18.0	14.0	6.0	1.5	1.5
Maximum age		83.0	89.0	68.00	86.0	89.0	68.0	86.0	89.0	89.0
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.

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 recorded¹⁴ 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.

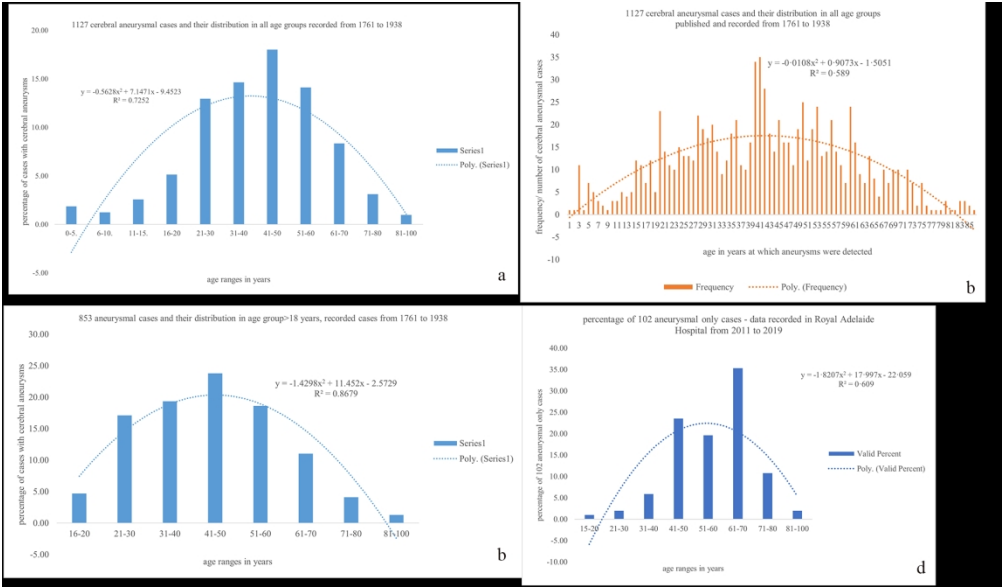
Ethical Approval Statement

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

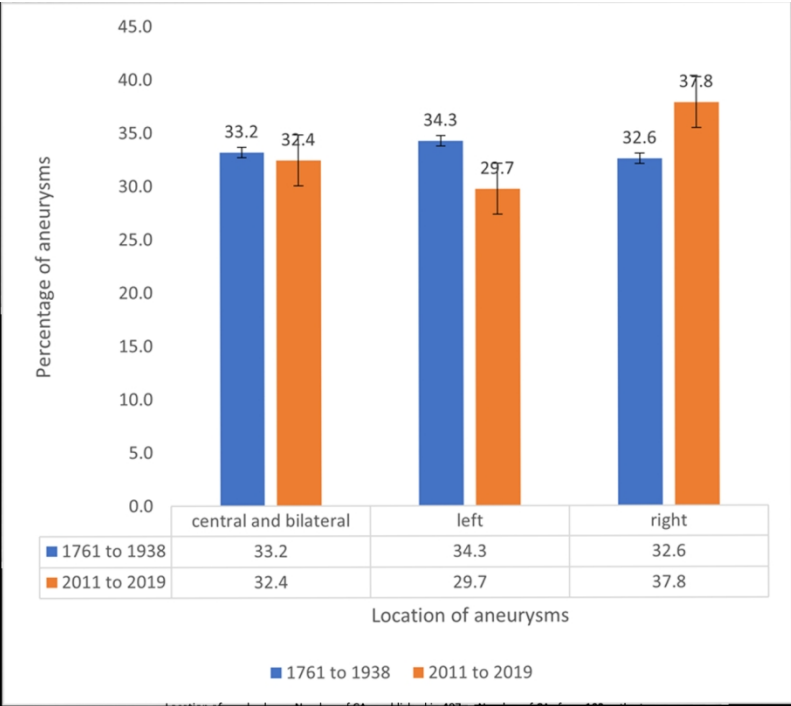
Reference

1. Burlakoti A, Kumaratilake J, Taylor J, Henneberg M. Relationship between cerebral aneurysms and variations in cerebral basal arterial network: A morphometric cross-sectional study in Computed Tomography Angiograms from a neurointerventional unit. *BMJ Open* 2021; 11: 1-8.
2. Menshawi K, Mohr JP, Gutierrez J. A Functional Perspective on the Embryology and Anatomy of the Cerebral Blood Supply. *Journal of stroke* 2015; 17(2): 144-58.
3. Mehrotra A, Nair AP, Das KK, Srivastava A, Sahu RN, Kumar R. Clinical and radiological profiles and outcomes in pediatric patients with intracranial aneurysms: Clinical article. *Journal of Neurosurgery: Pediatrics* PED 2012; 10(4): 340-6.
4. Roessler K, Cejna M, Zachenhofer I. Aneurysmatic subarachnoidal haemorrhage: Incidence and location of small ruptured cerebral aneurysms – a retrospective population-based study. *Wiener Klinische Wochenschrift* 2011; 123(13-14): 444-9.
5. Storrs BB, Humphreys RP, Hendrick E, Hoffman H. Intracranial aneurysms in the pediatric age-group. *Pediatric Neurosurgery* 1982; 9(5): 358-61.
6. Proust F, Toussaint P, Garniéri J, et al. Pediatric cerebral aneurysms. *Journal of neurosurgery* 2001; 94(5): 733-9.
7. Horikoshi T, Akiyama I, Yamagata Z, Nukui H. Retrospective Analysis of the Prevalence of Asymptomatic Cerebral Aneurysm in 4518 Patients Undergoing Magnetic Resonance Angiography. *Neurologia medico-chirurgica* 2002; 42(3): 105-13.
8. Froelich JJ, Neilson S, Peters-Wilke J, et al. Size and location of ruptured intracranial aneurysms: a 5-year clinical survey. *World neurosurgery* 2016; 91: 260-5.
9. Cadilhac DA, Carter R, Thrift AG, Dewey HM. Estimating the Long-Term Costs Of Ischemic and Hemorrhagic Stroke for Australia New Evidence Derived From the North East Melbourne Stroke Incidence Study (NEMESIS). *Stroke* 2009; 40(3): 915-21.
10. Jeong Y-G, Jung Y-T, Kim M-S, Eun C-K, Jang S-H. Size and location of ruptured intracranial aneurysms. *Journal of Korean Neurosurgical Society* 2009; 45(1): 11.
11. Korja M, Kivisaari R, Jahromi BR, Lehto H. Size and location of ruptured intracranial aneurysms: consecutive series of 1993 hospital-admitted patients. *Journal of neurosurgery* 2016; 127(4): 748-53.

12. Imaizumi Y, Mizutani T, Shimizu K, Sato Y, Taguchi J. Detection rates and sites of unruptured intracranial aneurysms according to sex and age: an analysis of MR angiography-based brain examinations of 4070 healthy Japanese adults. *J Neurosurg* 2018; 1(aop): 1-6.
13. Jordan LC, Johnston SC, Wu YW, Sidney S, Fullerton HJ. The Importance of Cerebral Aneurysms in Childhood Hemorrhagic Stroke: A Population-Based Study. *Stroke* (1970) 2009; 40(2): 400-5.
14. McDonald CA, Korb M. Intracranial aneurysms. *Archives of neurology and psychiatry* (Chicago) 1939; 42(2): 298-328.
15. Moore S, Simon JL. The greatest century that ever was. *New York Times* 1999.
16. McGuinness B, Chieng N, Skipworth C, Caldwell J, Molyneux A. Small ruptured cerebral aneurysms—do they rupture on formation or not? *Neuroradiology* 2022; 64(3): 597-602.
17. Long MT, Fox CS. The Framingham Heart Study-67 years of discovery in metabolic disease. *Nature reviews Endocrinology* 2016; 12(3): 177-83.
18. McCorry S, Miller J. *Literature and Meat Since 1900*. 1st 2019. ed. Cham: Springer International Publishing; 2019.
19. Alastruey J, Parker KH, Peiro J, Byrd SM, Sherwin SJ. Modelling the circle of Willis to assess the effects of anatomical variations and occlusions on cerebral flows. *J Biomech* 2007; 40(8): 1794-805.
20. Yoon NK, McNally S, Taussky P, Park MS. Imaging of cerebral aneurysms: a clinical perspective. *Neurovascular Imaging* 2016; 2(1): 1-7.
21. McGuinness B, Chieng N, Skipworth C, Caldwell J, Molyneux A. Small ruptured cerebral aneurysms—do they rupture on formation or not? *Neuroradiology* 2021: 1-6.
22. Brown RD, Broderick JP. Unruptured intracranial aneurysms: epidemiology, natural history, management options, and familial screening. *The Lancet Neurology* 2014; 13(4): 393-404.
23. Walendy V, Strauss C, Rachinger J, Stang A. Treatment of aneurysmal subarachnoid haemorrhage in Germany: A nationwide analysis of the years 2005-2009. *Neuroepidemiology* 2014; 42(2): 90-7.
24. Pasqualin A, Mazza C, Cavazzani P, Scienza R, DaPian R. Intracranial aneurysms and subarachnoid hemorrhage in children and adolescents. *Child's nervous system* 1986; 2(4): 185-90.
25. Matson DD. Intracranial Arterial Aneurysms in Childhood. *J Neurosurg* 1965; 23(6): 578-83.
26. Huisman TA, Poretti A. *Pediatric Neurovascular Imaging (CT/MRI/Ultrasound)*. *Pediatric Vascular Neurosurgery*: Springer; 2016: 77-109.
27. Krings T, Geibprasert S, Terbrugge KG. Pathomechanisms and treatment of pediatric aneurysms. *Child's Nervous System* 2010; 26(10): 1309-18.
28. Fung C, Mavrakis E, Filis A, et al. Anatomical evaluation of intracranial aneurysm rupture risk in patients with multiple aneurysms. *Neurosurgical review* 2019; 42(2): 539-47.
29. Verlhac S. Transcranial Doppler in children. *Pediatric radiology* 2011; 41(1): 153-65.



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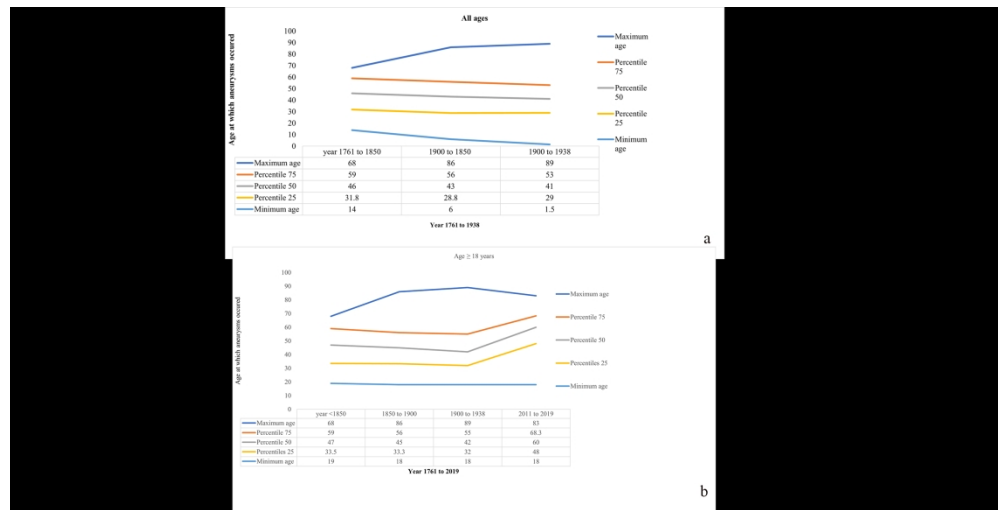
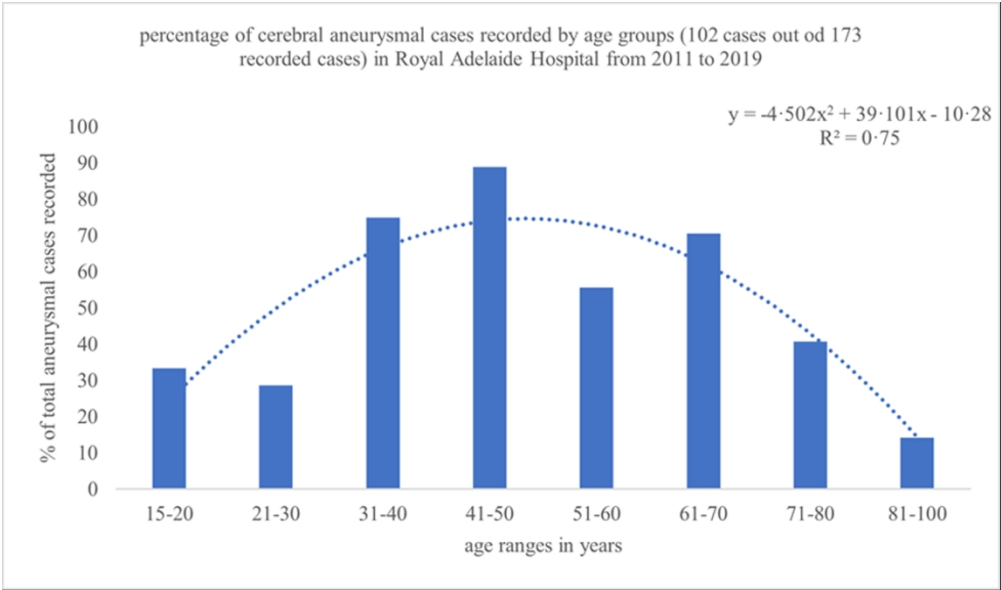


Figure 3: Comparison figures showing the trend of occurrence of cerebral aneurysms at different age groups (n=1127) from 1761 to 2019. (a)The values of the 25th, 50th, and 75th percentiles, as well as the minimum and maximum observed all ages of patients with aneurysms, from 1761 to 1938[14]; b) The 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 1938 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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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.

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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 1938							
		patients	1938							
		with								
		cerebral								
		aneurysmal								
		aneurysms								
		recorded in								
		RAH from								
		2011 to								
		2019								
Statistics - all cases with cerebral aneurysms		age>18,	age>18	age >=	age >=	age >=	all age,	all age,	all	all age
		2011 to	years, 1761	18 &	18 &	18 &	year	year <	ages,	group, all
		2019	to 1938	year <	year >=	year >=	<1850	1900 &	year >=	years, >400
				1850	1850 &	1900		year >=	1900	publications
					year <			1850		
Age in					1900					
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

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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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27 23-30	m	midline	BA	y	Syphilitic	1886
28 16-20	f	left	MCA	a	Embolic	1887
30 23-30	m	right	VA	y	Embolic (endocarditis)	1887
30 23-30	m	right	MCA	y	Embolic (endocarditis)	1887
31 11-15	m	right	ICA	a	no information available	1887
36 11-40	m	midline	BA	y	No embolism or atherosclerosis	1887
40 16-20	f	right	MCA	y	No embolism or atherosclerosis	1887
43 41-50	f	right	PCA	a	Arteries free of atherosclerosis	1887
49 41-50	f	undefined	CBAN	y	Embolic (endocarditis)	1887
60 51-60	f	left	MCA	y	no information available	1887
		left	VA	a	Arteriosclerosis	1887
		undefined	VA	y	Arteriosclerosis	1887
53 51-60	f	midline	BA	a	Arteriosclerosis	1887
26 23-30	m	midline	BA	a	Septic endocarditis	1889
43 41-50	m	midline	AortaA	a	no information available	1889
51 51-60	m	midline	AortaA	a	Arteries free of atherosclerosis	1889
56 51-60	m	midline	AortaA	a	Arteriosclerosis	1889
6 6-10	m	right	VA	y	Septic embolus	1890
15 11-15	m	right	PCA	a	Septic embolus endocarditis	1890
15 11-15	m	right	MCA	a	Septic embolus endocarditis	1890
15 11-15	m	right	MCA	a	Septic embolus endocarditis	1890
15 11-15	f	bilateral	ICA	y	Septic embolus endocarditis	1890
15 11-15	f	right	MCA	y	Septic embolus endocarditis	1890
16 16-20	f	right	MCA	y	Septic embolus endocarditis	1890
17 16-20	m	left	ICA	a	Septic embolus endocarditis	1890
18 16-20	m	right	MCA	y	Septic embolus endocarditis	1890
25 23-30	f	right	MCA	a	Septic embolus endocarditis	1890
25 23-30	m	left	MCA	a	Septic embolus endocarditis	1890
25 23-30	f	left	MCA	y	Atherosclerosis	1890
25 23-30	f	right	MCA	y	Septic embolus endocarditis	1890
25 23-30	m	right	MCA	y	Septic embolus endocarditis	1890
31 31-40	m	right	MCA	y	Septic embolus endocarditis	1890
35 31-40	f	left	MCA	a	Septic embolus endocarditis	1890
35 31-40	f	left	MCA	y	Atherosclerosis	1890
43 41-50	f	left	MCA	y	Atherosclerosis	1890
45 41-50	m	left	MCA	y	Atherosclerosis	1890
50 41-50	m	left	MCA	y	Septic embolus	1890
56 51-60	m	right	ICA	a	Atherosclerosis	1890
66 61-70	m	ICA	ICA	a	Atherosclerosis	1890
60 51-60	f	midline	BA	a	Atherosclerosis	1891
33 31-40	m	midline	BA	y	Other vessels healthy	1892
47 41-50	m	left	MCA	a	No atherosclerosis	1893
7 6-10	m	midline	BA	y	no information available	1894
10 6-10	f	VA	VA	y	no information available	1894
14 11-15	m	left	VA	y	no information available	1894
27 23-30	m	midline	BA	y	no information available	1894
26 23-30	f	right	ICA	y	Soft arteries	1894
26 23-30	m	right	ICA	y	no information available	1894
28 23-30	f	left	MCA	y	no information available	1894
28 23-30	m	midline	AortaA	y	no information available	1894
29 23-30	f	left	MCA	y	no information available	1894
30 23-30	f	right	MCA	y	no information available	1894
31 31-40	m	midline	AortaA	y	no information available	1894
32 31-40	f	left	MCA	y	no information available	1894
32 31-40	f	midline	BA	y	no information available	1894
32 31-40	m	midline	BA	y	no information available	1894
36 31-40	f	midline	PronA	y	no information available	1894
36 31-40	m	left	ACA	y	no information available	1894
40 31-40	f	midline	BA	y	no information available	1894
40 31-40	m	right	AortaA	y	no information available	1894
41 41-50	m	right	VA	y	no information available	1894
42 41-50	f	left	ICA	y	no information available	1894
42 41-50	m	left	MCA	y	no information available	1894
42 41-50	m	midline	BA	y	no information available	1894
42 41-50	f	right	ICA	y	no information available	1894
43 41-50	m	left	VA	y	no information available	1894
43 41-50	m	left	MCA	y	no information available	1894
43 41-50	m	right	MCA	y	no information available	1894
44 41-50	f	undefined	CBAN	y	no information available	1894
45 41-50	f	left	MCA	y	no information available	1894
45 41-50	f	midline	AortaA	y	no information available	1894
45 41-50	m	left	ICA	y	no information available	1894
46 41-50	f	midline	BA	y	no information available	1894
46 41-50	m	right	MCA	y	no information available	1894
46 41-50	m	right	MCA	y	no information available	1894
46 41-50	f	right	ICA	y	no information available	1894
48 41-50	f	right	ICA	y	no information available	1894
49 41-50	f	left	VA	y	no information available	1894
49 41-50	f	midline	PronA	y	no information available	1894
50 41-50	f	right	MCA	y	no information available	1894
50 41-50	m	left	MCA	y	no information available	1894
51 51-60	f	right	MCA	y	no information available	1894
52 51-60	f	left	MCA	y	no information available	1894
53 51-60	f	left	MCA	y	no information available	1894
53 51-60	f	midline	AortaA	y	no information available	1894
54 51-60	f	midline	AortaA	y	no information available	1894
54 51-60	m	right	MCA	y	no information available	1894
55 51-60	m	right	ICA	y	no information available	1894
55 51-60	m	left	VA	y	no information available	1894
55 51-60	m	midline	BA	y	no information available	1894
56 51-60	f	left	MCA	y	no information available	1894
56 51-60	f	right	MCA	y	no information available	1894
57 51-60	f	right	MCA	y	no information available	1894
57 51-60	f	right	ICA	y	no information available	1894
57 51-60	f	midline	AortaA	y	no information available	1894
60 51-60	f	left	VA	y	no information available	1894
60 51-60	f	left	ACA	y	no information available	1894
60 51-60	f	left	ACA	y	no information available	1894
60 51-60	f	left	ACA	y	no information available	1894
60 51-60	f	left	MCA	y	no information available	1894
61 61-70	f	midline	BA	y	no information available	1894
61 61-70	m	right	ICA	y	no information available	1894
62 61-70	f	midline	AortaA	y	no information available	1894
62 61-70	f	left	ACA	y	no information available	1894
63 61-70	f	midline	AortaA	y	no information available	1894
64 61-70	f	left	ICA	y	no information available	1894
64 61-70	f	midline	AortaA	y	no information available	1894
65 61-70	f	left	ICA	y	no information available	1894
67 61-70	f	left	MCA	y	no information available	1894
67 61-70	f	right	ICA	y	no information available	1894
69 61-70	f	left	ICA	y	no information available	1894
70 61-70	f	right	ICA	y	no information available	1894
72 71-80	f	left	VA	y	no information available	1894
72 71-80	f	right	ICA	y	no information available	1894
73 71-80	f	left	MCA	y	no information available	1894
73 71-80	f	right	VA	y	no information available	1894
73 71-80	f	midline	AortaA	y	no information available	1894
79 71-80	f	right	BA	y	no information available	1894
80 71-80	f	right	ACA	y	no information available	1894
81 81-100	f	left	MCA	y	no information available	1894
86 81-100	m	midline	AortaA	y	no information available	1894
		midline	CBAN	y	no information available	1894
21 21-30	m	right	ICA	y	other vessels healthy	1895
29 23-30	m	midline	BA	y	no information available	1895
34 31-40	f	right	ICA	y	Wall of aneurysm had two patches of atherosclerosis	1895
40 31-40	m	midline	BA	a	no information available	1897
47 41-50	f	right	MCA	a	no information available	1897
50 41-50	m	left	MCA	y	no information available	1897
53 51-60	m	left	MCA	y	no information available	1897
69 61-70	f	bilateral	ICA	a	no information available	1897
28 23-30	m	midline	BA	a	no information available	1898
54 51-60	m	midline	BA	a	no information available	1898
70 61-70	f	right	MCA	y	Extensive sclerosis with atherosclerotic plaques	1898
29 23-30	m	midline	BA	a	Syphilitic	1899
68 61-70	m	left	VA	a	Vessels atherosclerotic	1900
89 61-70	m	left	pul	y	Embolic (endocarditis)	1901
11 11-15	m	right	pul	y	Embolic (endocarditis)	1901
27 23-30	f	left	MCA	y	normal vessels	1901
28 23-30	m	midline	BA	a	no information available	1901
32 31-40	f	right	MCA	y	Embolic (endocarditis)	1901
50 41-50	m	right	MCA	y	Atherosclerosis	1901
76 71-80	f	right	MCA	y	no information available	1901
29 23-30	f	right	PronA	y	normal vessels	1902
34 31-40	m	undefined	CBAN	y	Syphilitic	1902
45 41-50	f	left	ICA	y	Wall of left internal carotid artery thickened	1902
22 23-30	f	right	ICA	y	healthy	1903
39 31-40	f	right	MCA	y	Line of atherosclerosis at point of aneurysm	1903
64 61-70	f	right	PronA	y	Syphilitic	1903
27 23-30	m	midline	AortaA	y	Wall of other arteries healthy	1904
40 31-40	f	right	ICA	y	no information available	1904
65 61-70	f	right	ACA	y	Atherosclerosis	1904
70 61-70	f	midline	BA	y	Atherosclerosis	1904
86 61-100	m	bilateral	ICA	a	no information available	1904
87 81-100	f	right	ICA	a	Atherosclerosis	1904
40 31-40	m	midline	BA	a	Syphilitic	1905
42 41-50	f	right	PronA	a	Marked sclerosis	1905
50 41-50	m	right	VA	a	Localized syphilitic periarthritis of aneurysm	1905
51 51-60	m	right	VA	y	no information available	1905
		midline	BA	a	Syphilitic	1905
6 6-10	f	left	MCA	y	Myxotic (nephrosclerotic endocarditis)	1906
28 23-30	m	midline	BA	y	no information available	1906
69 61-70	f	bilateral	ICA	a	Arteriosclerosis	1906
		bilateral	ICA	y	no information available	1906
14 11-15	m	left	BA	a	no information available	1907
40 41-50	m	left	ICA	a	Vessels normal	1907
48 41-50	f	left	ICA	a	no atherosclerosis	1907
50 41-50	m	right	MCA	y	Arteries healthy	1907
51 51-60	m	bilateral	AortaA	y	no information available	1907
55 51-60	f	left	MCA	y	no information available	1907
61 61-70	f	left	ICA	y	no information available	1907
63 61-70	f	midline	AortaA	a	no information available	1907
65 61-70	f	left	VA	y	Baile's artery tortuous and dilated	1907
68 61-70	m	midline	BA	y	no information available	1907
84 81-100	f	left	ICA	a	no information available	1907
		left	ICA	a	no information available	1907
28 23-30	m	left	AortaA	y	Impaired, curving vessels thickening of arteries at base	1908
65 61-70	m	right	MCA	a	Atherosclerosis	1908
30 23-30	m	left	ACA	y	Thickening right iliac endarteritis obliterans	1909
27 23-30	m	midline	BA	y	Other arteries normal	1910
44 41-50	f	right	MCA	y	Arteriosclerosis	1910
57 51-60	m	bilateral	VA	a	no information available	1910
64 61-70	m	left	MCA	y	Arteriosclerosis	1910
		left	VA	a	Thick and hard	1910
25 23-30	f	right	ACA	y	Thickening of vessels	1911
36 31-40	m	right	PCA	a	Aneurysm congenital	1911
37 31-40	m	right	ICA	a	no information available	1911
42 41-50	f	right	ICA	y	no information available	1911
42 41-50	m	left	VA	a	Both cerebral arteries thickened	1911
53 51-60	m	left	MCA	a	Syphilitic	1911
62 61-70	f	left	ICA	y	no information available	1911
		midline	BA	y	Healthy vessels	1911
21 23-30	f	right	ACA	y	Aneurysm congenital	1912
22 23-30	m	right	MCA	y	Embolic (endocarditis)	1912
25 23-30	f	right	ACA	y	Aneurysm congenital	1912
31 31-40	m	undefined	CBAN	a	No arteriosclerosis	1912
32 31-40	m	left	MCA	y	Aneurysm congenital	1912
37 31-40	f	right	PCA	y	With healthy (probably embolic)	1912
37 31-40	m	left	MCA	y	Embolic (endocarditis)	1912
38 31-40	f	midline	AortaA	y	Aneurysm congenital	1912
38 31-40	m	right	VA	y	Aneurysm congenital	1912
40 31-40	m	left	MCA	y	Aneurysm congenital	1912
42 41-50	m	left	ICA	y	Embolic (endocarditis)	1912
42 41-50	m	left	VA	y	Aneurysm congenital	1912
44 41-50	m	right	MCA	y	Vessels somewhat thickened; "congenital" (?)	1912
48 41-50	m	left	MCA	y	Arteriosclerosis	1912
51 51-60	f	left	ACA	y	Aneurysm congenital	1912
		left	ACA	y	Syphilitic endarteritis of cerebral arteries	1912

