Anxiety disorders and risk of stroke: a systematic review and meta-analysis

María Pérez-Piñar [a], Luis Ayerbe [a,b], Esteban González [c], Rohini Mathur [b], Quintí Foguet-Boreu [d,e], Salma Ayis [f]

a- The Westborough Road Health Centre. Westcliff on Sea. United Kingdom

b- Centre of Primary Care and Public Health. Queen Mary University of London. United Kingdom

c- Primary Care Unit. Department of Medicine. Autonoma University of Madrid, Spain.

d-Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol), Universitat Autònoma de Barcelona. Spain

e- Department of Medical Sciences, School of Medicine, University of Girona. Spain

f- Division of Health and Social care. Kings College London. United Kingdom

Correspondence to:

Luis Ayerbe

Centre of Primary Care and Public Health

Queen Mary University of London

Yvonne Carter Building

58 Turner Street. London E1 2AB

Tel: (0044)7984764868

l.garcia-morzon@qmul.ac.uk

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Abstract

Background: Anxiety disorders are the most common mental health problem worldwide. However, the evidence on the association between anxiety disorders and risk of stroke is limited. This systematic review and meta-analysis presents a critical appraisal and summary of the available evidence on the association between anxiety disorders and risk of stroke.

Methods: Cohort studies reporting risk of stroke among patients with anxiety disorders were searched in PubMed, Embase, PsycINFO, Scopus, and the Web of Science, from database inception to June 2016. The quality of the studies was assessed using standard criteria. A meta-analysis was undertaken to obtain pooled estimates of the risk of stroke among patients with anxiety disorders.

Results: Eight studies, including 950759 patients, from the 11764 references initially identified, were included in this review. A significantly increased risk of stroke for patients with anxiety disorders was observed, with an overall hazard ratio: 1.24 (1.09-1.41) p=0.001 No significant heterogeneity between studies was detected and the funnel plot suggested that publication bias was unlikely. Limited evidence suggests that the risk of stroke is increased shortly after the diagnosis of anxiety and that risk of stroke may be higher for patients with severe anxiety.

Conclusions: Anxiety disorders are a very prevalent modifiable condition associated with risk of stroke increased by 24%. This evidence could inform the development of interventions for the management of anxiety and the prevention of stroke. Further studies on the risk of stroke in patients with anxiety, and the explanatory factors for this association, are required.

Key words: Stroke, Cohort studies, Systematic review, Anxiety disorders

1. Introduction

Anxiety disorders are the most common mental health problem worldwide with lifetime prevalence in the general population, varying across countries, up to 29%.(1-3) It is also the sixth global leading cause of disability, with no discernible change observed from 1990.(4) Stroke is the second most common cause of death, and the third most common cause of reduced disability-adjusted life-years (DALYs), worldwide.(5, 6) Most of the burden of stroke affects low and middle-income countries.(7) Primary prevention of stroke is particularly important because 76% of strokes are first events.(8) Anxiety disorders can have a direct effect on incidence of stroke and also an indirect effect as they may be associated with other cardiovascular risk factors and markers of high cardiovascular risk.(9, 10) While the association between anxiety disorders and coronary artery disease is well established,(11) their impact on the risk of stroke has received less attention. Previous reviews on the associations between anxiety and cardiovascular disease (12-17) do not present specific results for stroke, or do not include the most updated studies. A better understanding of the association between anxiety disorders and stroke would strengthen the evidence for causality and, since anxiety disorders are modifiable conditions, it could also inform the development of clinical and public health interventions for the management of anxiety and the prevention of stroke. This systematic review and meta-analysis presents an up to date critical appraisal and summary of the available evidence on the association between anxiety disorders and risk of incident stroke.

2. Methods

The Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria were used to undertake this review (Appendix A).(18) Electronic searches were conducted by three authors

(MPP, EG and LA) in PubMed, Embase, PsycINFO, Scopus and the Web of Science, from database inception to the 7th June 2016.

We aimed to identify studies in compliance with the following inclusion criteria:

1) Cohort study design

2) Reporting of original research data

3) Anxiety disorder assessed as exposure

4) Incident strokes reported as outcome

5) Direct reporting of relative risk (RR), odds ratio (OR), or hazard ratio (HR) with corresponding 95% confidence intervals (CIs), or sufficient raw data such that estimates could be calculated.

