

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

María Pérez-Piñar <sup>a</sup>, Luis Ayerbe <sup>a,b</sup>, Esteban González <sup>c</sup>, Rohini Mathur <sup>b</sup>,  
Quintí Foguet-Boreu <sup>d,e</sup>, Salma Ayis <sup>f</sup>

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](mailto:l.garcia-morzon@qmul.ac.uk)

**Word count:** 2926

## **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%.<sup>(1-3)</sup> It is also the sixth global leading cause of disability, with no discernible change observed from 1990.<sup>(4)</sup> Stroke is the second most common cause of death, and the third most common cause of reduced disability-adjusted life-years (DALYs), worldwide.<sup>(5, 6)</sup> Most of the burden of stroke affects low and middle-income countries.<sup>(7)</sup> Primary prevention of stroke is particularly important because 76% of strokes are first events.<sup>(8)</sup> 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.<sup>(9, 10)</sup> While the association between anxiety disorders and coronary artery disease is well established,<sup>(11)</sup> their impact on the risk of stroke has received less attention. Previous reviews on the associations between anxiety and cardiovascular disease <sup>(12-17)</sup> 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 <sup>(Appendix A)</sup>.<sup>(18)</sup> 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 7<sup>th</sup> 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% ( $p=0.216$ ).<sup>(21)</sup>

Sensitivity analysis excluding the studies by Vogt and colleagues,<sup>(23)</sup> Stewart and colleagues,<sup>(24)</sup> 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<sup>(25)</sup> 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 states 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 criteria.(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 strokes 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) <sup>a</sup>	ICD-9 DSM-IV TR (PD) <sup>b</sup>	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 <sup>c</sup> Duration of health plan membership	Age sex	Age sex CV Risk factors <sup>d</sup> SES <sup>c</sup> Pmh <sup>e</sup> :MI Fh <sup>f</sup> stroke Antidepressant use	Age sex Comorbidities Regular medication	Age sex Ethnic. Education Marital status	Age sex Ethnic.	Age sex	Age sex Ethnic. CV Risk factors <sup>d</sup>
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

**Funding:** Luis Ayerbe is funded by an NIHR Clinical Lectureship. Salma Ayis is funded by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Guys and St Thomas NHS Foundation Trust and Kings College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health .

**Disclosures:** None

**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.

## References

1. Cross-national comparisons of the prevalences and correlates of mental disorders. WHO International Consortium in Psychiatric Epidemiology. *Bull World Health Organ.* 2000;78(4):413-26.
2. Alonso J, Angermeyer MC, Bernert S, Bruffaerts R, Brugha TS, Bryson H, de Girolamo G, Graaf R, Demyttenaere K, Gasquet I, Haro JM, Katz SJ, Kessler RC, Kovess V, Lépine JP, Ormel J, Polidori G, Russo LJ, Vilagut G, Almansa J, Arbabzadeh-Bouchez S, Autonell J, Bernal M, Buist-Bouwman MA, Codony M, Domingo-Salvany A, Ferrer M, Joo SS, Martínez-Alonso M, Matschinger H, Mazzi F, Morgan Z, Morosini P, Palacín C, Romera B, Taub N, Vollebergh WA; ESEMeD/MHEDEA 2000 Investigators, European Study of the Epidemiology of Mental Disorders (ESEMeD) Project. Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatr Scand Suppl.* 2004;(420):21-7.
3. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry.* 2005;62(6):593-602.
4. Baxter AJ, Vos T, Scott KM, Ferrari AJ, Whiteford HA. The global burden of anxiety disorders in 2010. *Psychol Med.* 2014;44(11):2363-74
5. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Barker-Collo S, Bartels DH, Bell ML, Benjamin EJ, Bennett D, Bhalla K, Bikbov B, Bin Abdulhak A, Birbeck G, Blyth F, Bolliger I, Boufous S, Bucello C, Burch M, Burney P, Carapetis J, Chen H, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE,



Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vacarro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahodwala N, De Leo D, Degenhardt L, Delossantos A, Denenberg J, Des Jarlais DC, Dharmaratne SD, Dorsey ER, Driscoll T, Duber H, Ebel B, Erwin PJ, Espindola P, Ezzati M, Feigin V, Flaxman AD, Forouzanfar MH, Fowkes FG, Franklin R, Fransen M, Freeman MK, Gabriel SE, Gakidou E, Gaspari F, Gillum RF, Gonzalez-Medina D, Halasa YA, Haring D, Harrison JE, Havmoeller R, Hay RJ, Hoen B, Hotez PJ, Hoy D, Jacobsen KH, James SL, Jasrasaria R, Jayaraman S, Johns N, Karthikeyan G, Kassebaum N, Keren A, Khoo JP, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Lipnick M, Lipshultz SE, Ohno SL, Mabweijano J, MacIntyre MF, Mallinger L, March L, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGrath J, Mensah GA, Merriman TR, Michaud C, Miller M, Miller TR, Mock C, Mocumbi AO, Mokdad AA, Moran A, Mulholland K, Nair MN, Naldi L, Narayan KM, Nasser K, Norman P, O'Donnell M, Omer SB, Ortblad K, Osborne R, Ozgediz D, Pahari B, Pandian JD, Rivero AP, Padilla RP, Perez-Ruiz F, Perico N, Phillips D, Pierce K, Pope CA 3rd, Porrini E, Pourmalek F, Raju M, Ranganathan D, Rehm JT, Rein DB, Remuzzi G, Rivara FP, Roberts T, De León FR, Rosenfeld LC, Rushton L, Sacco RL, Salomon JA, Sampson U, Sanman E, Schwebel DC, Segui-Gomez M, Shepard DS, Singh D, Singleton J, Sliwa K, Smith E, Steer A, Taylor JA, Thomas B, Tleyjeh IM, Towbin JA, Truelsen T, Undurraga EA, Venketasubramanian N, Vijayakumar L, Vos T, Wagner GR, Wang M, Wang W, Watt K, Weinstock MA, Weintraub R, Wilkinson JD, Woolf AD, Wulf S, Yeh PH, Yip P, Zabetian A, Zheng ZJ, Lopez AD, Murray CJ, AlMazroa MA, Memish ZA. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2095-128.

6. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, Aboyans V, Abraham J, Ackerman I, Aggarwal R, Ahn SY, Ali MK, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Bahalim AN, Barker-Collo S, Barrero LH, Bartels DH, Basáñez MG, Baxter A, Bell ML, Benjamin EJ, Bennett D, Bernabé E, Bhalla K, Bhandari B, Bikbov B, Bin Abdulhak A, Birbeck G, Black JA, Blencowe H, Blore JD, Blyth F, Bolliger I, Bonaventure A, Boufous S, Bourne R, Boussinesq M, Braithwaite T, Brayne C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-Hancock C, Bucello C, Buchbinder R, Buckle G, Budke CM, Burch M, Burney P, Burstein R, Calabria B, Campbell B, Canter CE, Carabin H, Carapetis J, Carmona L, Cella C, Charlson F, Chen H, Cheng AT, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahiya M, Dahodwala N, Damsere-Derry J, Danaei G, Davis A, De Leo D, Degenhardt L, Dellavalle R, Delossantos A, Denenberg J, Derrett S, Des Jarlais DC, Dharmaratne SD, Dherani M, Diaz-Torne C, Dolk H, Dorsey ER, Driscoll T, Duber H, Ebel B, Edmond K, Elbaz A, Ali SE, Erskine H, Erwin PJ, Espindola P, Ewoigbokhan SE, Farzadfar F, Feigin V, Felson DT, Ferrari A, Ferri CP, Fèvre EM, Finucane MM, Flaxman S, Flood L, Foreman K, Forouzanfar MH, Fowkes FG, Fransen M, Freeman MK, Gabbe BJ, Gabriel SE, Gakidou E, Ganatra HA, Garcia B, Gaspari F, Gillum RF, Gmel G, Gonzalez-Medina D, Gosselin R, Grainger R, Grant B, Groeger J, Guillemin F, Gunnell D, Gupta R, Haagsma J, Hagan H, Halasa YA, Hall W, Haring D, Haro JM, Harrison JE, Havmoeller R, Hay RJ, Higashi H, Hill C, Hoen B, Hoffman H, Hotez PJ, Hoy D, Huang JJ, Ibeanusi SE, Jacobsen KH, James SL, Jarvis D, Jasrasaria R, Jayaraman S, Johns N, Jonas JB, Karthikeyan G, Kassebaum N, Kawakami N, Keren A, Khoo JP, King CH, Knowlton LM, Kobusingye O,

