European Psychiatry 41 (2017) 102–108

Contents lists available at ScienceDirect

European Psychiatry

journal homepage: http://www.europsy-journal.com

Review

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

M. Pérez-Piñar [a], L. Ayerbe [a,b,*], E. González [c], R. Mathur [b], Q. Foguet-Boreu [d,e], S. 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, London, United Kingdom
[c] Primary Care Unit, Department of Medicine, Autonoma University of Madrid, Madrid, Spain
[d] Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol), Universitat Autònoma de Barcelona, Barcelona, Spain
[e] Department of Medical Sciences, School of Medicine, University of Girona, Girona, Spain
[f] Division of Health and Social Care, Kings College London, London, United Kingdom

ARTICLE INFO

Article history:
Received 25 August 2016
Received in revised form 31 October 2016
Accepted 2 November 2016
Available online 27 January 2017

Keywords:
Stroke
Cohort studies
Systematic review
Anxiety disorders

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 950,759 patients, from the 11,764 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.

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.

* Corresponding author. Centre of Primary Care and Public Health, Queen Mary University of London, Yvonne Carter Building, 58, Turner Street, E1 2AB London, United Kingdom.
E-mail address: l.garcia-morzon@qmul.ac.uk (L. Ayerbe).

http://dx.doi.org/10.1016/j.eurpsy.2016.11.004
0924-9338/

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:

- cohort study design;
- reporting of original research data;
- anxiety disorder assessed as exposure;
- incident strokes reported as outcome.
- 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:

- limited to specific clinical outcomes (e.g. haemorrhagic stroke);
- conducted in specific patient sub-populations (e.g. postmenopausal women);
- reporting a composite outcome (e.g. stroke and coronary artery disease combined) unless separate results for stroke patients were identified;
- cross-sectional in design;
- 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^2 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 5 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 11,764 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 (Fig. 1). The characteristics of these studies are presented in Table 1. All of them were considered to be of high quality (Appendix C) [19], they were all population based, and included a total of 950,759 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 10 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), $P = 0.001$ (Fig. 2). Heterogeneity between studies was low and not significant, I^2 index was 26.7% ($P = 0.216$) [21]. Sensitivity analysis excluding the studies by Vogt et al. [23], Stewart et al. [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 et al. [25] increased the heterogeneity to I^2 29.7%, but had negligible impact on the pooled estimate and its 95% confidence intervals. The funnel plot demonstrated a reasonable symmetry suggesting that