The search strategy is presented in appendix B. The titles and abstracts of all the references identified in the initial search were checked against inclusion criteria. Papers citing all the included studies, or relevant reviews (12-17) were also searched in the Web of Science and considered for inclusion. The bibliography of all papers fitting the inclusion criteria and relevant reviews (12-17) was checked as well for further articles. There were no restrictions on the basis of language, sample size or duration of follow-up. Studies were excluded if they were:

1) Limited to specific clinical outcomes (e.g. haemorrhagic stroke)

2) Conducted in specific patient sub-populations (e.g. postmenopausal women)

3) Reporting a composite outcome (e.g. stroke and coronary artery disease combined) unless separate results for stroke patients were identified.

4) Cross sectional in design

5) Studies with retrospective recruitment.

Authors of the studies were contacted in some cases, as similarities between articles indicated the possibility of multiple publications from the same cohort. Where several studies reported results from the same population, data were taken from the publication with the longest follow-up. Data were extracted from the included studies using a predefined template and the quality of each study was assessed using standard criteria (appendix C).(19) A meta-analysis was undertaken to obtain pooled estimates of the risk of stroke among patients with anxiety disorders. A random-effect model was used to summarise the mean estimated effect (hazard ratio), obtained from the included studies and results were graphically presented in a forest plot. The assumption made was that the size of the true effect varies from one study to the other, and that the studies considered in our analysis constitute a random sample of all possible effect sizes that could have been observed. The random-effect approach was considered preferable to the fixed-effect approach where the true effect size in the latter is assumed to be the same in all studies.(20) The heterogeneity between studies was measured using I-squared index that represents the percentage of the total variation which is due to differences between studies. Chi-squared statistic was used to test the significance of the heterogeneity.(21) When participants in the studies had been interviewed about symptoms of anxiety disorders at more than one time point, e.g. in the previous month and in the previous five years, the assessment referring to the time point closest to the date of study entry was included in the analysis as it was considered to be less affected by recall bias. When a study reported results from a multivariable model exploring the association between anxiety and stroke, and then further modeling had been conducted to explore potential explanatory factors for the association, only the results from the first model were included in the meta-analysis. When a study reported risk of stroke at one time point after the diagnosis of anxiety, and after examinations of the HRs for each year of follow up, an estimate of risk of

stroke at a different time point had also been calculated, data from the first estimate was included in the meta-analysis. A funnel plot was used to investigate possible publication bias, true heterogeneity and other methodological irregularities.(22) Sensitivity analyses were performed, first to exclude two studies, which differ in measures of anxiety and age categorization from the rest of the papers,(23, 24) one at a time and simultaneously, and second, to exclude one study with very large variance,(25) to examine the impact of each exclusion on the pooled estimate and on the heterogeneity of the studies included.

3. Results:

The electronic and hand searches identified 11764 references, six of which were reviews relevant to the topic.(12-17) A total of 46 full text studies were assessed for inclusion. Finally, eight studies were considered to comply with inclusion criteria and were included in this review (Figure one). The characteristics of these studies are presented in table one. All of them were considered to be of high quality (Appendix C),(19) they were all population based, and included a total of 950759 patients.(23-30) Three studies had been conducted in the USA, two in the UK, one in Canada, one in Taiwan, and another one in The Netherlands. Three of them used medical records,(26, 27, 29) and five included participants from epidemiological surveys.(23-25, 28, 30) Six studies included patients with all types of anxiety disorders, in one study participants were examined specifically for generalised anxiety disorder,(25) and in another one for panic disorder.(27) The identification of patients with anxiety disorders was conducted in two studies, (26, 27) with DSM III, DSM IV, and ICD-9 criteria,(31-33) another five studies used scales,(23-25, 28, 30) and diagnoses recorded in primary care notes were used in another study.(29) The follow up time ranged from ten to 22 years and the proportion of incidents strokes observed

ranged from 0.2 to 12.6% with larger proportions of strokes observed in studies with longer follow up.(28, 30) Three studies excluded patients with past medical history of stroke,(25, 28, 29) two excluded patients with history of stroke in the year before study entry,(26, 27) and one excluded those with past medical history of cardiovascular disease.(24) The eight papers studied potential associations between anxiety and all types of strokes. One study observed only the association between anxiety and non-fatal strokes.(29) Another one reported the associations of anxiety with all types of strokes, and specifically with ischaemic strokes, which were not significant in either analyses.(30)