Koranteng A, Krishnamurthi R, Laden F, Lalloo R, Laslett LL, Lathlean T, Leasher JL, Lee YY, Leigh J, Levinson D, Lim SS, Limb E, Lin JK, Lipnick M, Lipshultz SE, Liu W, Loane M, Ohno SL, Lyons R, Mabweijano J, MacIntyre MF, Malekzadeh R, Mallinger L, Manivannan S, Marcenes W, March L, Margolis DJ, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGill N, McGrath J, Medina-Mora ME, Meltzer M, Mensah GA, Merriman TR, Meyer AC, Miglioli V, Miller M, Miller TR, Mitchell PB, Mock C, Mocumbi AO, Moffitt TE, Mokdad AA, Monasta L, Montico M, Moradi-Lakeh M, Moran A, Morawska L, Mori R, Murdoch ME, Mwaniki MK, Naidoo K, Nair MN, Naldi L, Narayan KM, Nelson PK, Nelson RG, Nevitt MC, Newton CR, Nolte S, Norman P, Norman R, O'Donnell M, O'Hanlon S, Olives C, Omer SB, Ortblad K, Osborne R, Ozgediz D, Page A, Pahari B, Pandian JD, Rivero AP, Patten SB, Pearce N, Padilla RP, Perez-Ruiz F, Perico N, Pesudovs K, Phillips D, Phillips MR, Pierce K, Pion S, Polanczyk GV, Polinder S, Pope CA 3rd, Popova S, Porrini E, Pourmalek F, Prince M, Pullan RL, Ramaiah KD, Ranganathan D, Razavi H, Regan M, Rehm JT, Rein DB, Remuzzi G, Richardson K, Rivara FP, Roberts T, Robinson C, De Leòn FR, Ronfani L, Room R, Rosenfeld LC, Rushton L, Sacco RL, Saha S, Sampson U, Sanchez-Riera L, Sanman E, Schwebel DC, Scott JG, Segui-Gomez M, Shahraz S, Shepard DS, Shin H, Shivakoti R, Singh D, Singh GM, Singh JA, Singleton J, Sleet DA, Sliwa K, Smith E, Smith JL, Stapelberg NJ, Steer A, Steiner T, Stolk WA, Stovner LJ, Sudfeld C, Syed S, Tamburlini G, Tavakkoli M, Taylor HR, Taylor JA, Taylor WJ, Thomas B, Thomson WM, Thurston GD, Tleyjeh IM, Tonelli M, Towbin JA, Truelsen T, Tsilimbaris MK, Ubeda C, Undurraga EA, van der Werf MJ, van Os J, Vavilala MS, Venketasubramanian N, Wang M, Wang W, Watt K, Weatherall DJ, Weinstock MA, Weintraub R, Weisskopf MG, Weissman MM, White RA, Whiteford H, Wiebe N, Wiersma ST, Wilkinson JD, Williams HC, Williams SR, Witt E, Wolfe F, Woolf AD, Wulf S, Yeh PH,

Zaidi AK, Zheng ZJ, Zonies D, Lopez AD, AlMazroa MA, Memish ZA. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2197-223.

7. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, Moran AE, Sacco RL, Anderson L, Truelsen T, O'Donnell M, Venketasubramanian N, Barker-Collo S, Lawes CM, Wang W, Shinohara Y, Witt E, Ezzati M, Naghavi M, Murray C; Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010) and the GBD Stroke Experts Group. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet*. 2014;383(9913):245-54.

8. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Judd SE, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Mackey RH, Magid DJ, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER 3rd, Moy CS, Mussolino ME, Neumar RW, Nichol G, Pandey DK, Paynter NP, Reeves MJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Wong ND, Woo D, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation*. 2014;129(3):e28-e292.

9. Moylan S, Jacka FN, Pasco JA, Berk M. Cigarette smoking, nicotine dependence and anxiety disorders: a systematic review of population-based, epidemiological studies. *BMC Med*. 2012;10:123.

10. Furtado M, Katzman MA. Neuroinflammatory pathways in anxiety, posttraumatic stress, and obsessive compulsive disorders. *Psychiatry Res*. 2015;229(1-2):37-48.

11. Roest AM, Martens EJ, de Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease: a meta-analysis. *J Am Coll Cardiol.* 2010;56(1):38-46
12. Coughlin SS. Post-traumatic Stress Disorder and Cardiovascular Disease. *Open Cardiovasc Med J.* 2011;5:164-70.
13. Olafiranye O, Jean-Louis G, Zizi F, Nunes J, Vincent M. Anxiety and cardiovascular risk: Review of Epidemiological and Clinical Evidence. *Mind Brain.* 2011;2(1):32-7.
14. Scott KM. Depression, anxiety and incident cardiometabolic diseases. *Curr Opin Psychiatry.* 2014;27(4):289-93.
15. Thurston RC, Rewak M, Kubzansky LD. An Anxious Heart: Anxiety and the Onset of Cardiovascular Diseases. *Prog Cardiovasc Dis.* 2013;55(6):524-37.
16. Batelaan NM, Seldenrijk A, Bot M, van Balkom AJ, Penninx BW. Anxiety and new onset of cardiovascular disease: critical review and meta-analysis. *Br J Psychiatry.* 2016;208(3):223-31.
17. Player MS, Peterson LE. Anxiety disorders, hypertension, and cardiovascular risk: a review. *Int J Psychiatry Med.* 2011;41(4):365-77.
18. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA.* 2000;283(15):2008-12.
19. Methodology Checklist: Cohort studies. Scottish Intercollegiate Guidelines Network; 2012; Available from: <http://www.sign.ac.uk/index.html>. (Accessed July 2016)
20. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods.* 2010;1(2):97-111.

21. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-60.
22. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-34.
23. Vogt T, Pope C, Mullooly J, Hollis J. Mental health status as a predictor of morbidity and mortality: a 15-year follow-up of members of a health maintenance organization. *Am J Public Health*. 1994;84(2):227-31.
24. Stewart JC, Hawkins MA, Khambaty T, Perkins AJ, Callahan CM. Depression and Anxiety Screens as Predictors of 8-Year Incidence of Myocardial Infarction and Stroke in Primary Care Patients. *Psychosom Med*. 2016;78(5):593-601.
25. Surtees PG, Wainwright NW, Luben RN, Wareham NJ, Bingham SA, Khaw KT. Psychological distress, major depressive disorder, and risk of stroke. *Neurology*. 2008;70(10):788-94.
26. Bowen RC, Senthilselvan A, Barale A. Physical illness as an outcome of chronic anxiety disorders. *Can J Psychiatry*. 2000;45(5):459-64.
27. Chou PH, Lin CH, Loh el W, Chan CH, Lan TH. Panic disorder and risk of stroke: a population-based study. *Psychosomatics*. 2012;53(5):463-9
28. Lambiase MJ, Kubzansky LD, Thurston RC. Prospective study of anxiety and incident stroke. *Stroke*. 2014;45(2):438-43
29. Mathur R, Perez-Pinar M, Foguet Q, Ayis S, Ayerbe L. Risk of incident cardiovascular events amongst individuals with anxiety and depression in east London. Faculty of General Adult Psychiatry Annual Conference; London, UK 2015.