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52	51-60	m	right	MCA	y	Syphilitic endarteritis obliterans of cerebral vessels	1912
55	51-60	m	left	ICA	a	no information available	1912
56	51-60	f	midline	BA	y	Aneurysm congenital	1912
56	51-60	f	left	PICA	y	Aneurysm congenital	1912
57	51-60	f	right	MCA	y	Arteriosclerosis	1912
63	61-70	f	right	MCA	y	Arteriosclerosis	1912
6	6-10	f	right	PICA	y	Atherosclerosis	1913
12	11-15	m	left	MCA	y	no information available	1913
18	16-20	m	left	PICA	y	Aneurysm congenital	1913
30	21-30	f	right	Ponoma	y	No arteriosclerosis	1913
31	31-40	f	right	VA	a	Syphilia	1913
33	31-40	m	undetermined	CBAN	y	no information available	1913
36	31-40	m	right	PICA	y	Syphilia, gummatous arteritis	1913
37	31-40	m	right	VA	a	Endarteritis	1913
40	31-40	f	left	ACA	y	Aneurysm congenital	1913
41	41-50	m	left	ICA	a	no information available	1913
42	41-50	f	left	MCA	y	Small sclerotic plaques	1913
42	41-50	m	right	ACA	y	Soft vessels	1913
56	51-60	m	undetermined	CBAN	y	Small grayish white flecks on vessels	1913
58	51-60	f	right	MCA	y	Only slight thickening	1913
72	71-80	m	right	MCA	y	Arteriosclerosis	1913
72	71-80	m	right	MCA	y	Marked arteriosclerosis	1913
57	51-60	m	right	MCA	y	Atherosclerosis	1913
40	31-40	f	right	VA	a	no information available	1914
59	41-50	m	left	Aosoma	y	proliferative endocarditis embolism (endocarditis)	1915
7	6-10	m	right	PICA	y	no information available	1915
15	11-15	f	left	ICA	y	embolic	1916
16	16-20	f	right	MCA	y	embolic	1916
16	16-20	m	left	MCA	y	embolic	1916
19	16-20	m	left	Ponoma	y	healthy artery	1916
22	21-30	m	right	MCA	a	embolic	1916
22	21-30	m	left	Aosoma	y	congenital aneurysm	1916
22	21-30	m	right	MCA	y	congenital aneurysm	1916
28	21-30	m	left	ICA	y	congenital aneurysm	1916
31	31-40	m	right	MCA	y	embolic	1916
36	31-40	f	left	Ponoma	y	slight arterial degeneration	1916
36	31-40	m	left	ICA	y	Atherosclerosis	1916
36	31-40	m	left	MCA	y	embolic	1916
40	31-40	f	right	Ponoma	y	no information available	1916
40	31-40	m	right	ICA	y	healthy artery	1916
41	41-50	m	right	Aosoma	y	no atherosclerosis	1916
41	41-50	m	right	MCA	y	embolic	1916
42	41-50	f	left	PICA	y	no atherosclerosis	1916
44	41-50	f	left	Aosoma	y	no information available	1916
40	41-50	f	right	Aosoma	y	arterial degeneration	1916
47	41-50	m	right	ICA	a	no information available	1916
48	41-50	f	right	MCA	a	no information available	1916
48	41-50	f	right	MCA	y	arterial degeneration	1916
49	41-50	f	left	Aosoma	y	Atherosclerosis	1916
49	41-50	m	left	Aosoma	y	no information available	1916
50	41-50	m	right	Aosoma	y	no information available	1916
51	51-60	m	right	MCA	y	Atherosclerosis	1916
53	51-60	m	right	MCA	a	no information available	1916
53	51-60	m	left	Aosoma	y	Arteriosclerosis	1916
55	51-60	m	right	Aosoma	y	no information available	1916
58	51-60	f	right	ICA	y	congenital aneurysm	1916
60	51-60	m	right	MCA	y	embolic	1916
67	61-70	f	left	MCA	y	Atherosclerosis	1916
70	61-70	f	left	ICA	a	no information available	1916
72	71-80	f	left	Aosoma	y	arterial degeneration	1916
75	71-80	m	undetermined	CBAN	y	no information available	1916
86	81-100	m	right	MCA	a	no information available	1916
			left	ACA	a	embolic	1916
			midline	BA	a	embolic	1916
			undetermined	CBAN	a	embolic	1916
			left	MCA	a	no information available	1916
			left	ACA	y	embolic	1916
			right	MCA	y	embolic	1916
12	11-15	f	right	Aosoma	y	vessel healthy	1917
32	31-40	f	bilateral	ICA	y	no information available	1917
47	41-50	m	left	VA	y	vessel left	1917
52	51-60	m	right	ICA	y	no information available	1917
53	51-60	m	midline	BA	a	Arteriosclerosis	1917
21	21-30	m	right	MCA	y	no information available	1918
26	21-30	f	right	ICA	y	no information available	1918
53	51-60	f	left	MCA	y	Arteriosclerosis	1918
54	51-60	m	left	PICA	y	no information available	1918
87	81-100	f	right	MCA	y	no information available	1918
2	6-10	m	left	MCA	y	other vessel normal	1918
18	16-20	m	bilateral	MCA	y	Focal areas of intimal thickening	1919
27	21-30	m	right	VA	y	Vessels left and thin	1919
27	21-30	m	right	MCA	y	No trace of syphilis or arteriosclerosis; microscopically a decrease in elastic fibers in media of vessels	1919
35	31-40	m	right	MCA	y	Slight intimal thickening of other vessels	1919
36	31-40	f	right	Ponoma	y	atherosclerosis	1919
39	31-40	f	right	Aosoma	y	Vessels left	1919
42	41-50	m	left	MCA	y	Scattered patches of intimal thickening	1919
45	41-50	m	left	MCA	y	Arteriosclerosis	1919
53	51-60	m	midline	BA	y	Arteriosclerosis	1919
53	51-60	m	left	Ponoma	y	Scattered patches of intimal thickening	1919
55	51-60	m	midline	BA	y	Vessels thickened with plaques	1919
56	51-60	m	right	Ponoma	y	Scattered plaques	1919
68	61-70	f	left	Aosoma	y	Marked thickening of vessels	1919
			right	MCA	y	Scattered thickening	1919
			midline	Aosoma	y	Scattered yellow patches on intima	1919
28	21-30	m	midline	Aosoma	y	no information available	1920
29	21-30	f	midline	Aosoma	y	no information available	1920
36	31-40	m	midline	BA	a	no information available	1920
37	31-40	f	midline	Aosoma	y	no information available	1920
59	41-50	f	right	Aosoma	y	no information available	1920
55	51-60	m	midline	Aosoma	y	Sclerosis of cerebral arteries	1920
56	51-60	m	right	Aosoma	y	no information available	1920
67	61-70	f	midline	Aosoma	y	no information available	1920
9	6-10	m	left	PICA	y	infected embolus; other vessels normal	1921
13	11-15	m	midline	Aosoma	y	no information available	1921
20	16-20	m	undetermined	CBAN	y	no information available	1921
27	21-30	f	midline	Aosoma	y	no information available	1921
37	31-40	f	left	Aosoma	a	Atherosclerosis	1921
39	31-40	m	undetermined	CBAN	y	Medial sclerosis and fibrous intimal thickening	1921
44	41-50	m	left	Aosoma	y	Arteriosclerosis	1921
44	41-50	m	left	Aosoma	y	Infected embolus; slight intimal thickening of other vessels	1921
46	41-50	m	midline	Aosoma	y	Other vessels normal	1921
46	41-50	m	right	Aosoma	y	Atherosclerosis	1921
50	41-50	m	right	VA	a	Atherosclerosis	1921
52	51-60	f	bilateral	VA	a	no information available	1921
61	61-70	f	midline	Aosoma	y	Atherosclerosis	1921
13	11-15	m	bilateral	MCA	a	Constriction of aorta	1922
15	11-15	f	midline	BA	a	no information available	1922
36	31-40	m	midline	BA	a	no information available	1922
39	31-40	m	midline	Aosoma	y	Embolism (endocarditis)	1922
40	41-50	m	midline	BA	a	no information available	1922
50	41-50	f	right	ICA	a	Arteriosclerosis	1922
54	51-60	m	left	VA	a	Arteriosclerosis	1922
16	16-20	f	left	MCA	y	Myotic embolism	1922
18	16-20	f	left	Aosoma	y	Myotic embolism	1922
22	21-30	m	right	MCA	y	Embolism (endocarditis)	1922
22	21-30	m	left	PICA	y	no information available	1922
24	21-30	m	right	MCA	y	Embolism (endocarditis)	1922
25	21-30	m	undetermined	CBAN	y	no information available	1922
29	21-30	m	left	MCA	y	Embolism (endocarditis)	1922
29	21-30	m	left	MCA	y	Embolism (endocarditis)	1922
31	31-40	m	right	MCA	y	Embolism (endocarditis)	1922
33	31-40	m	left	MCA	a	Myotic embolism	1922
36	31-40	f	left	ICA	a	no information available	1922
42	41-50	m	right	ICA	y	Embolism (endocarditis)	1922
42	41-50	m	midline	Aosoma	y	Embolism (endocarditis)	1922
43	41-50	f	right	MCA	y	Arteriosclerosis	1922
45	41-50	f	undetermined	CBAN	a	no information available	1922
45	41-50	f	left	ICA	y	Arteriosclerosis	1922
49	41-50	m	midline	Aosoma	y	no information available	1922
50	41-50	f	left	ICA	a	Arteriosclerosis	1922
52	51-60	f	right	ICA	a	no information available	1922
52	51-60	f	midline	Aosoma	y	Arteriosclerosis	1922
52	51-60	f	right	ICA	y	no information available	1922
55	51-60	f	right	Ponoma	y	Arteriosclerosis	1922
56	51-60	f	right	MCA	y	Arteriosclerosis	1922
57	51-60	f	left	ICA	a	Syphilia and arterio sclerosis	1922
57	51-60	f	right	ICA	a	Arteriosclerosis	1922
60	51-60	f	left	ICA	y	Arteriosclerosis	1922
61	61-70	f	right	ICA	y	Arteriosclerosis	1922
64	61-70	f	midline	Aosoma	a	Arteriosclerosis	1922
65	61-70	f	left	PICA	y	Arteriosclerosis	1922
65	61-70	f	left	ICA	y	no information available	1922
69	61-70	f	left	Ponoma	y	Arteriosclerosis	1922
70	61-70	f	bilateral	MCA	a	Arteriosclerosis	1922
70	61-70	f	left	MCA	y	Arteriosclerosis	1922
70	61-70	f	right	PICA	y	Arteriosclerosis	1922
74	71-80	m	left	Aosoma	a	Arteriosclerosis	1922
75	71-80	f	left	Ponoma	a	Arteriosclerosis	1922
84	81-100	f	right	MCA	y	Embolism (endocarditis)	1922
24	21-30	m	right	Aosoma	y	Arteriosclerosis	1923
25	21-30	m	right	MCA	y	No atherosclerosis	1923
29	21-30	f	right	ICA	y	Healthy vessels	1923
29	21-30	f	right	ICA	y	Healthy vessels	1923
30	21-30	m	midline	BA	a	Healthy vessels	1923
30	21-30	f	left	Aosoma	y	Gummatous arteritis	1923
41	41-50	f	left	ICA	y	Arteriosclerosis	1923
41	41-50	f	left	ICA	y	Endocarditis or arteriosclerosis	1923
41	41-50	f	left	Aosoma	y	Internal sclerosis (endocarditis)	1923
43	41-50	f	right	ICA	y	no information available	1923
47	41-50	m	midline	BA	a	no information available	1923
49	41-50	m	right	ICA	y	Arteriosclerosis	1923
49	41-50	m	right	ICA	y	no information available	1923
60	51-60	m	right	Ponoma	y	Atherosclerosis	1923