Three papers reported a significantly increased risk of stroke in patients with anxiety,(26-28) out of which one study reported also a dose–response relation, with a 17% increased risk of stroke for every standard deviation increase in anxiety.(28) A significantly increased pooled risk of stroke for patients with anxiety disorders was observed, with an overall hazard ratio (HR) estimated from the meta-analysis: 1.24 (95% CI: 1.09-1.41) p=0.001 (Figure two). Heterogeneity between studies was low and not significant, I-squared index was 26.7% (p=0.216).(21) Sensitivity analysis excluding the studies by Vogt and colleagues,(23) Stewart and colleagues,(24) and both at the same time, only altered the magnitude of the pooled estimate by a negligible amount and the heterogeneity remained insignificant. The removal of the study by Surtees and colleagues(25) increased the heterogeneity to I-Squared 29.7%, but had negligible impact on the pooled estimate and its 95% confidence intervals. The funnel plot demonstrated a reasonable symmetry suggesting that publication bias, and other sources of biases due to methodology, quality, and small studies effect are unlikely (Figure three).

In two papers, after examination of the HRs for each year of follow up, the time between symptoms of anxiety and risk stroke was investigated. One of them reported an increased risk of

stroke only within three years of the detection of anxiety, HR: 2.55 (1.45–4.46) but not in the longer term.(30) The other paper did not find an association between anxiety and stroke but reported an increased risk for cardiovascular disease (myocardial infarction or stroke) within three years of the detection of anxiety, but not in the longer term (24) They both suggest a possible short-term effect for anxiety symptoms on the risk of stroke.

Three papers explored the role of cardiovascular risk factors in the association between anxiety and stroke (28-30) Only one of them observed an association between anxiety and stroke, which became weaker but remained significant after adjusting for blood pressure, cholesterol, diabetes mellitus, body mass index, alcohol use, physical activity, smoking, and antihypertensive medication, in a multivariable model.(28)

Three papers explored the role of depression in the association between anxiety and stroke. In all three the risk of stroke was not increased for patients with anxiety and this did not change when depression was included in the models.(24, 29, 30) None of the studies included in this review explored biological explanatory factors for the association between anxiety and stroke, such as inflammatory markers.

4. Discussion

The risk of stroke among patients with anxiety disorders has been investigated in a limited number of cohort studies, which were considered to be of good quality. The meta-analysis provides strong evidence for an association between anxiety and stroke, with a pooled risk of stroke increased by 24% among patients suffering anxiety disorders. There is limited evidence suggesting that the risk of stroke may be higher within three years of the diagnosis of anxiety, and that the risk of stroke may be further increased for patients with severe anxiety.

The evidence on the explanatory factors for the association between anxiety disorders and stroke is still limited. The increased prevalence of cardiovascular risk factors observed in patients with anxiety disorders may explain their higher risk of stroke (9, 34, 35) However, the only study that reported a significant association between anxiety and stroke, and adjusted at a later stage for cardiovascular risk factors, reported that the association became weaker but remained significant.(28) This suggests that cardiovascular risk factors do not fully explain the increased risk of stroke among patients with anxiety disorders. Therefore, a biological link between anxiety and stroke could also be considered. This would include the association of anxiety disorders with abnormal heart rhythm, raised inflammatory markers, dysfunctions of the hypothalamic pituitary adrenal axis, and an increased risk of developing carotid plaques or arterial stiffness. Persistent estates of anxiety induce a hypothalamic-pituitary-adrenal hyperactivity with continuous sympathetic nervous system activation. The elevation of several neuropeptides results in a high blood pressure and arrhythmias, and the release of cytokines has pro-inflammatory and pro-coagulant effects on endothelium. The persistent high levels of cortisol may also lead to a downregulation of the hypothalamic pituitary adrenal axis and contribute to abnormal lipid profiles.(10, 36-39)

The lack of significant association between anxiety and stroke, observed in five papers, may be related to the long follow up of these studies. The association may be underestimated by the observation of patients long time after the diagnosis of anxiety, when the risk of stroke may not be increased.