30. Portegies ML, Bos MJ, Koudstaal PJ, Hofman A, Tiemeier HW, Ikram MA. Anxiety and the Risk of Stroke: The Rotterdam Study. *Stroke*. 2016.
31. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Health Disorders: DSM-III*. Washington DC: American Psychiatric Association; 1987.
32. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*. Washington DC: American Psychiatric Association, 1994.
33. International Statistical Classification of Diseases and Related Health Problems (ICD-9). Geneva: World Health Organisation, 1978.
34. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation*. 1999;99(16):2192-217.
35. Perez-Pinar M, Mathur R, Foguet Q, Ayis S, Robson J, Ayerbe L. Cardiovascular risk factors among patients with schizophrenia, bipolar, depressive, anxiety, and personality disorders. *Eur Psychiatry*. 2016;35:8-15.
36. Compare A, Proietti R, Germani E, Janeway D. Anxiety and depression: Risk factors for cardiovascular disease. In: Dornelas EA, editor. *Stress proof the heart: Behavioral interventions for cardiac patients*. New York: Springer Science + Business Media; 2012, p. 139-66.
37. Lambert EA, Thompson J, Schlaich M, Laude D, Elghozi JL, Esler MD, Lambert GW. Sympathetic and cardiac baroreflex function in panic disorder. *J Hypertens*. 2002;20(12):2445-51.
38. Seldenrijk A, van Hout HP, van Marwijk HW, de Groot E, Gort J, Rustemeijer C, Diamant M, Penninx BW. Sensitivity to depression or anxiety and subclinical cardiovascular disease. *J Affect Disord*. 2013;146(1):126-31.

39. Tuttolomondo A, Di Raimondo D, di Sciacca R, Pinto A, Licata G. Inflammatory cytokines in acute ischemic stroke. *Curr Pharm Des.* 2008;14(33):3574-89.
40. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, Rangarajan S, Islam S, Pais P, McQueen MJ, Mondo C, Damasceno A, Lopez-Jaramillo P, Hankey GJ, Dans AL, Yusuf K, Truelsen T, Diener HC, Sacco RL, Ryglewicz D, Czlonkowska A, Weimar C, Wang X, Yusuf S; INTERSTROKE investigators. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet.* 2010;376(9735):112-23.
41. Brennan C, Worrall-Davies A, McMillan D, Gilbody S, House A. The Hospital Anxiety and Depression Scale: a diagnostic meta-analysis of case-finding ability. *J Psychosom Res.* 2010;69(4):371-8.
42. Spitzer RL, Williams JB, Kroenke K, Linzer M, deGruy FV, Hahn SR, Brody D, Johnson JG. Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. *JAMA.* 1994;272(22):1749-56.
43. Fazio AF. A concurrent validation study of the NCHS General Well-Being Schedule. *Vital Health Stat 2.* 1977(73):1-53.
44. Plummer F, Manea L, Trepel D, McMillan D. Screening for anxiety disorders with the GAD-7 and GAD-2: a systematic review and diagnostic metaanalysis. *Gen Hosp Psychiatry.* 2016;39:24-31.
45. National Institute of Clinical Excellence (NICE). Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults: Management in primary, secondary and community care. London: NICE. 2011



46. Olariu E, Forero CG, Castro-Rodriguez JI, Rodrigo-Calvo MT, Álvarez P, Martín-López LM, Sánchez-Toto A, Adroher ND, Blasco-Cubedo MJ, Vilagut G, Fullana MA, Alonso J. Detection of anxiety disorders in primary care: a meta-analysis of assisted and unassisted diagnoses. *Depress Anxiety*. 2015;32(7):471-84.
47. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. *J Clin Epidemiol*. 2000;53(11):1119-29.
48. DeJean D, Giacomini M, Vanstone M, Brundisini F. Patient experiences of depression and anxiety with chronic disease: a systematic review and qualitative meta-synthesis. *Ont Health Technol Assess Ser*. 2013;13(16):1-33..