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20 16-20	f	right	PotomA	y
22 21-30	m	right	MCA	y
28 21-30	m	left	MCA	a
31 31-40	f	left	ICA	a
31 31-40	m	right	MCA	y
39 31-40	m	right	ICA	y
44 41-50	f	left	ICA	y
44 41-50	f	right	VIA	y
46 41-50	f	right	ICA	y
48 41-50	m	right	ICA	y
50 41-50	f	midline	AortaA	y
53 51-60	m	left	ICA	y
57 51-60	m	left	ICA	a
58 51-60	m	undefined	CBAN	a
61 61-70	m	left	PotomA	y
65 61-70	m	right	MCA	a
74 71-80	m	midline	AortaA	y
2 6-10	m	right	VIA	y
6 6-10	f	bilateral	MCA	y
9 6-10	m	undefined	CBAN	y
20 16-20	f	undefined	CBAN	y
20 16-20	m	undefined	CBAN	y
23 21-30	m	left	ICA	a
24 21-30	m	midline	BA	y
26 21-30	f	right	ICA	y
28 21-30	m	undefined	CBAN	y
29 21-30	f	right	PCA	y
32 31-40	m	left	AortaA	y
34 31-40	f	undefined	CBAN	a
35 31-40	m	bilateral	VIA	y
36 31-40	f	right	AortaA	y
36 31-40	m	undefined	CBAN	y
37 31-40	m	left	AortaA	y
38 31-40	f	midline	AortaA	y
39 31-40	m	undefined	CBAN	y
40 31-40	m	left	PCA	y
42 41-50	m	right	ICA	y
43 41-50	f	left	ICA	y
44 41-50	f	undefined	CBAN	y
44 41-50	m	midline	AortaA	a
46 41-50	f	right	ICA	y
48 41-50	f	undefined	CBAN	a
49 41-50	f	undefined	CBAN	a
49 41-50	f	bilateral	ICA	y
49 41-50	m	undefined	CBAN	y
49 41-50	m	right	MCA	y
50 41-50	f	left	ICA	a
50 41-50	m	midline	AortaA	y
51 51-60	f	undefined	CBAN	y
51 51-60	f	right	MCA	y
53 51-60	f	right	ICA	a
54 51-60	f	left	PotomA	y
54 51-60	m	undefined	CBAN	y
56 51-60	f	left	ICA	a
58 51-60	f	right	AortaA	y
58 51-60	m	undefined	CBAN	y
61 61-70	f	undefined	CBAN	y
62 61-70	f	right	AortaA	y
62 61-70	f	undefined	CBAN	y
62 61-70	m	undefined	CBAN	y
63 61-70	f	midline	BA	y
65 61-70	f	bilateral	PCA	y
67 61-70	f	right	CBAN	y
67 61-70	m	undefined	CBAN	a
69 61-70	f	right	MCA	y
71 71-80	m	undefined	CBAN	y
72 71-80	f	left	PotomA	a
73 71-80	f	BA	y	
75 71-80	m	left	ICA	a
75 71-80	m	midline	AortaA	y
84 81-100	f	right	ICA	a
84 81-100	f	right	VIA	y
16 16-20	m	midline	AortaA	y
31 31-40	m	right	AortaA	y
38 31-40	f	right	MCA	y
41 41-50	f	right	AortaA	y
42 41-50	m	left	AortaA	y
60 51-60	f	right	MCA	y
62 61-70	f	midline	AortaA	y
66 61-70	f	midline	AortaA	y
31 31-40	m	midline	BA	y

	age range	Frequency	Percent	Valid Percent	Cumulative Percent
Valid	age range	192.00	17.88	17.88	
	25-5	21.00	1.86	1.86	
	6-10	14.00	1.24	1.24	
	11-15	28.00	2.47	2.47	
	16-20	58.00	5.15	5.15	
	21-30	146.00	12.95	12.95	
	31-40	165.00	14.64	14.64	
	41-50	203.00	18.03	18.03	
	51-60	159.00	14.11	14.11	
	61-70	94.00	8.34	8.34	
	71-80	55.00	5.11	5.11	
	81-100	11.00	0.98	0.98	
Total		1127.00	100.00	100.00	

occurrence of aneurysms in all age groups (15 months to 89 years), recorded from 1761 to 1938, (McDonald & Korb 1939)	age	sex	side
all cases N	Valid	955.00	1127.00
	Missing	955.00	0.00
Mean		41.69	
Median		41.00	
Mode		17.69	
Std. Deviation		1.50	
Minimum		89.00	
Maximum			

sex	Frequency	Percent	Valid Percent	Cumulative Percent
Valid	f	28.00	2.50	2.50
	m	573.00	50.80	50.80
	Total	1127.00	100.00	100.00
side	Frequency	Percent	Valid Percent	Cumulative Percent
Valid	bilateral	33.00	2.90	2.90
	left	386.00	34.30	34.30
	midline	279.00	24.80	24.80
	right	367.00	32.60	32.60
	undefined	62.00	5.50	5.50
Total		1127.00	100.00	100.00

arteries- all cases of cerebral aneurysms in all age groups ≥15 months, recorded from 1761 to 1938, (McDonald CA, Korb M. Intracranial aneurysms. Archives of neurology and psychiatry (Chicago) (1939); 42): 298-328)		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	ACA	22.00	2.80	2.80	
	AortaA	237.00	21.80	21.80	
	ACA	5.00	0.40	0.40	
	BA	142.00	12.60	12.60	
	CBAN	49.00	4.30	4.30	
	ICA	187.00	16.60	16.60	
	MCA	311.00	27.60	27.60	
	PCA	33.00	2.90	2.90	
	PotomA	61.00	5.40	5.40	
	ptal	2.00	0.20	0.20	
	PCA	9.00	0.80	0.80	
	ICA	2.00	0.20	0.20	
	VIA	67.00	5.90	5.90	
Total		1127.00	100.00	100.00	

rupture	Frequency	Percent	Valid Percent	Cumulative Percent
Valid	a	54.00	4.80	4.80
	1	198.00	17.60	17.60
	2	875.00	77.60	77.60
Total		1127.00	100.00	100.00

occurrence of aneurysms in age groups ≥18 years, recorded from 1761 to 1938, (McDonald & Korb 1939)	Statistics	age	age range	sex	side
N	Valid	853.00	853.00		853.00
	Missing	0.00	0.00		0.00
Mean		44.68			
Median		43.00			
Mode		41.00			
Std. Deviation		15.46			
Minimum		18.00			
Maximum		89.00			
Percentiles		25	32.00		
		50	43.00		
		75	56.00		

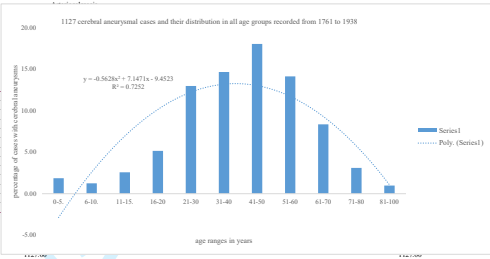
Frequency Table = cases of cerebral aneurysms in age groups ≥18 years, recorded from 1761 to 1938, (McDonald & Korb 1939)	age range	Frequency	Percent	Valid Percent	Cumulative Percent
Valid	16-20	40.00	4.69	4.69	
	21-30	146.00	17.12	17.12	
	31-40	165.00	19.34	19.34	
	41-50	203.00	23.80	23.80	
	51-60	159.00	18.64	18.64	
	61-70	94.00	11.02	11.02	
	71-80	55.00	6.46	6.46	
	81-100	11.00	1.29	1.29	
Total		853.00	100.00	100.00	

sex = cases of cerebral aneurysms in age groups ≥18 years, recorded from 1761 to 1938, (McDonald & Korb 1939)	Frequency	Percent	Valid Percent	Cumulative Percent
Valid	f	4.00	0.70	0.70
	m	438.00	51.35	51.35
	Total	408.00	47.95	47.95
	Total	853.00	100.00	100.00

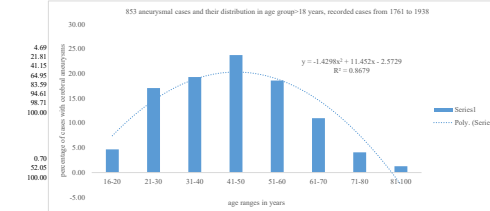
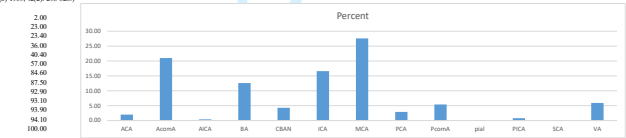
side involved- cases of cerebral aneurysms in age groups ≥18 years, recorded from 1761 to 1938, (McDonald & Korb 1939)	Frequency	Percent	Valid Percent	Cumulative Percent
Valid	bilateral	24.00	2.81	2.81
	left	295.00	34.58	34.58
	midline	181.00	21.22	21.22
	right	305.00	35.76	35.76
	undefined	48.00	5.63	5.63
Total		853.00	100.00	100.00

arteries involved- cases of cerebral aneurysms in age groups ≥18 years, recorded from 1761 to 1938, (McDonald & Korb 1939)					
	arteries	Frequency	Percent	Valid Percent	Cumulative Percent
Valid	ACA	18.00	2.11	2.11	

syphilis	1936
Wall of aneurysm showed diffuse inflammation, of aseptic origin	1936
no information available	1936
no information available	1936
Atherosclerosis	1936
no information available	1936
Inflammation of intima	1936
Arteries covered with yellow plaques; seen at operation	1936
no information available	1936
no information available	1936
no information available	1936
Arteriosclerosis	1936
no information available	1936
no information available	1936
Atherosclerosis	1936
coarctated aneurysm	1936
Atherosclerosis	1936
Congested (1) narrow media	1937
Infective (endocarditis)	1937
No change in wall; Hareman probably septic embolus	1937
no information available	1937
no information available	1937
Aneurysm seen at operation	1937
atherosclerotic, syphilitic aortitis	1937
Normal vessels	1937
no information available	1937
no information available	1937
Syphilis	1937
no information available	1937
Syphilis	1937
no information available	1937
Few small atherosclerosis plaques: acellular, hyalinized, thin media	1937
Normal vessels	1937
Thickening of wall of internal carotid artery	1937
Aneurysm seen at operation	1937
no information available	1937
Arteriosclerosis	1937
no information available	1937
no information available	1937
Syphilitic aortitis and atherosclerosis	1937
Atherosclerosis	1937
Syphilitic aortitis and atherosclerosis	1937
Aneurysm seen at operation	1937
Syphilis	1937
no information available	1937
Syphilis	1937
Aneurysm seen at operation	1937
Arteriosclerosis	1937
no information available	1937
Atherosclerosis	1937
no information available	1937
Atherosclerosis	1937
Atherosclerosis	1937
no information available	1937
Atherosclerosis	1937
no information available	1937
Syphilis	1937
Aneurysm seen at operation	1937
no information available	1937
Syphilis	1937
Atherosclerosis	1937
Syphilis	1937
Atherosclerosis	1937
Atherosclerosis	1937
Syphilis	1937
Embolus (endocarditis)	1937
Vessel healthy	1937
Arteriosclerosis	1937
Vessel healthy	1937
Vessel healthy	1937
Vessel healthy	1937
Vessel healthy	1937
Vessel healthy	1937
Vessel healthy	1937



arterial case year	1127	1127.00	0.00
0	0.00	0.00	
	1909.81		
	1928.00		
	28.13		
	1761.00		
	1938.00		

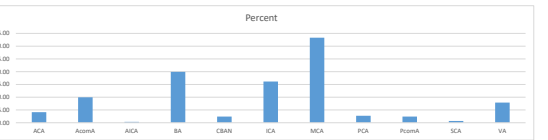
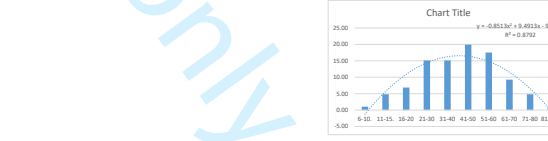
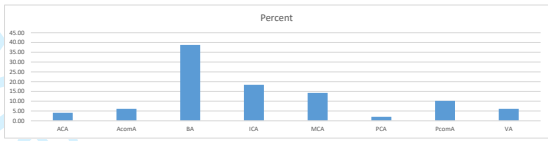
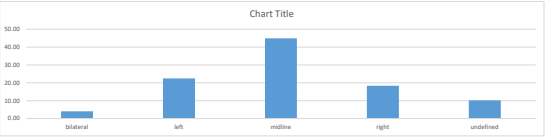
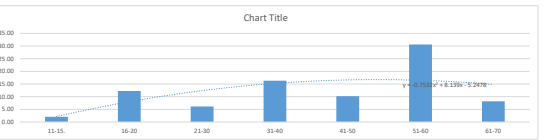
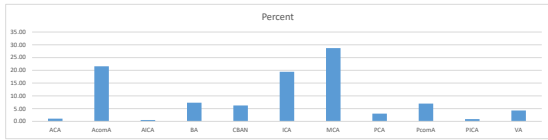
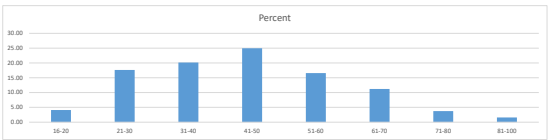


Percent	2.11
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Median		42.00		
Mode		41.00		
Std. Deviation		15.39		
Minimum		18.00		
Maximum		89.00		
Percentiles				
		25	32.00	
		50	42.00	
		75	55.00	
age range				
Valid	age range	Frequency	Percent Valid Percent Cumulative Percent	
	16-20	23.00	4.10 4.10	4.10
	21-30	99.00	17.65 17.65	21.75
	31-40	113.00	20.14 20.14	41.89
	41-50	140.00	24.96 24.96	66.84
	51-60	63.00	10.98 10.98	77.82
	61-70	63.00	11.23 11.23	89.05
	71-80	21.00	3.74 3.74	92.79
	81-100	9.00	1.60 1.60	94.39
	Total	561.00	100.00 100.00	
sex				
Valid		Frequency	Percent Valid Percent Cumulative Percent	
	f	5.00	0.89 0.89	0.89
	m	286.00	50.98 50.98	51.87
	Total	561.00	100.00 100.00	
side				
Valid		Frequency	Percent Valid Percent Cumulative Percent	
	bilateral	20.00	3.57 3.57	3.57
	left	195.00	34.76 34.76	38.32
	midline	93.00	16.59 16.59	54.91
	right	231.00	41.18 41.18	96.09
	undefined	34.00	6.06 6.06	100.00
arteries				
Valid	arteries involved	Frequency	Percent Valid Percent Cumulative Percent	
	ACA	6.00	1.07 1.07	1.07
	AcomA	121.00	21.57 21.57	22.64
	ACA	3.00	0.53 0.53	23.17
	BA	41.00	7.31 7.31	30.48
	CBAN	35.00	6.24 6.24	36.72
	ICA	109.00	19.43 19.43	56.15
	MCA	161.00	28.70 28.70	84.85
	PCA	17.00	3.03 3.03	87.88
	PcomA	39.00	6.95 6.95	94.83
	PICA	5.00	0.89 0.89	95.72
	VA	24.00	4.28 4.28	100.00
	Total	561.00	100.00 100.00	
rupture				
Valid		Frequency	Percent Valid Percent Cumulative Percent	
	a	99.00	17.65 17.65	17.65
	y	462.00	82.35 82.35	100.00
	Total	561.00	100.00 100.00	
Frequency: cases of cerebral aneurysms in all age (i.e., >15 months to 89 years) & year <1850 (McDonald & Kurb 1939)				
Statistics				
N	age	age range	sex	
	Valid	42.00	49.00	
	Missing	7.00	0.00	
	Mean	43.60		
	Median	46.00		
	Mode	20.00		
	Std. Deviation	16.11		
	Minimum	14.00		
	Maximum	68.00		
	Percentiles			
	25	31.75		
	50	46.00		
	75	59.00		
age range				
Valid		Frequency	Percent Valid Percent Cumulative Percent	
	11-15	7.00	14.29 14.29	14.29
	16-20	1.00	2.04 2.04	16.33
	21-30	6.00	12.24 12.24	28.57
	31-40	3.00	6.12 6.12	34.69
	41-50	8.00	16.33 16.33	51.02
	51-60	5.00	10.20 10.20	61.22
	61-70	15.00	30.61 30.61	91.84
	71-80	4.00	8.16 8.16	100.00
	Total	49.00	100.00 100.00	
sex				
Valid		Frequency	Percent Valid Percent Cumulative Percent	
	f	3.00	6.12 6.12	6.12
	m	16.00	32.65 32.65	38.78
	Total	49.00	100.00 100.00	
side				
Valid		Frequency	Percent Valid Percent Cumulative Percent	
	bilateral	2.00	4.08 4.08	4.08
	left	11.00	22.45 22.45	26.53
	midline	22.00	44.90 44.90	71.43
	right	9.00	18.37 18.37	89.80
	undefined	5.00	10.20 10.20	100.00
arteries				
Valid	arteries involved	Frequency	Percent Valid Percent Cumulative Percent	
	ACA	2.00	4.08 4.08	4.08
	AcomA	3.00	6.12 6.12	10.20
	BA	19.00	38.78 38.78	48.98
	ICA	9.00	18.37 18.37	67.35
	MCA	7.00	14.29 14.29	81.63
	PCA	1.00	2.04 2.04	83.67
	PcomA	5.00	10.20 10.20	93.88
	VA	3.00	6.12 6.12	100.00
	Total	49.00	100.00 100.00	
rupture				
Valid		Frequency	Percent Valid Percent Cumulative Percent	
	a	2.00	4.08 4.08	4.08
	y	13.00	26.53 26.53	30.61
	Total	49.00	100.00 100.00	
Frequency: cases of cerebral aneurysms in all age (i.e., >15 months to 89 years) & year >= 1850 (McDonald & Kurb 1939)				
Statistics				
N	age	age range	sex	
	Valid	277.00	291.00	
	Missing	14.00	0.00	
	Mean	42.47		
	Median	43.00		
	Mode	40.00		
	Std. Deviation	17.50		
	Minimum	6.00		
	Maximum	86.00		
	Percentiles			
	25	28.50		
	50	43.00		
	75	56.00		
age range				
Valid		Frequency	Percent Valid Percent Cumulative Percent	
	6-10	14.00	4.81 4.81	4.81
	11-15	3.00	1.03 1.03	5.83
	16-20	14.00	4.81 4.81	9.64
	21-30	20.00	6.87 6.87	16.51
	31-40	44.00	15.12 15.12	31.62
	41-50	44.00	15.12 15.12	46.74
	51-60	58.00	19.93 19.93	66.67
	61-70	51.00	17.53 17.53	84.22
	71-80	27.00	9.28 9.28	93.50
	81-100	14.00	4.81 4.81	98.31
	Total	291.00	100.00 100.00	
sex				
Valid		Frequency	Percent Valid Percent Cumulative Percent	
	f	5.00	1.72 1.72	1.72
	m	147.00	50.52 50.52	52.23
	Total	291.00	100.00 100.00	
side				
Valid		Frequency	Percent Valid Percent Cumulative Percent	
	bilateral	3.00	1.03 1.03	1.03
	left	104.00	35.74 35.74	36.77
	midline	90.00	30.93 30.93	67.70
	right	78.00	26.80 26.80	94.50
	undefined	16.00	5.50 5.50	100.00
arteries				
Valid	arteries involved	Frequency	Percent Valid Percent Cumulative Percent	
	ACA	12.00	4.12 4.12	4.12
	AcomA	29.00	9.97 9.97	14.09
	ACA	1.00	0.34 0.34	14.43
	BA	58.00	19.93 19.93	34.36
	CBAN	7.00	2.41 2.41	36.77
	ICA	47.00	16.15 16.15	52.92
	MCA	97.00	33.33 33.33	86.25
	PCA	8.00	2.75 2.75	89.00
	PcomA	7.00	2.41 2.41	91.41
	VA	2.00	0.69 0.69	92.10
	Total	291.00	100.00 100.00	
rupture				
Valid		Frequency	Percent Valid Percent Cumulative Percent	
	a	3.00	1.03 1.03	1.03
	y	73.00	25.09 25.09	26.12
	Total	291.00	100.00 100.00	
Cases of cerebral aneurysms in all age (i.e., >15 months to 89 years) & year >= 1900 (McDonald & Kurb 1939)				
Statistics				
N	age	age range	sex	
	Valid	616.00	787.00	
	Missing	171.00	0.00	
	Mean	41.12		
	Median	41.00		
	Mode	41.00		
	Std. Deviation	17.88		
	Minimum	1.50		
	Maximum	89.00		
	Percentiles			
	25	29.00		
	50	41.00		
	75	53.00		
Frequency Table				



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age range		Frequency	Percent	Valid Percent	Cumulative Percent	
Valid		171.00	21.73	21.73	21.73	21.73
	0-5	21.00	2.67	2.67	24.40	24.40
	6-10	11.00	1.40	1.40	26.18	26.18
	11-15	14.00	1.78	1.78	27.96	27.96
	16-20	32.00	4.07	4.07	32.04	32.04
	21-30	99.00	12.58	12.58	44.62	44.62
	31-40	113.00	14.36	14.36	57.98	57.98
	41-50	140.00	17.79	17.79	74.97	74.97
	51-60	93.00	11.82	11.82	86.79	86.79
	61-70	63.00	8.01	8.01	94.80	94.80
	71-80	21.00	2.67	2.67	97.47	97.47
Total	787.00	100.00	100.00			
sex		Frequency	Percent	Valid Percent	Cumulative Percent	
Valid		20.00	2.54	2.54	2.54	2.54
	f	410.00	52.10	52.10	54.64	54.64
	m	357.00	45.36	45.36	100.00	100.00
Total	787.00	100.00	100.00			
side		Frequency	Percent	Valid Percent	Cumulative Percent	
Valid		28.00	3.56	3.56	3.56	3.56
	bilateral	271.00	34.43	34.43	37.99	37.99
	left	167.00	21.22	21.22	59.21	59.21
	midline	280.00	35.58	35.58	94.79	94.79
	right	41.00	5.21	5.21	100.00	100.00
	undefined	787.00	100.00	100.00		
arteries		Frequency	Percent	Valid Percent	Cumulative Percent	
Valid		8.00	1.02	1.02	1.02	1.02
	arteries involved	205.00	26.05	26.05	27.06	27.06
	ACA	4.00	0.51	0.51	27.57	27.57
	AnteriorA	65.00	8.26	8.26	35.83	35.83
	BA	42.00	5.34	5.34	41.17	41.17
	CBAN	131.00	16.65	16.65	57.81	57.81
	ICA	207.00	26.30	26.30	84.12	84.12
	MCA	24.00	3.05	3.05	87.17	87.17
	PCA	49.00	6.23	6.23	93.39	93.39
	PosteriorA	2.00	0.25	0.25	93.65	93.65
	psd	9.00	1.14	1.14	94.79	94.79
	PCCA	41.00	5.21	5.21	99.99	99.99
	VA	787.00	100.00	100.00		
	Total	787.00	100.00	100.00		
rupture		Frequency	Percent	Valid Percent	Cumulative Percent	
Valid		49.00	6.23	6.23	6.23	6.23
	n	112.00	14.23	14.23	20.46	20.46
	y	626.00	79.54	79.54	100.00	100.00
Total	787.00	100.00	100.00			

Percent

y = 0.5333x^2 + 6.4955x - 8.24
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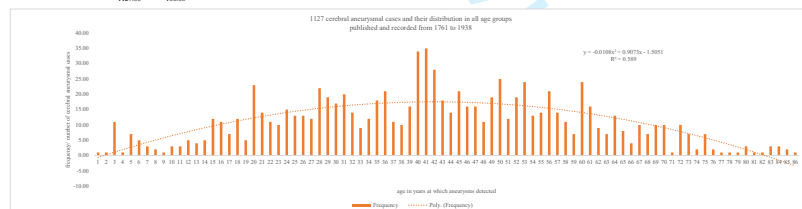
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Itt SCA an					
Valid	Frequency	Percent	Valid Percent	Cumulative Percent	
	n	101.00	99.02	99.02	99.02
	y	1.00	0.98	0.98	100.00
Total		102.00	100.00	100.00	
age range- patients with (n=102) and without aneurysms (n=71) included in the study					
Valid	Frequency	Percent	Valid Percent	Cumulative Percent	
	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	
	Sex				
Valid	Frequency	Percent	Valid Percent	Cumulative Percent	
	f	90	52	52	52
	m	83	48	48	100
Total		173	100	100	

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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, exposure, follow-up, and data collection
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
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 (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.