The results of this review are consistent with a retrospective multicentre study which reported that psychosocial stress was associated with high risk of stroke.(40) This systematic review builds on a previous article (16) that using a different inclusion criteria, reported an association

between anxiety and stroke across a number of papers, not including four recent studies which observed over half a million patients.(24, 28-30)

The different measures of anxiety used across the studies may have affected the final results. The DSM criteria, used in two studies, is considered the gold standard to diagnose anxiety.(41) The scales used in three studies (24, 25, 30) were all validated against the DSM criteria.(41, 42) The scales used in another two studies (23, 28) were also specifically developed to measure anxiety disorders.(28, 43) Finally, the study that used medical records to categorize participants as anxiety patients was based in the UK, where the national guidelines recommend the use of a scale that has also been validated against DSM citeria.(44, 45) Therefore, in all eight studies the diagnosis of anxiety was assisted with a diagnostic tool, which gives, according to a recent systematic review, a sensitivity 67% and specificity of 88%.(46) The proportion of patients wrongly categorized may have resulted in an underestimation of the risk between anxiety and stroke, which could be stronger than the one observed.

This review has some limitations. The diversity of the methods across studies, including the different statistical management, may have an effect on the external validity of each individual one. Furthermore, only one person extracted most of the data (MPP). Even so, all data were checked for accuracy on multiple occasions. The availability of only eight studies represents another limitation of this review. This study has some strengths as well. The comprehensive search and critical assessment of studies conducted in this review allows estimation of the association between anxiety disorders and stroke obtained on a large number of patients. The use of a random effect model based on the assumption that studies were independently conducted and do not necessarily share a common effect size, allowing for more uncertainty of the final summary estimate was a conservative choice. The overall estimate remained significant

despite the increased width of the confidence intervals, providing support to the significance of the findings. The reasonably symmetrical funnel plot supports the theory that there is no publication bias. While this is re-assuring, the plots may also be used to assess "small study effects", where smaller studies in a meta-analysis tends to show larger effects.(47) Although all the studies included were large, nonetheless they do vary in size. The funnel plot highlighted the random distribution of the estimates, indicating that large effects were not associated with smaller studies.

5. Conclusion

Clinicians should consider the relevance of anxiety disorders, which are not only a distressing problem on their own, but also a predictors of coronary artery disease,(11) and stroke. Many patients have little understanding of the association between anxiety and physical disease,(48) therefore clinicians may have to highlight this link to help patients understand the clinical relevance of anxiety disorders. Given the high prevalence of anxiety disorders,(1-3) the magnitude of their association with major cardiovascular events, and provided that they are a treatable conditions, interventions on anxiety disorders should have a positive impact on the incidence of both coronary artery disease and stroke.

Future studies on the risk of stroke in patients with anxiety disorders, and the explanatory factors for this association, are required in order to confirm, modify and/or expand these results. It is not possible to differentiate, with the available evidence, the risk of stroke associated with different anxiety disorders which may not be similar for panic disorders, agoraphobia, or other anxiety disorders. Therefore, the association between the different types of anxiety disorders, of different degrees of severity, and stroke, remains a matter for further research. Future studies

may also address the impact of anxiety disorders, on specific types of stroke, which may vary for ischaemic and haemorrhagic ones. All these studies are needed to develop effective clinical and public health interventions for the treatment of anxiety disorders and the prevention of stroke. While a long follow up is normally considered a strength of observational research, future studies may look at stokes within three years of the diagnosis of anxiety, which seems to be the moment of highest risk.(24, 30)