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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 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

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(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, $p \geq 0.36$) (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

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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.

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 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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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.

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).

Reference

1. Burlakoti A, Kumaratilake J, Taylor J, Henneberg M. Relationship between cerebral aneurysms and variations in cerebral basal arterial network: A morphometric cross-sectional study in Computed Tomography Angiograms from a neurointerventional unit. *BMJ Open* 2021; 11: 1-8.
2. Menshawi K, Mohr JP, Gutierrez J. A Functional Perspective on the Embryology and Anatomy of the Cerebral Blood Supply. *Journal of stroke* 2015; 17(2): 144-58.
3. Mehrotra A, Nair AP, Das KK, Srivastava A, Sahu RN, Kumar R. Clinical and radiological profiles and outcomes in pediatric patients with intracranial aneurysms: Clinical article. *Journal of Neurosurgery: Pediatrics PED* 2012; 10(4): 340-6.
4. Roessler K, Cejna M, Zachenhofer I. Aneurysmatic subarachnoidal haemorrhage: Incidence and location of small ruptured cerebral aneurysms – a retrospective population-based study. *Wiener Klinische Wochenschrift* 2011; 123(13-14): 444-9.
5. Storrs BB, Humphreys RP, Hendrick E, Hoffman H. Intracranial aneurysms in the pediatric age-group. *Pediatric Neurosurgery* 1982; 9(5): 358-61.
6. Proust F, Toussaint P, Garniéri J, et al. Pediatric cerebral aneurysms. *Journal of neurosurgery* 2001; 94(5): 733-9.
7. Horikoshi T, Akiyama I, Yamagata Z, Nukui H. Retrospective Analysis of the Prevalence of Asymptomatic Cerebral Aneurysm in 4518 Patients Undergoing Magnetic Resonance Angiography. *Neurologia medico-chirurgica* 2002; 42(3): 105-13.
8. Froelich JJ, Neilson S, Peters-Wilke J, et al. Size and location of ruptured intracranial aneurysms: a 5-year clinical survey. *World neurosurgery* 2016; 91: 260-5.
9. Cadilhac DA, Carter R, Thrift AG, Dewey HM. Estimating the Long-Term Costs Of Ischemic and Hemorrhagic Stroke for Australia New Evidence Derived From the North East Melbourne Stroke Incidence Study (NEMESIS). *Stroke* 2009; 40(3): 915-21.
10. Jeong Y-G, Jung Y-T, Kim M-S, Eun C-K, Jang S-H. Size and location of ruptured intracranial aneurysms. *Journal of Korean Neurosurgical Society* 2009; 45(1): 11.
11. Korja M, Kivisaari R, Jahromi BR, Lehto H. Size and location of ruptured intracranial aneurysms: consecutive series of 1993 hospital-admitted patients. *Journal of neurosurgery* 2016; 127(4): 748-53.

12. Imaizumi Y, Mizutani T, Shimizu K, Sato Y, Taguchi J. Detection rates and sites of unruptured intracranial aneurysms according to sex and age: an analysis of MR angiography-based brain examinations of 4070 healthy Japanese adults. *J Neurosurg* 2018; 1(aop): 1-6.

13. Jordan LC, Johnston SC, Wu YW, Sidney S, Fullerton HJ. The Importance of Cerebral Aneurysms in Childhood Hemorrhagic Stroke: A Population-Based Study. *Stroke* (1970) 2009; 40(2): 400-5.

14. McDonald CA, Korb M. Intracranial aneurysms. *Archives of neurology and psychiatry* (Chicago) 1939; 42(2): 298-328.

15. Moore S, Simon JL. The greatest century that ever was. *New York Times* 1999.

16. McGuinness B, Chieng N, Skipworth C, Caldwell J, Molyneux A. Small ruptured cerebral aneurysms—do they rupture on formation or not? *Neuroradiology* 2022; 64(3): 597-602.

17. Long MT, Fox CS. The Framingham Heart Study-67 years of discovery in metabolic disease. *Nature reviews Endocrinology* 2016; 12(3): 177-83.

18. McCorry S, Miller J. *Literature and Meat Since 1900*. 1st 2019. ed. Cham: Springer International Publishing; 2019.

19. Alastruey J, Parker KH, Peiro J, Byrd SM, Sherwin SJ. Modelling the circle of Willis to assess the effects of anatomical variations and occlusions on cerebral flows. *J Biomech* 2007; 40(8): 1794-805.

20. Yoon NK, McNally S, Taussky P, Park MS. Imaging of cerebral aneurysms: a clinical perspective. *Neurovascular Imaging* 2016; 2(1): 1-7.

21. McGuinness B, Chieng N, Skipworth C, Caldwell J, Molyneux A. Small ruptured cerebral aneurysms—do they rupture on formation or not? *Neuroradiology* 2021: 1-6.

22. Brown RD, Broderick JP. Unruptured intracranial aneurysms: epidemiology, natural history, management options, and familial screening. *The Lancet Neurology* 2014; 13(4): 393-404.

23. Walendy V, Strauss C, Rachinger J, Stang A. Treatment of aneurysmal subarachnoid haemorrhage in Germany: A nationwide analysis of the years 2005-2009. *Neuroepidemiology* 2014; 42(2): 90-7.

24. Pasqualin A, Mazza C, Cavazzani P, Scienza R, DaPian R. Intracranial aneurysms and subarachnoid hemorrhage in children and adolescents. *Child's nervous system* 1986; 2(4): 185-90.

25. Matson DD. Intracranial Arterial Aneurysms in Childhood. *J Neurosurg* 1965; 23(6): 578-83.

26. Huisman TA, Poretti A. *Pediatric Neurovascular Imaging (CT/MRI/Ultrasound)*. *Pediatric Vascular Neurosurgery*: Springer; 2016: 77-109.

27. Krings T, Geibprasert S, Terbrugge KG. Pathomechanisms and treatment of pediatric aneurysms. *Child's Nervous System* 2010; 26(10): 1309-18.

28. Fung C, Mavrakis E, Filis A, et al. Anatomical evaluation of intracranial aneurysm rupture risk in patients with multiple aneurysms. *Neurosurgical review* 2019; 42(2): 539-47.

29. Verlhac S. Transcranial Doppler in children. *Pediatric radiology* 2011; 41(1): 153-65.

Figure legend -

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.

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.

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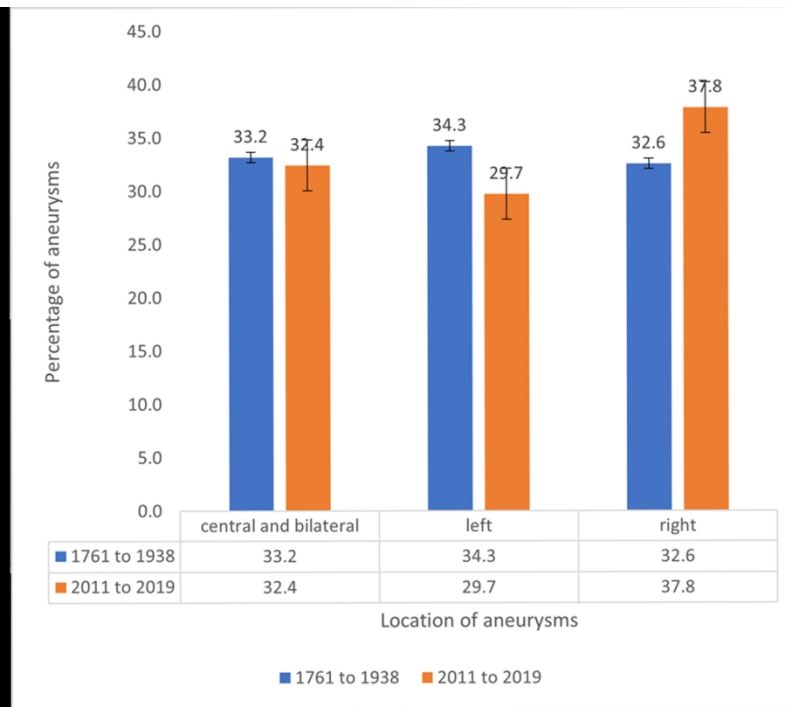


Figure 1 - Comparison of the location of cerebral aneurysms between Royal Adelaide Hospital sample (2011 to 2019) (n=135 CAs from 102 patients, orange colour) with those recorded in 407 publications[14] (1761 to 1938) (n=1127 CAs, blue colour). CAs=cerebral aneurysms, 14 = McDonald, CA & Korb, M 1939,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

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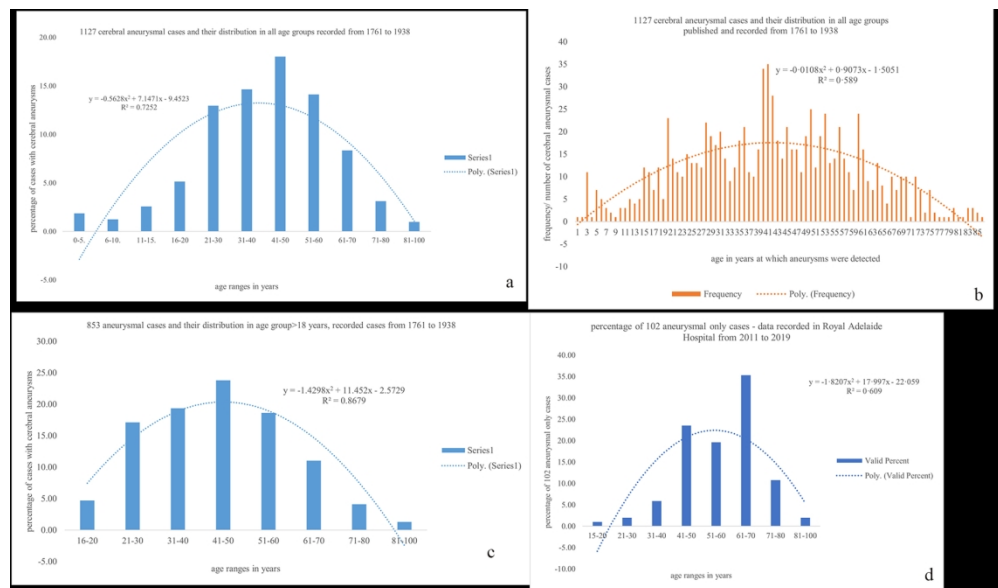


Figure 2 - Figures displaying the distribution patterns of cerebral aneurysms in different age groups recorded from 1761 to 1938 and from 2011 to 2019. A polynomial regression lines show the number and distribution of cerebral aneurysm cases across all age groups. a) The distribution of cerebral aneurysmal 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 recorded 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), recorded 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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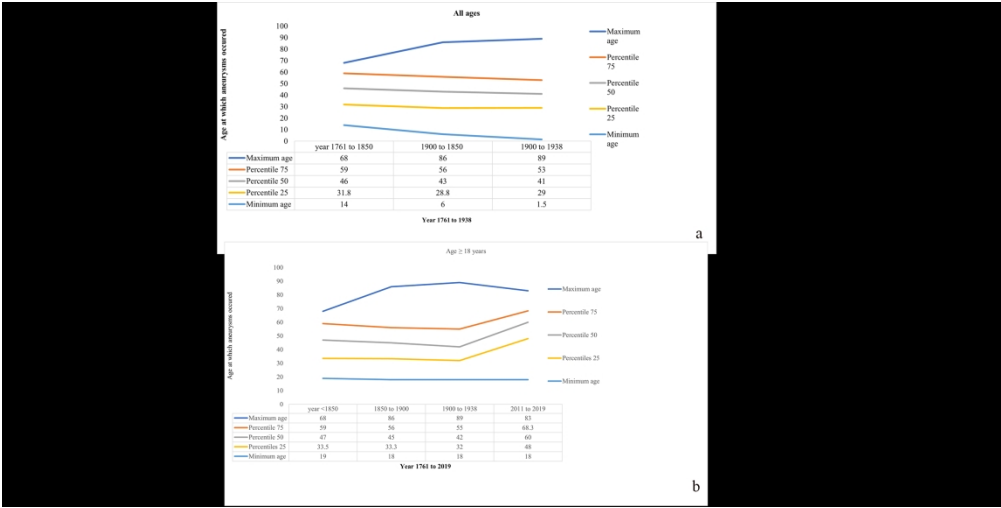


Figure 3: Comparison figures showing the trend of occurrence of cerebral aneurysms at different age groups (n=1127) from 1761 to 2019. (a)The values of the 25th, 50th, and 75th percentiles, as well as the minimum and maximum observed all ages of patients with aneurysms, from 1761 to 1938[14]; b) The 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 1938 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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27 23-30	m	midline	BA	y	Syphilitic	1886
28 16-20	f	left	MCA	a	Embolic (endocarditis)	1887
30 23-30	m	right	VA	y	Embolic (endocarditis)	1887
30 23-30	m	right	MCA	y	Embolic (endocarditis)	1887
31 11-15	m	right	ICA	a	no information available	1887
36 11-40	m	midline	BA	y	No embolism or atherosclerosis	1887
40 16-70	f	right	MCA	y	No embolism or atherosclerosis	1887
43 41-50	f	right	PCA	a	Arteries free of atherosclerosis	1887
49 41-50	f	undefined	CBAN	y	Embolic (endocarditis)	1887
60 51-60	f	left	MCA	y	no information available	1887
		left	VA	a	Arteriosclerosis	1887
		undefined	VA	y	Arteriosclerosis	1887
53 51-60	f	midline	BA	y	no information available	1888
26 23-30	m	midline	BA	a	Septic endocarditis	1889
43 41-50	m	midline	Aorta/A	a	no information available	1889
51 51-60	m	midline	Aorta/A	y	Arteries free of atherosclerosis	1889
56 51-60	f	midline	Aorta/A	y	Arteriosclerosis	1889
6 6-10	m	right	VA	y	Septic emboli	1890
15 11-15	m	right	PCA	a	Septic emboli endocarditis	1890
15 11-15	m	right	MCA	a	Septic emboli endocarditis	1890
15 11-15	m	right	MCA	a	Septic emboli endocarditis	1890
15 11-15	f	bilateral	ICA	y	Septic emboli endocarditis	1890
16 16-20	f	right	MCA	y	Septic emboli	1890
17 16-20	m	left	ICA	a	Septic emboli endocarditis	1890
18 16-20	m	right	MCA	y	Septic emboli	1890
25 23-30	f	right	MCA	y	Septic emboli endocarditis	1890
25 23-30	m	left	MCA	a	Septic emboli endocarditis	1890
25 23-30	f	left	MCA	y	Atherosclerosis	1890
25 23-30	f	right	MCA	y	Septic emboli endocarditis	1890
25 23-30	m	right	MCA	y	Septic emboli endocarditis	1890
31 31-40	m	right	MCA	y	Septic emboli	1890
35 31-40	f	left	MCA	a	Septic emboli endocarditis	1890
35 31-40	f	left	MCA	y	Atherosclerosis	1890
43 41-50	f	left	MCA	y	Atherosclerosis	1890
45 41-50	m	left	MCA	y	Septic emboli	1890
50 41-50	m	left	MCA	y	Atherosclerosis	1890
56 51-60	m	right	ICA	a	Atherosclerosis	1890
66 61-70	m	ICA	ICA	a	Atherosclerosis	1890
60 51-60	f	midline	BA	a	Atherosclerosis	1891
33 31-40	m	midline	BA	y	Other vessels healthy	1892
47 41-50	m	left	MCA	a	No atherosclerosis	1893
7 6-10	m	midline	BA	y	no information available	1894
10 6-10	f	VA	VA	y	no information available	1894
14 11-15	m	left	VA	y	no information available	1894
27 23-30	m	midline	BA	y	no information available	1894
26 23-30	f	right	ICA	y	Soft arteries	1894
26 23-30	m	right	ICA	y	no information available	1894
28 23-30	f	left	MCA	y	no information available	1894
28 23-30	m	midline	Aorta/A	y	no information available	1894
29 23-30	f	left	MCA	y	no information available	1894
30 23-30	f	right	MCA	y	no information available	1894
31 31-40	m	midline	Aorta/A	y	no information available	1894
32 31-40	f	left	MCA	y	no information available	1894
32 31-40	f	midline	BA	y	no information available	1894
32 31-40	m	midline	BA	y	no information available	1894
36 31-40	f	midline	Post/A	y	no information available	1894
36 31-40	m	left	ACA	y	no information available	1894
40 31-40	f	midline	BA	y	no information available	1894
41 31-40	m	right	Aorta/A	y	no information available	1894
41 41-50	m	right	VA	y	no information available	1894
42 41-50	f	left	ICA	y	no information available	1894
42 41-50	m	left	MCA	y	no information available	1894
42 41-50	m	midline	BA	y	no information available	1894
43 41-50	f	right	ICA	y	no information available	1894
43 41-50	m	left	VA	y	no information available	1894
43 41-50	m	left	MCA	y	no information available	1894
43 41-50	m	right	MCA	y	no information available	1894
44 41-50	f	midline	CBAN	y	no information available	1894
45 41-50	f	left	MCA	y	no information available	1894
45 41-50	f	midline	Aorta/A	y	no information available	1894
45 41-50	m	left	ICA	y	no information available	1894
46 41-50	f	midline	BA	y	no information available	1894
46 41-50	m	right	MCA	y	no information available	1894
46 41-50	m	right	MCA	y	no information available	1894
46 41-50	m	right	MCA	y	no information available	1894
48 41-50	f	right	ICA	y	no information available	1894
49 41-50	f	left	VA	y	no information available	1894
49 41-50	f	midline	Post/A	y	no information available	1894
50 41-50	f	right	MCA	y	no information available	1894
50 41-50	m	left	MCA	y	no information available	1894
51 51-60	f	right	MCA	y	no information available	1894
52 51-60	f	left	MCA	y	no information available	1894
53 51-60	f	left	MCA	y	no information available	1894
53 51-60	f	midline	Aorta/A	y	no information available	1894
54 51-60	f	midline	Aorta/A	y	no information available	1894
54 51-60	m	right	MCA	y	no information available	1894
55 51-60	m	right	ICA	y	no information available	1894
55 51-60	m	left	VA	y	no information available	1894
55 51-60	m	midline	BA	y	no information available	1894
56 51-60	f	left	MCA	y	no information available	1894
56 51-60	f	right	MCA	y	no information available	1894
57 51-60	f	right	MCA	y	no information available	1894
57 51-60	f	right	MCA	y	no information available	1894
57 51-60	f	midline	Aorta/A	y	no information available	1894
60 51-60	f	left	VA	y	no information available	1894
60 51-60	f	left	ACA	y	no information available	1894
60 51-60	f	left	ACA	y	no information available	1894
60 51-60	f	left	MCA	y	no information available	1894
61 61-70	f	midline	BA	y	no information available	1894
61 61-70	m	right	ICA	y	no information available	1894
62 61-70	f	midline	Aorta/A	y	no information available	1894
63 61-70	f	left	ACA	y	no information available	1894
63 61-70	f	midline	Aorta/A	y	no information available	1894
64 61-70	f	left	ICA	y	no information available	1894
64 61-70	f	midline	Aorta/A	y	no information available	1894
65 61-70	f	left	ICA	y	no information available	1894
67 61-70	f	left	MCA	y	no information available	1894
67 61-70	f	right	ICA	y	no information available	1894
69 61-70	f	left	ICA	y	no information available	1894
70 61-70	f	right	ICA	y	no information available	1894
72 71-80	f	left	VA	y	no information available	1894
72 71-80	f	right	ICA	y	no information available	1894
73 71-80	f	left	MCA	y	no information available	1894
73 71-80	f	right	VA	y	no information available	1894
73 71-80	f	midline	Aorta/A	y	no information available	1894
79 71-80	f	right	BA	y	no information available	1894
80 71-80	f	right	ACA	y	no information available	1894
81 81-100	f	left	MCA	y	no information available	1894
86 81-100	m	midline	Aorta/A	y	no information available	1894
		midline	CBAN	y	no information available	1894
21 23-30	m	right	ICA	y	other vessels healthy	1895
29 23-30	m	midline	BA	y	no information available	1895
34 31-40	f	right	ICA	y	Wall of aneurysm had two patches of atherosclerosis	1895
40 31-40	m	midline	BA	a	no information available	1897
47 41-50	f	right	MCA	y	no information available	1897
50 41-50	m	left	MCA	y	no information available	1897
53 51-60	m	left	MCA	y	no information available	1897
69 61-70	f	bilateral	ICA	a	no information available	1897
28 23-30	m	midline	BA	a	no information available	1898
54 51-60	m	midline	BA	a	no information available	1898
70 61-70	f	right	MCA	y	Extensive sclerosis with atherosclerotic plaques	1898
29 23-30	m	midline	BA	a	Syphilitic	1899
68 61-70	m	left	VA	a	Vessels atherosclerotic	1900
11 11-15	m	left	pul	y	Embolic (endocarditis)	1901
27 23-30	f	left	MCA	y	Embolic (endocarditis)	1901
28 23-30	m	right	BA	a	normal vessels	1901
32 31-40	f	right	MCA	y	Embolic (endocarditis)	1901
50 41-50	m	right	MCA	y	Atherosclerosis	1901
73 71-80	f	right	MCA	y	no information available	1901
73 71-80	f	right	VA	y	no information available	1901
29 23-30	f	right	Post/A	y	normal vessels	1902
34 31-40	m	undefined	CBAN	y	Syphilitic	1902
45 41-50	f	left	ICA	y	Wall of left internal carotid artery thickened	1902
22 23-30	m	right	ICA	y	healthy	1903
39 31-40	f	right	MCA	y	Line of atherosclerosis at point of aneurysm	1903
64 61-70	f	right	Post/A	y	Syphilitic	1903
27 23-30	m	midline	Aorta/A	y	Wall of other arteries healthy	1904
40 31-40	f	right	ICA	y	no information available	1904
65 61-70	f	right	ACA	y	Atherosclerosis	1904
70 61-70	f	midline	BA	y	Atherosclerosis	1904
86 81-100	m	bilateral	ICA	a	no information available	1904
87 81-100	f	right	ICA	a	Atherosclerosis	1904
40 31-40	m	midline	BA	a	Syphilitic	1905
42 41-50	f	right	Post/A	y	Marked sclerosis	1905
50 41-50	m	right	VA	a	Localized syphilitic periarthritis of aneurysm	1905
51 51-60	m	right	VA	y	no information available	1905
		midline	BA	a	Syphilitic	1905
6 6-10	f	left	MCA	y	Myxotic (nephrosclerotic endocarditis)	1906
28 23-30	m	midline	BA	y	no information available	1906
69 61-70	f	bilateral	ICA	a	Arteriosclerosis	1906
14 11-15	m	left	BA	a	no information available	1906
40 41-50	m	left	MCA	y	Vessels normal	1907
48 41-50	f	left	ICA	a	no atherosclerosis	1907
50 41-50	m	right	MCA	y	Arteries healthy	1907
51 51-60	m	bilateral	Aorta/A	y	no information available	1907
61 61-70	f	left	ICA	y	no information available	1907
63 61-70	f	midline	Aorta/A	a	no information available	1907
65 61-70	f	left	VA	y	Baile's artery tortuous and dilated	1907
68 61-70	m	midline	BA	y	no information available	1907
84 81-100	f	left	ICA	a	no information available	1907
		right	ICA	a	no information available	1907
28 23-30	m	left	Aorta/A	y	Irregular, cord-like thickening of arteries at base	1908
65 61-70	m	right	MCA	a	Atherosclerosis	1908
30 23-30	m	ACA	ICA	y	Thickening right left endarteritis obliterans	1909
27 23-30	m	midline	BA	y	Other arteries normal	1910
44 41-50	f	right	MCA	y	Arteriosclerosis	1910
57 51-60	m	bilateral	VA	a	no information available	1910
64 61-70	m	left	MCA	y	Arteriosclerosis	1910
		left	VA	a	Thick and hard	1910
25 23-30	f	right	ACA	y	Thickening of vessels	1911
36 31-40	m	right	PCA	y	Aneurysm congenital	1911
37 31-40	m	right	ICA	a	no information available	1911
42 41-50	f	right	ICA	y	Both cerebral arteries thickened	1911
42 41-50	m	left	VA	a	Syphilitic	1911
53 51-60	m	left	MCA	a	no information available	1911
62 61-70	f	left	ICA	y	Healthy vessels	1911
21 23-30	m	right	ACA	y	Aneurysm congenital	1912
22 23-30	m	right	MCA	y	Embolic (endocarditis)	1912
25 23-30	f	right	ACA	y	Aneurysm congenital	1912
31 31-40	m	undefined	CBAN	a	No arteriosclerosis	1912
32 31-40	m	left	MCA	y	Aneurysm congenital	1912
37 31-40	f	right	PCA	y	With healthy (probably embolic)	1912
37 31-40	m	left	MCA	y	Embolic (endocarditis)	1912
38 31-40	f	midline	Aorta/A	y	Aneurysm congenital	1912
38 31-40	m	right	VA	y	Aneurysm congenital	1912
40 31-40	m	left	MCA	y	Embolic (endocarditis)	1912
42 41-50	m	left	ICA	y	Aneurysm congenital	1912
42 41-50	m	left	MCA	y	Embolic (endocarditis)	1912
44 41-50	m	right	MCA	y	Vessels somewhat thickened; "congenital" (?)	1912
48 41-50	f	left	MCA	y	Arteriosclerosis	1912
51 51-60	f	left	ACA	y	Aneurysm congenital	1912
		left	ACA	y	Syphilitic endarteritis of cerebral arteries	1912

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	20 16-20	f	right	PotomA	y	syphilis	1936
	22 21-30	m	right	MCA	a	Wall of aneurysm showed diffuse inflammation, of aseptic origin	1936
	28 21-30	m	left	MCA	a	no information available	1936
	31 31-40	f	left	ICA	a	no information available	1936
	31 31-40	m	right	MCA	a	Atherosclerosis	1936
	39 31-40	f	left	ICA	y	no information available	1936
	44 41-50	f	left	ICA	y	Inflammation of intima	1936
	45 41-50	f	left	AsomaA	y	Arteries covered with yellow plaques; seen at operation	1936
	46 41-50	m	right	ICA	y	no information available	1936
	48 41-50	f	right	ICA	y	no information available	1936
	50 41-50	f	midline	AsomaA	y	no information available	1936
	53 51-60	m	left	ICA	y	Arteriosclerosis	1936
	57 51-60	m	left	ICA	a	no information available	1936
	58 51-60	m	undefined	CBAN	a	no information available	1936
	61 61-70	m	left	PotomA	y	Atherosclerosis	1936
	62 61-70	m	right	MCA	a	cerebral aneurysm	1936
	74 71-80	m	midline	AsomaA	y	Atherosclerosis	1936
	2 6-10	f	right	ICA	y	Congenital (?) narrow media	1937
	6 6-10	f	bilateral	MCA	y	Infective (endocarditis)	1937
	9 6-10	m	undefined	CBAN	y	No change in wall; Hämman probably septic embolus	1937
	20 16-20	f	undefined	CBAN	y	no information available	1937
	20 16-20	m	undefined	CBAN	y	no information available	1937
	23 21-30	m	left	ICA	a	Aneurysm seen at operation	1937
	24 21-30	m	midline	BA	y	atherosclerotic, syphilitic aortitis	1937
	26 21-30	f	right	ICA	y	Normal vessels	1937
	28 21-30	m	undefined	CBAN	y	no information available	1937
	29 21-30	f	right	PICA	y	no information available	1937
	32 31-40	m	left	AsomaA	y	no information available	1937
	34 31-40	f	undefined	CBAN	a	no information available	1937
	35 31-40	m	bilateral	ICA	y	Syphilis	1937
	36 31-40	f	right	AsomaA	y	no information available	1937
	36 31-40	m	undefined	CBAN	y	no information available	1937
	37 31-40	m	left	AsomaA	y	Atherosclerosis	1937
	38 31-40	f	midline	AsomaA	y	Syphilis	1937
	39 31-40	m	undefined	CBAN	y	no information available	1937
	40 31-40	m	left	PICA	y	Few small atherosclerosis plaques: acellular, hyalinized, thin media	1937
	42 41-50	m	right	ICA	y	Normal vessels	1937
	43 41-50	f	left	ICA	y	Thickening of wall of internal carotid artery	1937
	44 41-50	f	undefined	CBAN	a	Aneurysm seen at operation	1937
	44 41-50	m	midline	AsomaA	a	no information available	1937
	44 41-50	m	right	ICA	y	Arteriosclerosis	1937
	46 41-50	f	undefined	CBAN	y	no information available	1937
	48 41-50	f	undefined	CBAN	a	no information available	1937
	49 41-50	f	bilateral	ICA	y	Syphilitic aortitis and atherosclerosis	1937
	49 41-50	m	undefined	CBAN	y	Atherosclerosis	1937
	49 41-50	m	right	MCA	y	Syphilitic aortitis and atherosclerosis	1937
	50 41-50	f	left	ICA	a	Aneurysm seen at operation	1937
	50 41-50	m	midline	AsomaA	y	Syphilis	1937
	51 51-60	f	undefined	CBAN	y	no information available	1937
	51 51-60	f	right	MCA	y	Syphilis	1937
	53 51-60	f	right	ICA	y	Aneurysm seen at operation	1937
	54 51-60	f	left	PotomA	y	Arteriosclerosis	1937
	54 51-60	m	undefined	CBAN	y	no information available	1937
	56 51-60	f	left	ICA	a	Aneurysm seen at operation	1937
	58 51-60	f	right	ICA	y	Arteriosclerosis	1937
	58 51-60	m	undefined	CBAN	y	no information available	1937
	61 61-70	f	undefined	CBAN	y	no information available	1937
	62 61-70	f	right	AsomaA	y	Atherosclerosis	1937
	62 61-70	f	undefined	CBAN	y	no information available	1937
	62 61-70	m	undefined	CBAN	y	Atherosclerosis	1937
	63 61-70	f	midline	BA	y	no information available	1937
	65 61-70	f	bilateral	PICA	y	Syphilis	1937
	67 61-70	f	right	ICA	y	Aneurysm seen at operation	1937
	67 61-70	m	undefined	CBAN	y	no information available	1937
	69 61-70	f	right	MCA	y	Syphilis	1937
	71 71-80	m	undefined	CBAN	y	Atherosclerosis	1937
	72 71-80	f	left	PotomA	a	Atherosclerosis	1937
	73 71-80	f	midline	BA	y	Syphilis	1937
	75 71-80	m	left	ICA	y	Arteriosclerosis	1937
	75 71-80	m	midline	AsomaA	y	Atherosclerosis	1937
	84 81-100	f	right	ICA	a	Arteriosclerosis	1937
	84 81-100	f	right	ICA	a	Syphilis	1937
	16 16-20	m	midline	AsomaA	y	Embolus (endocarditis)	1937
	33 31-40	m	right	AsomaA	y	Vessel healthy	1937
	38 31-40	f	MCA	y	Arteriosclerosis	1937	
	41 41-50	f	right	AsomaA	y	Vessel healthy	1937
	42 41-50	f	left	AsomaA	y	Vessel healthy	1937
	60 51-60	f	right	MCA	y	Vessel healthy	1937
	62 61-70	f	midline	AsomaA	y	Vessel healthy	1937
	66 61-70	f	midline	AsomaA	y	Vessel healthy	1937
	31 31-40	m	midline	BA	y	Vessel healthy	1937

age range				
Frequency	Percent	Valid Percent	Cumulative Percent	
Valid	age range	955.00	1127.00	1127.00
Missing		0.00	0.00	0.00
Mean		41.69		
Median		41.00		
Mode		41.00		
Std. Deviation		17.69		
Minimum		1.50		
Maximum		89.00		

recurrence of aneurysms in all age groups (15 months to 89 years), recorded from 1761 to 1938, (McDonald & Korb 1939)

age range				
Frequency	Percent	Valid Percent	Cumulative Percent	
Valid	age range	28.00	2.50	2.50
	f	573.00	50.40	50.40
	m	526.00	46.70	46.70
Total		1127.00	100.00	100.00

side

Frequency				
Percent	Valid Percent	Cumulative Percent		
Valid	side	33.00	2.90	2.90
	bilateral	386.00	34.30	34.30
	midline	279.00	24.80	24.80
	right	367.00	32.60	32.60
	undefined	62.00	5.50	5.50
Total		1127.00	100.00	100.00

arteries- all cases of cerebral aneurysms in all age groups ≥15 months, recorded from 1761 to 1938, (McDonald CA, Korb M. Intracranial aneurysms. Archives of neurology and psychiatry (Chicago) 1939; 42): 298-328)

Frequency				
Percent	Valid Percent	Cumulative Percent		
Valid	arteries	22.00	2.00	2.00
	ACA	237.00	21.00	21.00
	AsomaA	5.00	0.40	0.40
	ICA	142.00	12.60	12.60
	CBAN	49.00	4.30	4.30
	ICA	187.00	16.60	16.60
	MCA	311.00	27.60	27.60
	PotomA	33.00	2.90	2.90
	PotomA	61.00	5.40	5.40
	ptal	2.00	0.20	0.20
	PICA	9.00	0.80	0.80
	ICA	2.00	0.20	0.20
	VA	67.00	5.90	5.90
Total		1127.00	100.00	100.00

rupture

Frequency				
Percent	Valid Percent	Cumulative Percent		
Valid	rupture	54.00	4.80	4.80
	a	198.00	17.60	17.60
	y	875.00	77.60	77.60
Total		1127.00	100.00	100.00

recurrence of aneurysms in age groups ≥18 years, recorded from 1761 to 1938, (McDonald & Korb 1939)

age				
age range	sex	side		
Valid	age range	853.00	853.00	853.00
Missing		0.00	0.00	0.00
Mean		44.68		
Median		43.00		
Mode		41.00		
Std. Deviation		15.46		
Minimum		18.00		
Maximum		89.00		
Percentiles		25	32.00	
		50	43.00	
		75	56.00	

Frequency Table = cases of cerebral aneurysms in age groups ≥18 years, recorded from 1761 to 1938, (McDonald & Korb 1939)

age range				
Frequency	Percent	Valid Percent	Cumulative Percent	
Valid	age range	48.00	4.69	4.69
	16-20	146.00	17.12	17.12
	21-30	165.00	19.34	19.34
	31-40	203.00	23.80	23.80
	41-50	159.00	18.64	18.64
	51-60	94.00	11.62	11.62
	61-70	35.00	4.10	4.10
	71-80	11.00	1.29	1.29
Total		853.00	100.00	100.00

sex = cases of cerebral aneurysms in age groups ≥18 years, recorded from 1761 to 1938, (McDonald & Korb 1939)

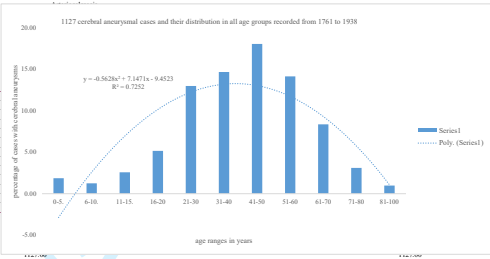
Frequency				
Percent	Valid Percent	Cumulative Percent		
Valid	sex	4.00	0.76	0.76
	f	438.00	51.35	51.35
	m	409.00	47.95	47.95
Total		853.00	100.00	100.00

side involved- cases of cerebral aneurysms in age groups ≥18 years, recorded from 1761 to 1938, (McDonald & Korb 1939)

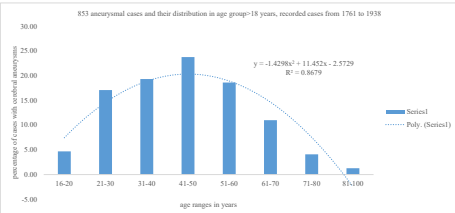
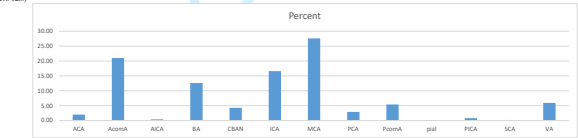
Frequency				
Percent	Valid Percent	Cumulative Percent		
Valid	side	24.00	2.81	2.81
	bilateral	295.00	34.58	34.58
	midline	181.00	21.22	21.22
	right	305.00	35.76	35.76
	undefined	48.00	5.63	5.63
Total		853.00	100.00	100.00

arteries involved- cases of cerebral aneurysms in age groups ≥18 years, recorded from 1761 to 1938, (McDonald & Korb 1939)

Frequency				
Percent	Valid Percent	Cumulative Percent		
Valid	arteries	18.00	2.11	2.11
	ACA			



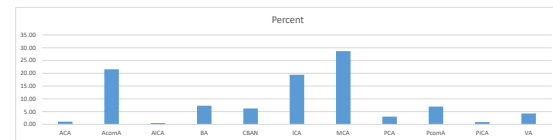
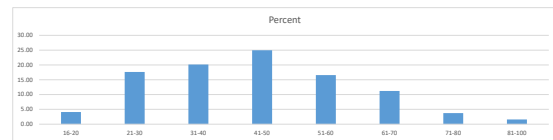
arterial con year	1127	1127.00	0.00
Mean	0.00		
Median	1909.81		
Mode	1926.00		
Std. Deviation	28.13		
Minimum	1761.00		
Maximum	1938.00		



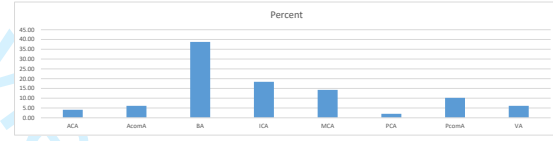
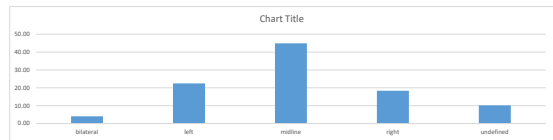
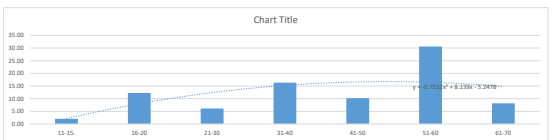
Percent				
2.11				

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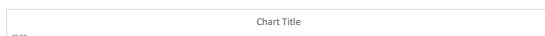
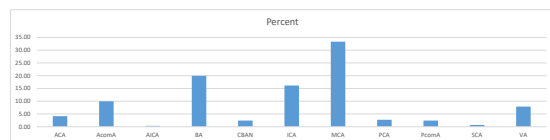
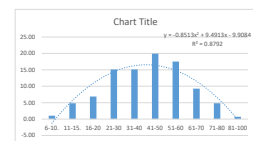
Frequency Table



	rupture		arterial condition
	49.00	49	49.00
	0.00	0	0.00



	rupture	arterial condition	
	291.00	291	291.00
	0.00	0	0.00



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age range		Frequency	Percent	Valid Percent	Cumulative Percent	
Valid	0-5	171.00	21.73	21.73	21.73	21.73
	6-10	21.00	2.67	2.67	24.40	24.40
	11-15	11.00	1.40	1.40	25.80	25.80
	16-20	14.00	1.78	1.78	27.58	27.58
	21-30	32.00	4.07	4.07	31.65	31.65
	31-40	99.00	12.58	12.58	44.23	44.23
	41-50	113.00	14.36	14.36	58.59	58.59
	51-60	140.00	17.79	17.79	76.38	76.38
	61-70	93.00	11.82	11.82	88.20	88.20
	71-80	63.00	8.01	8.01	96.21	96.21
	81-100	21.00	2.67	2.67	98.88	98.88
Total	787.00	100.00	100.00	100.00	100.00	

sex		Frequency	Percent	Valid Percent	Cumulative Percent	
Valid	f	20.00	2.54	2.54	2.54	2.54
	m	400.00	52.30	52.30	54.84	54.84
	Total	377.00	47.36	47.36	100.00	100.00

side		Frequency	Percent	Valid Percent	Cumulative Percent	
Valid	bilateral	28.00	3.56	3.56	3.56	3.56
	left	271.00	34.43	34.43	37.99	37.99
	midline	187.00	23.72	23.72	61.71	61.71
	right	280.00	35.58	35.58	97.29	97.29
	undefined	41.00	5.21	5.21	100.00	100.00

arteries		Frequency	Percent	Valid Percent	Cumulative Percent	
Valid	arteries involved	8.00	1.02	1.02	1.02	1.02
	ACA	205.00	26.05	26.05	27.06	27.06
	AsomaA	4.00	0.51	0.51	27.57	27.57
	ACA	65.00	8.26	8.26	35.83	35.83
	CBAN	42.00	5.34	5.34	41.17	41.17
	ICA	131.00	16.65	16.65	57.81	57.81
	MCA	207.00	26.30	26.30	84.12	84.12
	PCA	24.00	3.05	3.05	87.17	87.17
	PostmA	49.00	6.23	6.23	93.39	93.39
	paal	2.00	0.25	0.25	93.65	93.65
	PCA	9.00	1.14	1.14	94.79	94.79
	VA	41.00	5.21	5.21	100.00	100.00
	Total	787.00	100.00	100.00		

rupture		Frequency	Percent	Valid Percent	Cumulative Percent	
Valid	a	49.00	6.23	6.23	6.23	6.23
	y	112.00	14.23	14.23	20.46	20.46
	Total	626.00	79.54	79.54	100.00	100.00

Cases of cerebral aneurysms in all age (i.e., >15 months to 89 years) & year/year= 1900 to 1938 (McDonald & Korb 1939)