	Vogt 1994	Bowen 2000	Surtees 2008	Chou 2012	Lambiase 2014	Mathur 2015	Portegies 2016	Stewart 2016
Country	USA	Canada	UK	Taiwan	USA	UK	The Netherlands	USA
Data source	Epidemiological	Medical records	Epidemiological	Medical records	Epidemiological	Medical records	Epidemiological	Epidemiological
N	1529	2657	20627	390309	6019	524952	2625	2041
Age	≥18	>15	41 to 80	≥20	25-74	≥20	≥45	≥60
Female %	54	59	57	46	54	47	55	73
Follow-up	15 years	12 years	12 years	10 years	22 years	10 years	20 years	9 years
Anxiety assessment	Bradburn Worries Index	ICD-9 DSM-III DSMIIIR	Health & Life Experience (GAD)[a]	ICD-9 DSM-IV TR (PD) [b]	General Wellbeing scale	Primary care records	Hospital Anxiety Depression scale	Patient Questionnaire
Anxiety N	817	866	NR	1725	1953	22128	343	849
Stroke assessment	ICD-7	ICD-9	ICD-9 ICD-10	ICD-9	ICD-9	Medical records	Medical records	ICD-9 ICD-10
Stroke n (%)	Not reported	44 (1.6)	595 (2.9)	19148 (4.9)	419 (7.0)	987 (0.2)	332 (12.6)	235 (11.5)
Adjustment for covariates	Age, sex, smoking, Health status, SES [c] Duration of health plan membership	Age sex	Age sex CV Risk factors [d] SES [c] Pmh[e]:MI Fh[f] stroke Antidepre-ssant use	Age sex Comorbi-dities Regular medication	Age sex Ethnic. Education Marital status	Age sex Ethnic.	Age sex	Age sex Ethnic. CV Risk factors [d]
Hazard Ratio (CI)	0.91 (0.63-1.33)	2.00 (1.09-3.64)	0.81 (0.33-1.98)	1.38 (1.12-1.71)	1.43 (1.14-1.80)	1.17 (0.91-1.51)	1.06 (0.76-1.48)	1.20 (0.92-1.56)

Table 1. Characteristics of the studies included in this review. a- GAD: Generalised anxiety disorder, b- PD: Panic disorder, c- SES: Socioeconomic Status, d- CV Risk factors: Blood pressure , cholesterol, diabetes, smoking, obesity. e- PMH: Past medical history, f- FH: Family history

Figures titles:

Figure 1: Results of literature search

Figure 2: Pooled risk of stroke in patients with anxiety disorders

Figure 3: Funnel plot of studies included in the review

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Contributors: All authors conceived the idea and designed the study. MPP and EG conducted the searches and extracted the data under the supervision of LA, SA, QF and RM. SA conducted the analysis. MPP wrote the first draft that was later modified with input from all other authors.

Vitae:

María Pérez-Piñar is a medical doctor. She qualified in medicine in Madrid (Spain) and then trained in General Practice. Since 2008 she has been practicing in the UK. Most of her research work is related to the management of common disorders in primary care, and has a holistic approach.

Luis Ayerbe is a medical doctor. He qualified in Madrid (Spain) and then became a general practitioner. Since 2004 he has been practicing in the UK where he trained in Epidemiology and then did a PhD. His research work is mostly on the interface between cardiovascular and mental health disorders.

Esteban González is a medical doctor. He qualified, and then became a General Practitioner, and a PhD, in Madrid, where he has been practicing for over 30 years. For all his career, Esteban has combined his clinical practice with teaching medical students and trainee doctors.

Rohini Mathur trained in Health Studies & Gerontology in Ontario (Canada). She recently gained her PhD in the London School of Hygiene and Tropical Medicine. She is an epidemiologist who specializes in the use of large databases and studies with longitudinal design. Her main interests are in health care inequalities and diseases managed in primary care.

Quintí Foguet-Boreu is a medical doctor. He trained in General Practice and Psychiatry and gained his PhD in Catalonia (Spain). He is currently a clinical psychiatrist in Hospital de Campdevanol, in Lleida (Spain) His research is mostly on the interface between mental and physical health problems

Salma Ayis is a medical statistician. She trained in Khartoum (Sudan) and then she did her PhD in the University of Southampton (UK). Her research covers large areas of medical statistics including longitudinal methods of analysis, systematic reviews, clinical trials. The main clinical topics in her papers are cardiovascular and psychiatric diseases.

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