Statistics		age	age range	sex	side	arteries	rupture	arterial condition
N	Valid	616.00	787.00	787.00	787.00	787.00	787.00	787.00
	Missing	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Mean		41.12						
Median		41.00						
Mode		41.00						
Std. Deviation		17.88						
Minimum		1.50						
Maximum		89.00						
Percentiles								
	25	29.00						
	50	41.00						
	75	53.00						

age range		Frequency	Percent	Valid Percent	Cumulative Percent	
Valid	0-5	171.00	21.73	21.73	21.73	21.73
	6-10	21.00	2.67	2.67	24.40	24.40
	11-15	11.00	1.40	1.40	25.80	25.80
	16-20	14.00	1.78	1.78	27.58	27.58
	21-30	32.00	4.07	4.07	31.65	31.65
	31-40	99.00	12.58	12.58	44.23	44.23
	41-50	113.00	14.36	14.36	58.59	58.59
	51-60	140.00	17.79	17.79	76.38	76.38
	61-70	93.00	11.82	11.82	88.20	88.20
	71-80	63.00	8.01	8.01	96.21	96.21
	81-100	21.00	2.67	2.67	98.88	98.88
Total	787.00	100.00	100.00	100.00	100.00	

sex		Frequency	Percent	Valid Percent	Cumulative Percent	
Valid	f	20.00	2.54	2.54	2.54	2.54
	m	400.00	52.30	52.30	54.84	54.84
	Total	377.00	47.36	47.36	100.00	100.00

side		Frequency	Percent	Valid Percent	Cumulative Percent	
Valid	bilateral	28.00	3.56	3.56	3.56	3.56
	left	271.00	34.43	34.43	37.99	37.99
	midline	187.00	23.72	23.72	61.71	61.71
	right	280.00	35.58	35.58	97.29	97.29
	undefined	41.00	5.21	5.21	100.00	100.00

arteries		Frequency	Percent	Valid Percent	Cumulative Percent	
Valid	arteries involved	8.00	1.02	1.02	1.02	1.02
	ACA	205.00	26.05	26.05	27.06	27.06
	AsomaA	4.00	0.51	0.51	27.57	27.57
	ACA	65.00	8.26	8.26	35.83	35.83
	CBAN	42.00	5.34	5.34	41.17	41.17
	ICA	131.00	16.65	16.65	57.81	57.81
	MCA	207.00	26.30	26.30	84.12	84.12
	PCA	24.00	3.05	3.05	87.17	87.17
	PostmA	49.00	6.23	6.23	93.39	93.39
	paal	2.00	0.25	0.25	93.65	93.65
	PCA	9.00	1.14	1.14	94.79	94.79
	VA	41.00	5.21	5.21	100.00	100.00
	Total	787.00	100.00	100.00		

rupture		Frequency	Percent	Valid Percent	Cumulative Percent	
Valid	a	49.00	6.23	6.23	6.23	6.23
	y	112.00	14.23	14.23	20.46	20.46
	Total	626.00	79.54	79.54	100.00	100.00

All 1127 cases of cerebral aneurysms in all age (i.e., >15 months to 89 years) & year/year= 1761 to 1938 (McDonald & Korb 1939)

Statistics		age	age range	sex	side	arteries	rupture	arterial condition
N	Valid	935.00	1127.00	1127.00	1127.00	1127.00	1127.00	1127.00
	Missing	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Mean		41.69						
Median		41.00						
Mode		41.00						
Std. Deviation		17.69						
Minimum		1.50						
Maximum		89.00						
Percentiles								
	25	29.00						
	50	41.00						
	75	54.00						

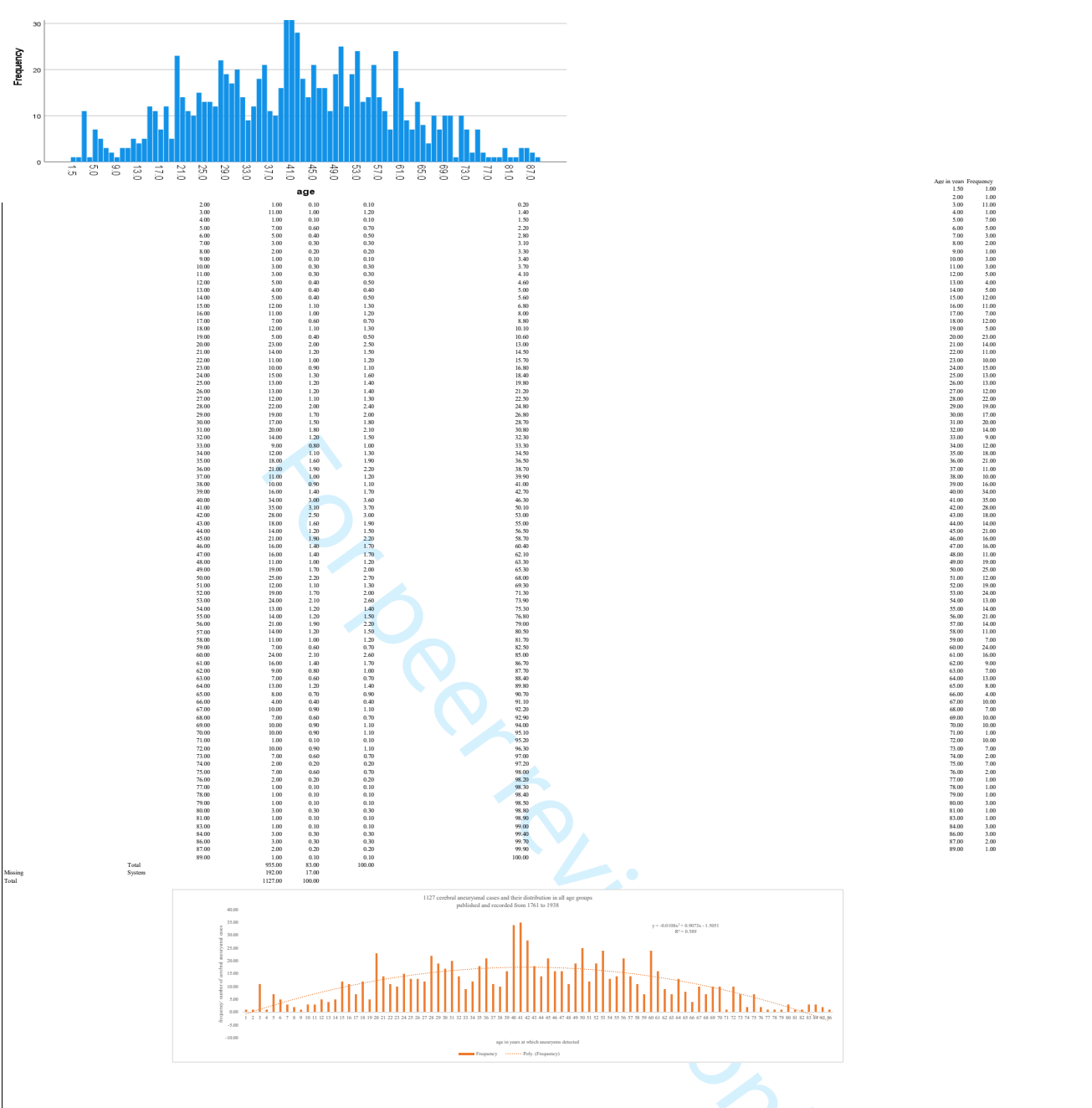
Frequency Table		age range	Frequency	Percent	Valid Percent	Cumulative Percent	
Valid	0-5	171.00	17.64	17.64	17.64	17.64	
	6-10	21.00	1.86	1.86	18.90	18.90	
	11-15	14.00	1.24	1.24	20.14	20.14	
	16-20	29.00	2.57	2.57	21.47	21.47	
	21-30	58.00	5.15	5.15	26.62	26.62	
	31-40	146.00	12.95	12.95	39.57	39.57	
	41-50	165.00	14.64	14.64	54.21	54.21	
	51-60	203.00	18.01	18.01	72.23	72.23	
	61-70	159.00	14.11	14.11	86.34	86.34	
	71-80	94.00	8.34	8.34	94.68	94.68	
	81-100	11.00	0.98	0.98	99.02	99.02	
Total	1127.00	100.00	100.00	100.00	100.00		

sex		Frequency	Percent	Valid Percent	Cumulative Percent	
Valid	f	28.00	2.48	2.48	2.48	2.48
	m	573.00	50.84	50.84	53.31	53.31
	Total	526.00	46.67	46.67	100.00	100.00

side		Frequency	Percent	Valid Percent	Cumulative Percent	
Valid	bilateral	33.00	2.93	2.93	2.93	2.93
	left	386.00	34.27	34.27	37.18	37.18
	midline	279.00	24.76	24.76	61.93	61.93
	right	367.00	32.56	32.56	94.50	94.50
	undefined	62.00	5.50	5.50	100.00	100.00

arteries		Frequency	Percent	Valid Percent	Cumulative Percent	
Valid	arteries involved	22.00	1.95	1.95	1.95	1.95
	ACA	237.00	21.03	21.03	22.98	22.98
	AsomaA	5.00	0.44	0.44	23.43	23.43
	ACA	142.00	12.60	12.60	36.02	36.02
	CBAN	49.00	4.35	4.35	40.37	40.37
	ICA	187.00	16.59	16.59	56.97	56.97
	MCA	311.00	27.60	27.60	84.56	84.56
	PCA	33.00	2.93	2.93	87.49	87.49
	PostmA	61.00	5.41	5.41	92.90	92.90
	paal	2.00	0.18	0.18	93.08	93.08
	PCA	9.00	0.80	0.80	93.88	93.88
	VA	2.00	0.18	0.18	94.06	94.06
	Total	67.00	5.94	5.94	100.00	100.00

rupture		Frequency	Percent	Valid Percent	Cumulative Percent	
Valid	a	54.00	4.79	4.79	4.79	4.79
	y	198.00	17.57	17.57	22.36	22.36
	Total	875.00	77.64	77.64	100.00	100.00



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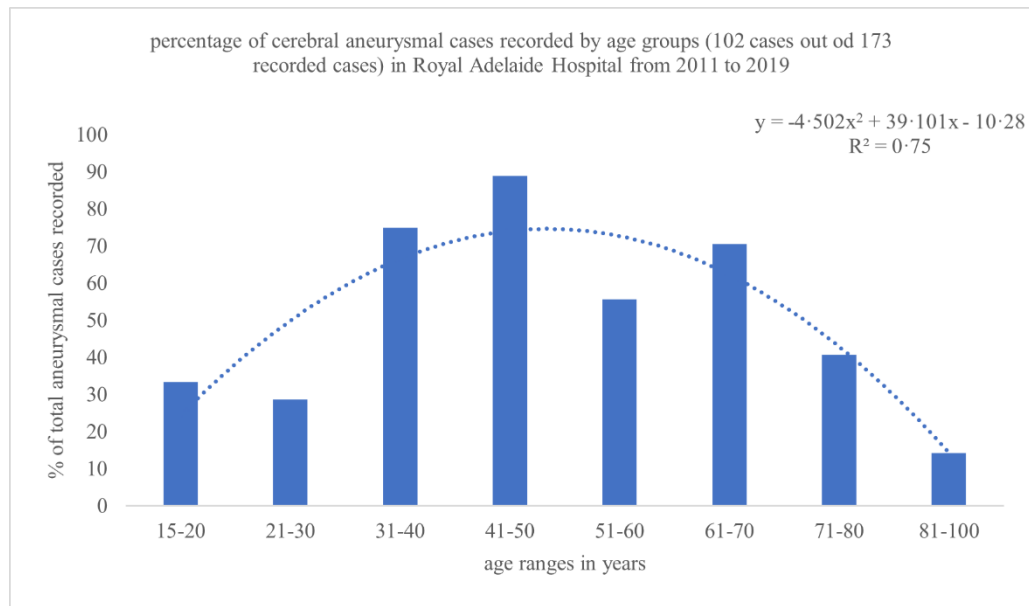
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Valid	n	102.00	100.00	100.00	100.00
Rt SCA an					
	Frequency	Percent	Valid Percent	Cumulative Percent	
Valid	n	101.00	99.02	99.02	99.02
	y	1.00	0.98	0.98	100.00
	Total	102.00	100.00	100.00	
age range- patients with (n=102) and without aneurysms (n=71) included in the study					
	Frequency	Percent	Valid Percent	Cumulative Percent	
Valid	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	31	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	
Sex					
	Frequency	Percent	Valid Percent	Cumulative Percent	
Valid	f	99	52	52	52
	m	83	48	48	100
	Total	173	100	100	

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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

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

For peer review only

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, exposure, follow-up, and data collection
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
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 (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.

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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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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 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.
- 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

76 Not applicable, none

77 **Competing interests**

78 None declared. All authors have nothing to disclose.

80 **Introduction**

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

86 Cerebral aneurysms of all sizes have been observed to cause SAH in adults[4] (incidence 6-10/100000),
87 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
88 the occurrence of anatomical variation-related aneurysms is limited to any specific age. The management of
89 complicated CAs is costly and the CAs can leave permanent disabilities or even become fatal costing millions of
90 dollars to families and governments.[7-12] The majority of childhood SAH (i.e., incidence 1.4-2 per 100000
91 children) are caused by the pre-existing cerebral aneurysms.[13] About 5% of the total cerebral aneurysmal
92 cases diagnosed in the clinical setup were in the age group 0 to 19 years and the incidence of childhood SAH is
93 significantly greater in the older age children.[13] The clinical manifestation of aneurysmal cases seen later in
94 life might be the consequence of aneurysms that developed in early childhood. Therefore, this study aims to
95 review cases of CAs using data collected from a tertiary medical center (Royal Adelaide Hospital - South
96 Australia) and published sources to investigate the recent pattern of CAs and how it has changed over the past
97 260 years. The null hypothesis is that the advancement of medical science did not lead to a reduction in the
98 prevalence of aneurysms by age.

99 **Material and method**

100 **Study design, and setting**

101 Two types of data were used in this study.

102 Type-1 data are composed of 1127 cerebral aneurysmal cases that were published in the 407 papers from 1761
103 to 1938, as compiled by McDonald and, Korb.[14] These CAs were identified at autopsy and included patients
104 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).

106 Type-2 data were Cerebral Computed Tomography Angiography (CTA) images obtained from 173 randomly
107 selected patients, who visited the Royal Adelaide Hospital (RAH), South Australia, between January 2011 and
108 December 2019 for a variety of cranial pathologies; their age ranged from 18 to 100 years, males = 83, female =
109 90, mean age=60 years, median age=62 years, mode age=61, SD=15.72) with (n=102) or without (n=71)
110 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
112 research activities. The consent documents taken from each patient were not provided to the researchers to
113 ensure privacy. The Human Ethics permit (approval number: H2014-176, Research Ethics Committee, Office of
114 Research Ethics, Compliance and Integrity, Faculty of Health Sciences, University of Adelaide) granted
115 permission to access and use the deidentified data set from the Carestream data registry system (Vue-RIS-
116 version-11.0.14.35) for research. Thus, the research materials used in this study comprised 1229 observed cases
117 of CAs that spread across all age groups, spanning a period of approximately 260 years.

118 **Data sources and size**

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

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3 121 file, rearranged and subjected to analysis (Supplementary File 1). Type-2 data: The cerebral CTA of 173-
4 122 patients recorded from 2011 to 2019 in RAH were accessed to study the presence and absence of CAs in
5 123 different locations of CBAN based on diagnoses made by clinicians. Some cases had multiple aneurysms
6 124 located in the various segments of CBAN (Supplementary File 3).

8 125 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,
9 126 61-70, 71-80, and over 81 years and transferred into the SPSS v. 25 software, for analyses (Supplementary File
10 127 1). The observation error has been tested by repeating the observation of the location of CAs in the cerebral
11 128 CTA images in 20-cases, a month after the first study. There was 100% agreement of repeated observations with
12 129 those of the first one. The sites of the formation of aneurysms were recorded as the left and right, internal
13 130 carotid artery (ICA), middle cerebral artery (MCA), anterior cerebral artery (ACA), anterior communicating
14 131 artery complex (AcomAC), posterior communicating artery (PcomA), posterior cerebral artery (PCA), vertebral
15 132 artery (VA), basilar artery (BA), posterior inferior cerebellar artery (PICA), anterior inferior cerebellar artery
16 133 (AICA), superior cerebellar (SCA) and pial arterial regions. In some cases, the areas of location of aneurysms
17 134 seemed not to have been mentioned and those cases were tabulated under the heading of 'aneurysms located in
18 135 CBAN (CBAN-an)'. Overall, the locations of nearly 1229 aneurysmal cases from both data sets were broadly
19 136 divided into four categories: central and bilateral, left and right (Figure 1) before being plotted in the bar charts
20 137 to study the location and distribution trends of aneurysms in the arterial network over the past 260-years (Figure
21 138 2). The aneurysms located in the AcomAC, and basilar arterial regions were classified as the central group of
22 139 aneurysms. Additionally, in a few cases aneurysms were located simultaneously on left and right sides and those
23 140 cases were grouped as 'bilateral' (Supplementary File 1 and Supplementary File 3 and Figure 1).

26 141 **Statistical methods**

28 142 Data were analysed using Excel and Statistical Package for the Social Sciences (SPSS-IBM, version-25)
29 143 program (e.g., descriptive, and Chi squared tests). The p values less than 0.05 were considered as statistically
30 144 significant.

32 145 **Patient and public involvement**

34 146 Involving patients was challenging for conducting and planning this research, since researchers were allowed
35 147 the access only to anonymised raw data recorded in the database. As per the ethics permit (details in the method
36 148 section), we accessed retrospective anonymized data, precluding patient involvement in research planning and
37 149 execution. The shared outcome of this study will be informed to the public, families and patients who attend
38 150 medical centres for various clinical visits, through a series of meetings, seminars, and media releases.

40 151 **Findings**

42 152 This study reviewed 1127 aneurysmal cases of patients of all ages from a total of 407 published articles prior to
43 153 the year 1939. The ages of these patients (male=526, female=573, unknown sex=28) ranged from 18 months to
44 154 89 years of age with an average of 41.70 years, mode of 41 years and median of 41 years (SD=17.7)
45 155 (Supplementary File 2, Figure 2a, Figure 2b, Figure 2c and Supplementary File 1). The second group of patients
46 156 with CAs (44 males and 58 females, and n=102) from the RAH (2011 to 2019) with the age range 18-100 years
47 157 showed that the most common age for diagnosis or complication of CAs ranged from 31-60 years with the
48 158 calculated mean, median, mode, and standard deviation (SD), 57.60, 60.00, 48.00, and 13.12 years, respectively
49 159 (Figure 2d and Supplementary File 4). Analysis of both sets of data revealed that the majority of the patients
50 160 who presented with complicated aneurysms were in their 3rd to 6th decades of life (Supplementary File2).

52 161 The most important aspect of the two sets of data was the wide age range of occurrence of CAs and the fact that
53 162 some of the complicated aneurysmal cases appeared at an early age (Figure 2a, Figure 2b, Supplementary File
54 163 1). A separate analysis was conducted for 853 out of the 1127 cases of CAs recorded before 1938 (male=409,
55 164 female=438, unknown sex=6), specifically focusing on the age range of 18 to 89 years to align the age groups
56 165 with the RAH recorded data from 2011 to 2019 (Supplementary File 2, Figure 2c and Figure 2d). The
57 166 similarities of standard deviation (15.45) of those 853 cases (from 1761-1938) and the cases that were recorded
58 167 from 2011 to 2019 in RAH (13.12 years) validated the comparability of our data and the findings
59 168 (Supplementary File 2). The values of the 25th, 50th, and 75th percentiles, as well as the minimum and

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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, $p \geq 0.36$) (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

Figure 2 - about here

Figure 3 - about here

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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.

238

239 **Discussion**

240 The age and locations at which CAs occur in the CBAN has not changed over past 260 years (Figures 1, 2 and
 241 3, Table 1 and Table 1) despite the life expectancy has increased over time worldwide and the progress in
 242 medicine. In the past people had shorter life span on average, and yet the CAs occurred at the same ages as they
 243 do now.[15] The life expectancy recorded at below 50 years in 1940 and even below 40 years in 1850 was way
 244 lower compared to the one recorded above 80 years of age since the year 2000 in Australia.[15] A separate
 245 analysis was done for 853 out of the 1127 CAs recorded[14] before 1938 focusing on the age range of 18 to 89
 246 years to align the age group with the currently RAH recorded data from 2011 to 2019, since there were no
 247 aneurysmal cases of children (age<18years) in the RAH dataset. In Adelaide there is a separate hospital for
 248 children where aneurysmal cases would have been treated, but the authors had no access to these data
 249 (Supplementary File 3). Royal Adelaide Hospital is a general hospital, thus individuals of 18 years and less are
 250 not admitted. Current study compared the cases of CAs diagnosed by CTA imaging technique (from 2011-2019)
 251 with those verified by surgery and autopsy[14], since there were no cerebral angiogram facilities in early years
 252 (i.e., before 1938). The cases of aneurysms are commonly diagnosed, when the patients are presented at medical
 253 centres after attacks of stroke.[16] Cerebral aneurysms in the past seemed to be ruptured and complicated as
 254 early as 18 months of age and as late as 89 years of age with a wide range of age (Supplementary File 1). The
 255 findings suggested that the change in lifestyle nor medical practice had no effect at the age/time of formation of
 256 CAs in general population. Clinical investigation of lipid profiles in patients commenced after 1950,[17] and
 257 they started attributing arterial diseases and aneurysms to the hyperlipidaemia, however, the manifestation of
 258 occurrence of aneurysms by age in the past 260 years seems not to be different from the current age of
 259 occurrence. Although the lifestyle and the external influences, including medical practice, changed over more
 260 than two centuries, aneurysms still occur at approximately the same age. Therefore, aneurysms occur and
 261 rupture on their own internal circumstances and are not related to the diet, environmental, and external
 262 factors.[18] The most likely internal factor is the severity of the variation on the segments of CBAN that
 263 adversely affects the hemodynamics resulting in the formation of aneurysms.[1,19] The condition of the arterial
 264 wall should not have changed over the last 260 years and that seems to be less significant than the variation in
 265 the components of CBAN. The segmental and communicating arteries play a crucial role in dampening the
 266 systolic pressure within the CBAN and reducing the likelihood of aneurysm formation.[1,19] The severity of
 267 arterial variation can have negative effects on the blood flow dynamics through the variant segment of the
 268 component of the CBAN.[1,19] The incidence of CAs is about 3.3% in the general population and may not be
 269 diagnosed, until they get enlarged as the size of the aneurysm <3mm in diameter can be missed.[20] Imaizumi
 270 and colleagues found that the prevalence rate of CAs was 4.32% in Japan.[12] The incidence rate of CAs in
 271 childhood (age <18 years) has been reported to be 0.5- 4.6%, which is almost as common as the incidence rate
 272 observed among adults.[13] Treating cases of CAs with a diameter less than 3 mm requires careful
 273 consideration, as pre-existing small aneurysms of ≤ 3 mm could rupture, resulting in spontaneous SAH.[21] The
 274 majority of CAs are detected only when they cause a stroke or other pathological effect (e.g., compression of the
 275 optic tract).[4] Individuals older than 18 years are no longer considered children.[6,13]

276 Most of the symptomatic cases of CAs in the paediatric age group were observed in older children (15 + years)
 277 [13], and only complicated cases of CAs were generally diagnosed and reported.[22,23] If the incidence of
 278 childhood CAs described (ranges from 0.17 to 4.6%),[24] is corrected for number of years lived, it would be
 279 18.4% of the total aneurysmal cases amongst adults. The adult patients included in CAs studies ideally have an
 280 age range of 18-years and above, which can include individuals up to the age of 100 years.[12,15] In contrast,
 281 the childhood group included in aneurysmal studies typically ranges from birth up to 18-years of age and a few
 282 studies have categorized patients who are 18-years or older under the adult group.[6,13] When the age range, 0-
 283 18 years and 19- 100 years is considered, the incidence of childhood CAs, that should be multiplied by 5 times
 284 to correct for the number of years lived, can be comparable to that in adults because the childhood period of life
 285 is much shorter than the adulthood. Therefore, the age range of adult group (≥ 20 years up to 100 years) included
 286 in the CAs and stroke studies would be about five times more than the age range of children (i.e., ≤ 18
 287 years).[22,23] That means adults have 5 times more years to develop CAs compared to children. Therefore, the
 288 incidence of childhood CAs per year is almost equivalent to adult.[21,25] Hence, CAs could develop in early

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3 289 childhood in the presence of a significantly variant component of cerebral arterial anatomy,[1,2] and it could
4 290 take years for them to balloon before becoming symptomatic and being observed in a tertiary medical center.
5 291 The overall pattern of location and distribution of childhood CAs was similar to adult as they commonly
6 292 occurred in ICA, MCA and AcomAC regions.[3] Therefore the development of CAs is not age related and
7 293 found to be prevalent in all age ranges.[10,12,13,26] Cerebral aneurysms may not always be associated to the
8 294 advanced age, history of smoking, drinking alcohol but start forming as early as in the childhood in the presence
9 295 of variant components of cranial blood vessels.[27] The mean age at which people were affected by cerebral
10 296 aneurysms was reported to be 55 to 57 years of age in a study conducted using 1085 aneurysmal cases from
11 297 2008 to 2016.[28] There are a few reports of CAs published between 1938 and 2011 that could have been
12 298 compiled for statistical analyses. However, their inclusion into this study, would not have changed its basic
13 299 conclusions: i.e., large age range and no change through time in the occurrence of CAs.

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16 300 Ultrasonographic video screening by placing the probe in the fontanelles of babies before they close has been
17 301 found to be safe and effective in studying brain vessels[26,29] and can be incorporated as a screening tool to
18 302 detect variations in intracranial vessels that could predispose to the development of cerebral aneurysms later in
19 303 life. One illustration of such possibility is that individuals with the left and right ACA proximal segment
20 304 diameter ratio greater than 1.4 have a 27-fold increased risk of developing cerebral aneurysms in the AcomAC
21 305 region.[1] Parents of children found to have variations in CBAN could be advised to schedule follow-up
22 306 screening periodically, especially if a more affordable and convenient technology for detecting brain aneurysms
23 307 becomes available. The current screening recommendation is based on the congenital variations of segments of
24 308 CBAN, but such variations could occur later on life in cases of pathology like atherosclerosis and could cause
25 309 aneurysms. Future studies to test the association of presence of anatomical variations in CBAN in infancy and
26 310 future risk of both unruptured and ruptured intracranial aneurysms in adulthood are recommended.

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29 311 The estimated cost of a single stroke is approximately \$300,000 in Australia.[9] With a haemorrhagic stroke
30 312 incidence of 10 per 100,000 the total cost amounts to \$45 million per year in a city the size of Adelaide[1],
31 313 South Australia, which has a population of 1.5 million. Regular screening for individuals with significantly
32 314 variant brain arteries identified, representing 50% of the population, once every 5 years, and assuming the cost
33 315 of a single computed tomography angiography or magnetic resonance angiogram is about \$100 each, the total
34 316 screening cost would be \$1.5 million per year, that means 30 times reduction in cost of strokes. Additionally, the
35 317 government would receive millions of dollars in return as tax revenue from working individuals who would
36 318 survive with little to no disability from potential strokes resulting from aneurysms. This study was not designed
37 319 to examine the characteristics of aneurysms, but the focus was on the distribution of aneurysms in different
38 320 segments of CBAN, trend of occurrence of aneurysms over the past 260-years, and the comparison of cerebral
39 321 aneurysms in all age ranges.

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41 322 **Limitations:**

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43 323 The insufficient data on the lack of personal and family history, history of smoking, lipid profile, and blood
44 324 pressure are limitations of this study. A larger survey and a prospective study could be conducted. A prospective
45 325 study could involve using ultrasound techniques to identify variations in brain vessels among infants.

46
47 326 **Conclusion**

48
49 327 Brain arterial aneurysms can develop early in the presence of variant arterial components. Screening children
50 328 under 24 months using transcranial ultrasonography for variant cerebral arteries may be practical. Those with
51 329 variations should undergo periodic tests for aneurysms, aiming to prevent some haemorrhagic strokes if an
52 330 affordable and convenient technology for detecting brain aneurysms becomes available.

53
54 331 **Data sharing statement**

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56 332 Additional data are available by emailing Arjun.Burlakoti@unisa.edu.au

57
58 333 **Funding**

59 334 None

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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.

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).

Reference

1. Burlakoti A, Kumaratilake J, Taylor J, Henneberg M. Relationship between cerebral aneurysms and variations in cerebral basal arterial network: A morphometric cross-sectional study in Computed Tomography Angiograms from a neurointerventional unit. *BMJ Open* 2021; 11: 1-8.
2. Menshawi K, Mohr JP, Gutierrez J. A Functional Perspective on the Embryology and Anatomy of the Cerebral Blood Supply. *Journal of stroke* 2015; 17(2): 144-58.
3. Mehrotra A, Nair AP, Das KK, Srivastava A, Sahu RN, Kumar R. Clinical and radiological profiles and outcomes in pediatric patients with intracranial aneurysms: Clinical article. *Journal of Neurosurgery: Pediatrics PED* 2012; 10(4): 340-6.
4. Roessler K, Cejna M, Zachenhofer I. Aneurysmatic subarachnoidal haemorrhage: Incidence and location of small ruptured cerebral aneurysms – a retrospective population-based study. *Wiener Klinische Wochenschrift* 2011; 123(13-14): 444-9.
5. Storrs BB, Humphreys RP, Hendrick E, Hoffman H. Intracranial aneurysms in the pediatric age-group. *Pediatric Neurosurgery* 1982; 9(5): 358-61.
6. Proust F, Toussaint P, Garniéri J, et al. Pediatric cerebral aneurysms. *Journal of neurosurgery* 2001; 94(5): 733-9.
7. Horikoshi T, Akiyama I, Yamagata Z, Nukui H. Retrospective Analysis of the Prevalence of Asymptomatic Cerebral Aneurysm in 4518 Patients Undergoing Magnetic Resonance Angiography. *Neurologia medico-chirurgica* 2002; 42(3): 105-13.
8. Froelich JJ, Neilson S, Peters-Wilke J, et al. Size and location of ruptured intracranial aneurysms: a 5-year clinical survey. *World neurosurgery* 2016; 91: 260-5.
9. Cadilhac DA, Carter R, Thrift AG, Dewey HM. Estimating the Long-Term Costs Of Ischemic and Hemorrhagic Stroke for Australia New Evidence Derived From the North East Melbourne Stroke Incidence Study (NEMESIS). *Stroke* 2009; 40(3): 915-21.

1
2
3 374 10. Jeong Y-G, Jung Y-T, Kim M-S, Eun C-K, Jang S-H. Size and location of ruptured intracranial
4 375 aneurysms. *Journal of Korean Neurosurgical Society* 2009; 45(1): 11.
5
6 376 11. Korja M, Kivisaari R, Jahromi BR, Lehto H. Size and location of ruptured intracranial aneurysms:
7 377 consecutive series of 1993 hospital-admitted patients. *Journal of neurosurgery* 2016; 127(4): 748-53.
8
9 378 12. Imaizumi Y, Mizutani T, Shimizu K, Sato Y, Taguchi J. Detection rates and sites of unruptured
10 379 intracranial aneurysms according to sex and age: an analysis of MR angiography-based brain examinations of
11 380 4070 healthy Japanese adults. *J Neurosurg* 2018; 1(aop): 1-6.
12
13 381 13. Jordan LC, Johnston SC, Wu YW, Sidney S, Fullerton HJ. The Importance of Cerebral Aneurysms in
14 382 Childhood Hemorrhagic Stroke: A Population-Based Study. *Stroke (1970)* 2009; 40(2): 400-5.
15
16 383 14. McDonald CA, Korb M. Intracranial aneurysms. *Archives of neurology and psychiatry (Chicago)*
17 384 1939; 42(2): 298-328.
18
19 385 15. Moore S, Simon JL. The greatest century that ever was. *New York Times* 1999.
20
21 386 16. McGuinness B, Chieng N, Skipworth C, Caldwell J, Molyneux A. Small ruptured cerebral aneurysms-
22 387 do they rupture on formation or not? *Neuroradiology* 2022; 64(3): 597-602.
23
24 388 17. Long MT, Fox CS. The Framingham Heart Study-67 years of discovery in metabolic disease. *Nature*
25 389 *reviews Endocrinology* 2016; 12(3): 177-83.
26
27 390 18. McCorry S, Miller J. Literature and Meat Since 1900. 1st 2019. ed. Cham: Springer International
28 391 Publishing; 2019.
29
30 392 19. Alastruey J, Parker KH, Peiro J, Byrd SM, Sherwin SJ. Modelling the circle of Willis to assess the
31 393 effects of anatomical variations and occlusions on cerebral flows. *J Biomech* 2007; 40(8): 1794-805.
32
33 394 20. Yoon NK, McNally S, Taussky P, Park MS. Imaging of cerebral aneurysms: a clinical perspective.
34 395 *Neurovascular Imaging* 2016; 2(1): 1-7.
35
36 396 21. McGuinness B, Chieng N, Skipworth C, Caldwell J, Molyneux A. Small ruptured cerebral
37 397 aneurysms—do they rupture on formation or not? *Neuroradiology* 2021: 1-6.
38
39 398 22. Brown RD, Broderick JP. Unruptured intracranial aneurysms: epidemiology, natural history,
40 399 management options, and familial screening. *The Lancet Neurology* 2014; 13(4): 393-404.
41
42 400 23. Walendy V, Strauss C, Rachinger J, Stang A. Treatment of aneurysmal subarachnoid haemorrhage in
43 401 Germany: A nationwide analysis of the years 2005-2009. *Neuroepidemiology* 2014; 42(2): 90-7.
44
45 402 24. Pasqualin A, Mazza C, Cavazzani P, Scienza R, DaPian R. Intracranial aneurysms and subarachnoid
46 403 hemorrhage in children and adolescents. *Child's nervous system* 1986; 2(4): 185-90.
47
48 404 25. Matson DD. Intracranial Arterial Aneurysms in Childhood. *J Neurosurg* 1965; 23(6): 578-83.
49
50 405 26. Huisman TA, Poretti A. Pediatric Neurovascular Imaging (CT/MRI/Ultrasound). *Pediatric Vascular*
51 406 *Neurosurgery*; Springer; 2016: 77-109.
52
53 407 27. Krings T, Geibprasert S, Terbrugge KG. Pathomechanisms and treatment of pediatric aneurysms.
54 408 *Child's Nervous System* 2010; 26(10): 1309-18.
55
56 409 28. Fung C, Mavrikakis E, Filis A, et al. Anatomical evaluation of intracranial aneurysm rupture risk in
57 410 patients with multiple aneurysms. *Neurosurgical review* 2019; 42(2): 539-47.
58
59 411 29. Verlhac S. Transcranial Doppler in children. *Pediatric radiology* 2011; 41(1): 153-65.
60 412
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Figure legend -

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

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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.

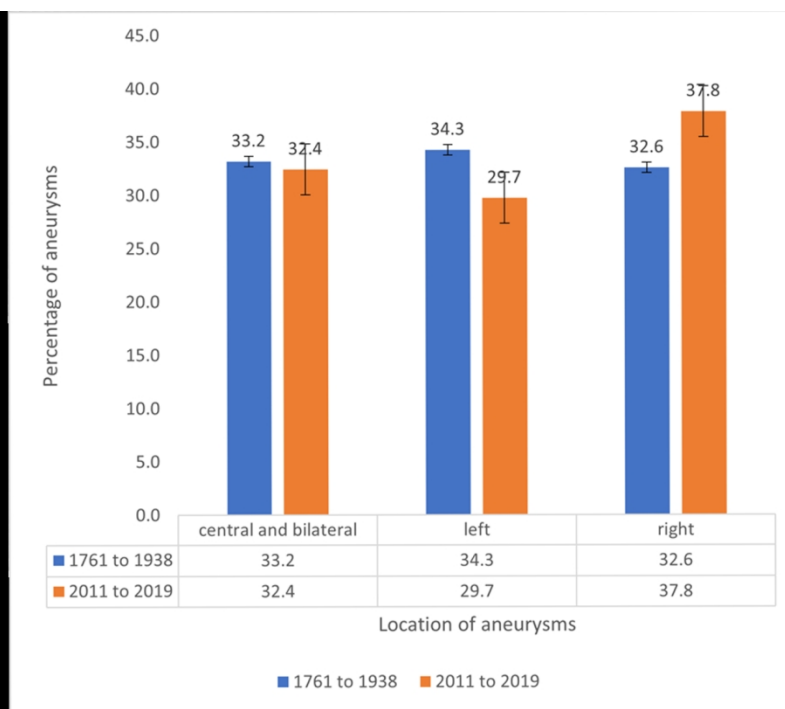


Figure 1 - Comparison of the location of cerebral aneurysms between Royal Adelaide Hospital sample (2011 to 2019) (n=135 CAs from 102 patients, orange colour) with those recorded in 407 publications[14] (1761 to 1938) (n=1127 CAs, blue colour). CAs=cerebral aneurysms, 14 = McDonald, CA & Korb, M 1939,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

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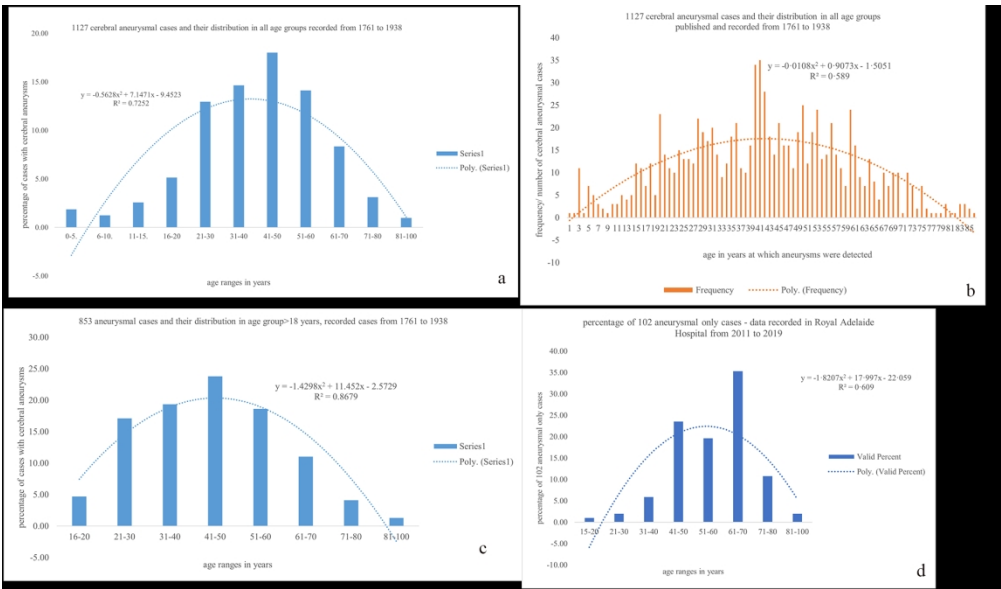


Figure 2 - Figures displaying the distribution patterns of cerebral aneurysms in different age groups recorded from 1761 to 1938 and from 2011 to 2019. A polynomial regression lines show the number and distribution of cerebral aneurysm cases across all age groups. a) The distribution of cerebral aneurysmal 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 recorded 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), recorded 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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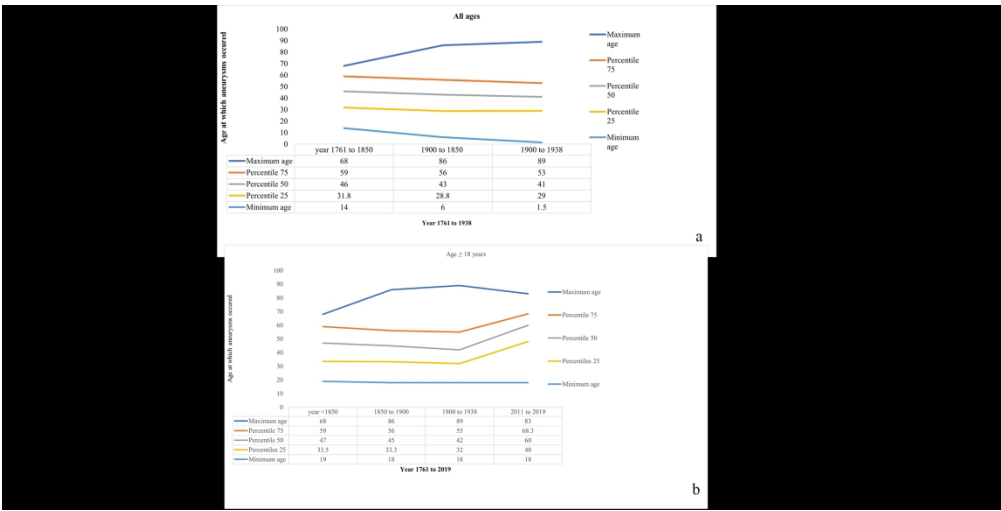


Figure 3: Comparison figures showing the trend of occurrence of cerebral aneurysms at different age groups (n=1127) from 1761 to 2019. (a)The values of the 25th, 50th, and 75th percentiles, as well as the minimum and maximum observed all ages of patients with aneurysms, from 1761 to 1938[14]; b) The 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 1938 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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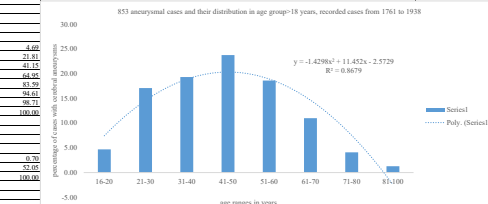
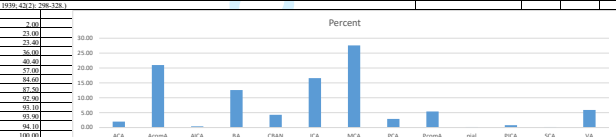
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Figure 1 is a bar chart titled "1127 cerebral aneurysms and their distribution in all age groups recorded from 1761 to 1938". The y-axis is labeled "percentage of cases with different aneurysms" and ranges from -5.00 to 20.00. The x-axis shows age groups: 0-5, 6-10, 11-15, 16-20, 21-30, 31-40, 41-50, 51-60, 61-70, 71-80, and 81-100. The bars represent the percentage of cases for each age group. A dashed blue line represents a polynomial trend line. The equation for the trend line is $y = -0.5626x^2 + 7.1471x - 9.4832$ and the coefficient of determination is $R^2 = 0.7252$. The legend indicates "Series1" for the bars and "Poly (Series1)" for the trend line.

Age Group	Percentage of Cases (%)
0-5	1.5
6-10	1.0
11-15	2.5
16-20	5.0
21-30	13.0
31-40	14.5
41-50	18.5
51-60	14.0
61-70	8.5
71-80	3.0
81-100	1.0



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AcomA		151.00	17.70	17.70	19.81	21.00
ACA		3.00	0.30	0.34	20.46	21.00
BA		109.00	12.70	12.70	17.68	21.00
CBAN		40.00	4.69	4.69	17.63	21.00
ICA		158.00	18.55	18.54	36.15	21.00
MCA		260.00	29.71	29.71	55.40	21.00
PCA		24.00	2.81	2.81	30.20	21.00
PcomA		71.00	8.09	8.09	34.20	21.00
PCA		5.00	0.59	0.58	39.88	21.00
SCA		2.00	0.23	0.23	41.00	21.00
VA		42.00	4.92	4.92	100.00	21.00
Total		851.00	100.00	100.00		

Frequency: cases of cerebral aneurysms in age groups ≥18 years, recorded from 1761 to 1938 (McDonald & Koth 1939)

Statistics		age		age range		sex		side		arteries		rupture		arterial condition	
N		Valid		170.00		18.81		19.85		19.91					
Mean		Valid		65.000		66.67		66.67		100.00					
Std. Deviation		Valid		83.000		100.00		100.00							

Statistics

age		age range		sex		side		arteries		rupture		arterial condition	
N		Valid		170.00		18.81		19.85		19.91			
Mean		Valid		65.000		66.67		66.67		100.00			
Std. Deviation		Valid		83.000		100.00		100.00					
Minimum		Valid		17.000		17.70		17.68					
Maximum		Valid		109.000		109.000		109.000					
Percentiles		Valid		25		50		75					

age range

age range in years		Frequency		Percent		Valid Percent		Cumulative Percent	
Valid		17.00		17.70		17.71		17.71	
Mean		Valid		65.000		66.67		66.67	
Std. Deviation		Valid		83.000		100.00		100.00	
Minimum		Valid		17.000		17.70		17.68	
Maximum		Valid		109.000		109.000		109.000	
Percentiles		Valid		25		50		75	

sex

Frequency		Percent		Valid Percent		Cumulative Percent	
Valid		17.00		17.70		17.71	
Mean		Valid		65.000		66.67	
Std. Deviation		Valid		83.000		100.00	
Minimum		Valid		17.000		17.70	
Maximum		Valid		109.000		109.000	
Percentiles		Valid		25		50	

side

Frequency		Percent		Valid Percent		Cumulative Percent	
Valid		17.00		17.70		17.71	
Mean		Valid		65.000		66.67	
Std. Deviation		Valid		83.000		100.00	
Minimum		Valid		17.000		17.70	
Maximum		Valid		109.000		109.000	
Percentiles		Valid		25		50	

arteries

Frequency		Percent		Valid Percent		Cumulative Percent	
Valid		17.00		17.70		17.71	
Mean		Valid		65.000		66.67	
Std. Deviation		Valid		83.000		100.00	
Minimum		Valid		17.000		17.70	
Maximum		Valid		109.000		109.000	
Percentiles		Valid		25		50	

rupture

Frequency		Percent		Valid Percent		Cumulative Percent	
Valid		17.00		17.70		17.71	
Mean		Valid		65.000		66.67	
Std. Deviation		Valid		83.000		100.00	
Minimum		Valid		17.000		17.70	
Maximum		Valid		109.000		109.000	
Percentiles		Valid		25		50	

arterial condition

Frequency		Percent		Valid Percent		Cumulative Percent	
Valid		17.00		17.70		17.71	
Mean		Valid		65.000		66.67	
Std. Deviation		Valid		83.000		100.00	
Minimum		Valid		17.000		17.70	
Maximum		Valid		109.000		109.000	
Percentiles		Valid		25		50	

Frequency: cases of cerebral aneurysms in age groups ≥18 years, recorded from 1761 to 1938 (McDonald & Koth 1939)

Statistics		age		age range		sex		side		arteries		rupture		arterial condition	
N		Valid		170.00		18.81		19.85		19.91					
Mean		Valid		65.000		66.67		66.67		100.00					
Std. Deviation		Valid		83.000		100.00		100.00							

Statistics

age		age range		sex		side		arteries		rupture		arterial condition	
N		Valid		170.00		18.81		19.85		19.91			
Mean		Valid		65.000		66.67		66.67		100.00			
Std. Deviation		Valid		83.000		100.00		100.00					
Minimum		Valid		17.000		17.70		17.68					
Maximum		Valid		109.000		109.000		109.000					
Percentiles		Valid		25		50		75					

age range

age range in years		Frequency		Percent		Valid Percent		Cumulative Percent	
Valid		17.00		17.70		17.71		17.71	
Mean		Valid		65.000		66.67		66.67	
Std. Deviation		Valid		83.000		100.00		100.00	
Minimum		Valid		17.000		17.70		17.68	
Maximum		Valid		109.000		109.000		109.000	
Percentiles		Valid		25		50		75	

sex

Frequency		Percent		Valid Percent		Cumulative Percent	
Valid		17.00		17.70		17.71	
Mean		Valid		65.000		66.67	
Std. Deviation		Valid		83.000		100.00	
Minimum		Valid		17.000		17.70	
Maximum		Valid		109.000		109.000	
Percentiles		Valid		25		50	

side

Frequency		Percent		Valid Percent		Cumulative Percent	
Valid		17.00		17.70		17.71	
Mean		Valid		65.000		66.67	
Std. Deviation		Valid		83.000		100.00	
Minimum		Valid		17.000		17.70	
Maximum		Valid		109.000		109.000	
Percentiles		Valid		25		50	

arteries

Frequency		Percent		Valid Percent		Cumulative Percent	
Valid		17.00		17.70		17.71	
Mean		Valid		65.000		66.67	
Std. Deviation		Valid		83.000		100.00	
Minimum		Valid		17.000		17.70	
Maximum		Valid		109.000		109.000	
Percentiles		Valid		25		50	

rupture

Frequency		Percent		Valid Percent		Cumulative Percent	
Valid		17.00		17.70		17.71	
Mean		Valid		65.000		66.67	
Std. Deviation		Valid		83.000		100.00	
Minimum		Valid		17.000		17.70	
Maximum		Valid		109.000		109.000	
Percentiles		Valid		25		50	

arterial condition

Frequency		Percent		Valid Percent		Cumulative Percent	
Valid		17.00		17.70		17.71	
Mean		Valid		65.000		66.67	
Std. Deviation		Valid		83.000		100.00	
Minimum		Valid		17.000		17.70	
Maximum		Valid		109.000		109.000	
Percentiles		Valid		25		50	

Frequency: cases of cerebral aneurysms in age groups ≥18 years, recorded from 1761 to 1938 (McDonald & Koth 1939)

Statistics		age		age range		sex		side		arteries		rupture		arterial condition	
N		Valid		170.00		18.81		19.85		19.91					
Mean		Valid		65.000		66.67		66.67		100.00					
Std. Deviation		Valid		83.000		100.00		100.00							

Statistics

age		age range		sex		side		arteries		rupture		arterial condition	
N		Valid		170.00		18.81		19.85		19.91			
Mean		Valid		65.000		66.67		66.67		100.00			
Std. Deviation		Valid		83.000		100.00		100.00					
Minimum		Valid		17.000		17.70		17.68					
Maximum		Valid		109.000		109.000		109.000					
Percentiles		Valid		25		50		75					

age range

age range in years		Frequency		Percent		Valid Percent		Cumulative Percent	
Valid		17.00		17.70		17.71		17.71	
Mean		Valid		65.000		66.67		66.67	
Std. Deviation		Valid		83.000		100.00		100.00	
Minimum		Valid		17.000		17.70		17.68	
Maximum		Valid		109.000		109.000		109.000	
Percentiles		Valid		25		50		75	

sex

Frequency		Percent		Valid Percent		Cumulative Percent	
Valid		17.00		17.70		17.71	
Mean		Valid		65.000		66.67	
Std. Deviation		Valid		83.000		100.00	
Minimum		Valid		17.000		17.70	
Maximum		Valid		109.000		109.000	
Percentiles		Valid		25		50	

side

Frequency		Percent		Valid Percent		Cumulative Percent	
Valid		17.00		17.70		17.71	
Mean		Valid		65.000		66.67	
Std. Deviation		Valid		83.000		100.00	
Minimum		Valid		17.000		17.70	
Maximum		Valid		109.000		109.000	
Percentiles		Valid		25		50	

arteries

Frequency		Percent		Valid Percent		Cumulative Percent	
Valid		17.00		17.70		17.71	
Mean		Valid		65.000		66.67	
Std. Deviation		Valid		83.000		100.00	
Minimum		Valid		17.000		17.70	
Maximum		Valid		109.000		109.000	
Percentiles		Valid		25		50	

rupture

Frequency		Percent		Valid Percent		Cumulative Percent	
Valid		17.00		17.70		17.71	
Mean		Valid		65.000		66.67	
Std. Deviation		Valid		83.000		100.00	
Minimum		Valid		17.000		17.70	
Maximum		Valid		109.000		109.000	
Percentiles		Valid		25		50	

arterial condition

Frequency		Percent		Valid Percent		Cumulative Percent	
Valid		17.00		17.70		17.71	
Mean		Valid		65.000		66.67	
Std. Deviation		Valid		83.000		100.00	
Minimum		Valid		17.000		17.70	
Maximum		Valid		109.000		109.000	
Percentiles		Valid		25		50	

Frequency: cases of cerebral aneurysms in age groups ≥18 years, recorded from 1761 to 1938 (McDonald & Koth 1939)

Statistics		age		age range		sex		side		arteries		rupture		arterial condition	
N		Valid		170.00		18.81		19.85		19.91					
Mean		Valid		65.000		66.67		66.67		100.00					
Std. Deviation		Valid		83.000		100.00		100.00							

Statistics

age		age range		sex		side		arteries		rupture		arterial condition	
N		Valid		170.00		18.81		19.85		19.91			
Mean		Valid		65.000		66.67		66.67		100.00			
Std. Deviation		Valid		83.000		100.00		100.00					
Minimum		Valid		17.000		17.70		17.68					
Maximum		Valid		109.000		109.000		109.000					
Percentiles		Valid		25		50		75					

age range

age range in years		Frequency		Percent		Valid Percent		Cumulative Percent	
Valid		17.00		17.70		17.71		17.71	
Mean		Valid		65.000		66.67		66.67	
Std. Deviation		Valid		83.000		100.00		100.00	
Minimum		Valid		17.000		17.70		17.68	
Maximum		Valid		109.000		109.000		109.000	
Percentiles		Valid		25		50		75	

sex

Frequency		Percent		Valid Percent		Cumulative Percent	
Valid		17.00		17.70		17.71	
Mean		Valid		65.000		66.67	
Std. Deviation		Valid		83.000		100.00	
Minimum		Valid		17.000		17.70	
Maximum		Valid		109.000		109.000	
Percentiles		Valid		25		50	

side

Frequency		Percent		Valid Percent		Cumulative Percent	
Valid		17.00		17.70		17.71	
Mean		Valid		65.000		66.67	
Std. Deviation		Valid		83.000		100.00	
Minimum							

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age range									
Valid									
	Frequency	Percent	Valid Percent	Cumulative Percent					
0-5	171.00	21.73	21.73	21.73					
6-10	21.00	2.67	2.67	24.40					
11-15	11.00	1.39	1.39	25.80					
16-20	14.00	1.78	1.78	27.58					
21-30	32.00	4.07	4.07	31.65					
31-40	99.00	12.50	12.50	44.15					
41-50	113.00	14.36	14.36	58.51					
51-60	180.00	22.79	22.79	81.30					
61-70	93.00	11.82	11.82	93.12					
71-80	63.00	8.00	8.00	101.12					
81-100	21.00	2.67	2.67	103.80					
Total	787.00	100.00	100.00						
sex									
Valid									
	Frequency	Percent	Valid Percent	Cumulative Percent					
F	20.00	2.54	2.54	2.54					
M	450.00	57.30	57.30	59.84					
Total	787.00	100.00	100.00						
side									
Valid									
	Frequency	Percent	Valid Percent	Cumulative Percent					
bilateral	28.00	3.56	3.56	3.56					
left	271.00	34.43	34.43	37.99					
midline	260.00	33.16	33.16	71.15					
right	260.00	33.16	33.16	104.31					
undefined	41.00	5.21	5.21	109.52					
Total	787.00	100.00	100.00						
arteries									
Valid									
	Frequency	Percent	Valid Percent	Cumulative Percent					
ACA	8.00	1.02	1.02	1.02					
AsymA	305.00	38.75	38.75	39.77					
ABCA	4.00	0.51	0.51	40.28					
BA	450.00	57.30	57.30	97.57					
CBAS	42.00	5.34	5.34	102.91					
ICA	113.00	14.36	14.36	117.27					
MCA	207.00	26.30	26.30	143.57					
PCA	24.00	3.05	3.05	146.62					
Protonk	49.00	6.22	6.22	152.84					
gall	4.00	0.51	0.51	153.35					
PCA	4.00	0.51	0.51	153.86					
Total	787.00	100.00	100.00						
regions									
Valid									
	Frequency	Percent	Valid Percent	Cumulative Percent					
0	49.00	6.22	6.22	6.22					
1	112.00	14.23	14.23	20.45					
2	626.00	79.54	79.54	100.00					
Total	787.00	100.00	100.00						
All 1127 cases of cerebral aneurysms in all age (ie, >15 months to 89 years) & year/year=1761 to 1938 (McDonald & Koth 1939)									
Statistics									
N	Valid	Missing	Percent	Valid Percent	Median	Mean	Standard Deviation	Minimum	Maximum
Age	935.00	1127.00	0.00	0.00	41.17	41.17	17.64	0	99
Sex	935.00	1127.00	0.00	0.00	41.17	41.17	17.64	0	99
Side	935.00	1127.00	0.00	0.00	41.17	41.17	17.64	0	99
Arteries	935.00	1127.00	0.00	0.00	41.17	41.17	17.64	0	99
Regions	935.00	1127.00	0.00	0.00	41.17	41.17	17.64	0	99
Frequency Table									
age range									
Valid									
	Frequency	Percent	Valid Percent	Cumulative Percent					
0-5	182.00	17.66	17.66	17.66					
6-10	21.00	1.86	1.86	19.52					
11-15	14.00	1.25	1.25	20.77					
16-20	29.00	2.57	2.57	23.34					
21-30	58.00	5.15	5.15	28.49					
31-40	146.00	12.97	12.97	41.46					
41-50	165.00	14.62	14.62	56.08					
51-60	280.00	24.61	24.61	80.69					
61-70	159.00	14.11	14.11	94.80					
71-80	94.00	8.34	8.34	103.14					
81-100	35.00	3.11	3.11	106.25					
Total	1127.00	100.00	100.00						
sex									
Valid									
	Frequency	Percent	Valid Percent	Cumulative Percent					
F	29.00	2.58	2.58	2.58					
M	573.00	50.82	50.82	53.40					
Total	1127.00	100.00	100.00						
side									
Valid									
	Frequency	Percent	Valid Percent	Cumulative Percent					
bilateral	33.00	2.93	2.93	2.93					
left	366.00	32.57	32.57	35.50					
midline	279.00	24.76	24.76	60.26					
right	267.00	23.76	23.76	84.02					
undefined	62.00	5.50	5.50	89.52					
Total	1127.00	100.00	100.00						
arteries									
Valid									
	Frequency	Percent	Valid Percent	Cumulative Percent					
ACA	22.00	1.95	1.95	1.95					
AsymA	337.00	29.91	29.91	31.86					
ABCA	5.00	0.44	0.44	32.30					
BA	462.00	40.99	40.99	73.29					
CBAS	49.00	4.35	4.35	77.64					
ICA	187.00	16.59	16.59	94.23					
MCA	311.00	27.60	27.60	121.83					
PCA	33.00	2.93	2.93	124.76					
Protonk	50.00	4.44	4.44	129.20					
gall	5.00	0.44	0.44	130.14					
PCA	5.00	0.44	0.44	130.58					
Total	1127.00	100.00	100.00						
regions									
Valid									
	Frequency	Percent	Valid Percent	Cumulative Percent					
0	54.00	4.79	4.79	4.79					
1	106.00	9.40	9.40	14.19					
2	874.00	77.62	77.62	100.00					
Total	1127.00	100.00	100.00						

Percent

age range	Percent
0-5	21.73
6-10	2.67
11-15	1.39
16-20	1.78
21-30	4.07
31-40	12.50
41-50	14.36
51-60	22.79
61-70	11.82
71-80	8.00
81-100	2.67

Percent

side	Percent
bilateral	3.56
left	34.43
midline	33.16
right	33.16

Percent

arteries	Percent
ACA	1.02
AsymA	38.75
ABCA	0.51
BA	57.30
CBAS	5.34
ICA	14.36
MCA	26.30
PCA	3.05
Protonk	6.22
gall	0.51
PCA	0.51

Percent

regions	Percent
0	6.22
1	14.23
2	79.54

Percent

age range	Percent
0-5	17.66
6-10	1.86
11-15	1.25
16-20	2.57
21-30	5.15
31-40	12.97
41-50	14.62
51-60	24.61
61-70	14.11
71-80	8.34
81-100	3.11

Percent

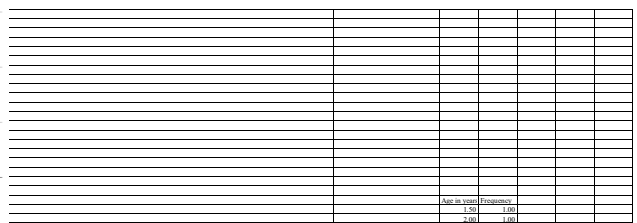
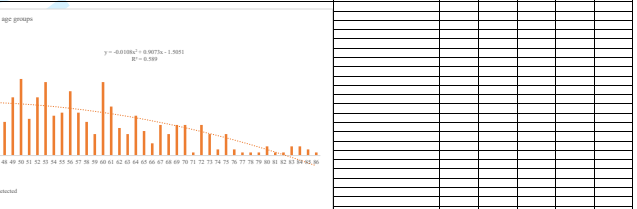
side	Percent
bilateral	2.93
left	32.57
midline	24.76
right	23.76

Percent

arteries	Percent
ACA	1.95
AsymA	29.91
ABCA	0.44
BA	40.99
CBAS	4.35
ICA	16.59
MCA	27.60
PCA	2.93
Protonk	4.44
gall	0.44
PCA	0.44

Percent

regions	Percent
0	4.79
1	9.40
2	77.62

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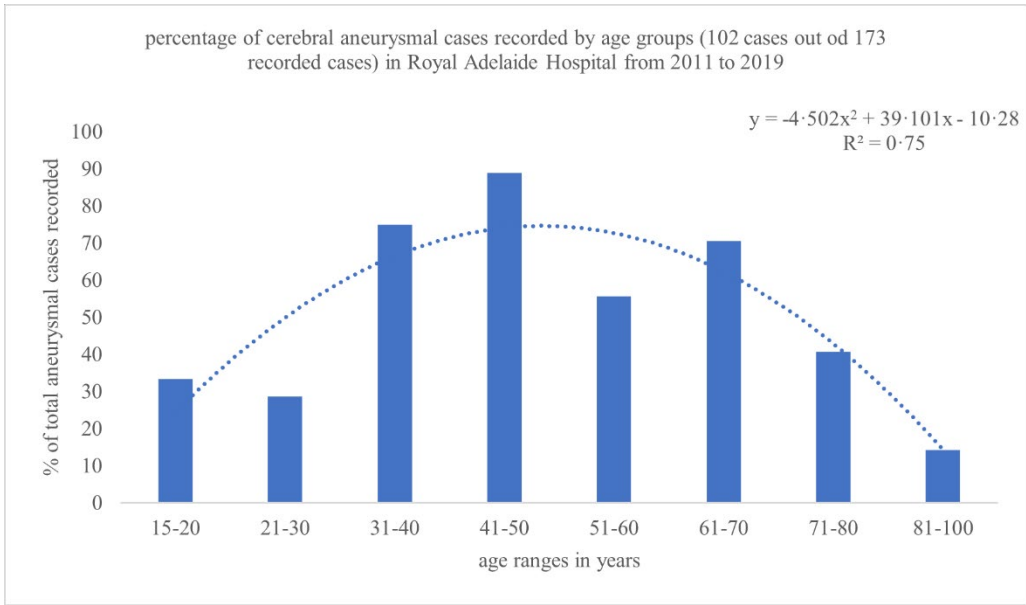
Supplementary File 2: Statistical parameters of distributions of aneurysmal cases reported from 1761-1938,¹⁴ and recorded in RAH from 2011 to 2019.

		102 patients with cerebral aneurysmal aneurysms recorded in RAH from 2011 to 2019	1127 patients with cerebral aneurysms recorded in 407 publications - published from 1761 to 1938							
Statistics - all cases with cerebral aneurysms		age>18, 2011 to 2019	age>18 years, 1761 to 1938	age >= 18 & year < 1850	age >= 18 & year >= 1850 & year < 1900	age >= 18 & year >= 1900	all age, year < 1850	all age, year < 1900 & year >= 1850	all ages, year >= 1900	all age group, all years, >400 publications
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 age		60.0	43.0	47.0	45.0	42.0	46.0	43.0	41.0	41.0
Mode age		48.0	41.0	20.0	40.0	41.0	20.0	40.0	41.0	41.0
Std. Deviation		13.1	15.5	15.6	15.6	15.4	16.1	17.5	17.9	17.7
Minimum age		18.0	18.0	19.0	18.0	18.0	14.0	6.0	1.5	1.5
Maximum age		83.0	89.0	68.0	86.0	89.0	68.0	86.0	89.0	89.0
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.

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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).

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 (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, exposure, follow-up, and data collection (not applicable)
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants (not applicable)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (lines 125 to 140)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (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 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)
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.