Published in final edited form as:
J Neurol. 2014 March ; 261(3): 533–545. doi:10.1007/s00415-013-7231-5.

Cortisol levels and the severity and outcomes of acute stroke: a systematic review

Amanda Jayne Barugh,
Department of Geriatric Medicine, University of Edinburgh, 51 Little France Crescent, Edinburgh EH16 4SA, UK

Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK

Paul Gray,
Department of Geriatric Medicine, University of Edinburgh, 51 Little France Crescent, Edinburgh EH16 4SA, UK

Susan Deborah Shenkin,
Department of Geriatric Medicine, University of Edinburgh, 51 Little France Crescent, Edinburgh EH16 4SA, UK

Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK

Alasdair Maurice Joseph MacLullich, and
Department of Geriatric Medicine, University of Edinburgh, 51 Little France Crescent, Edinburgh EH16 4SA, UK

Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK

Gillian Elizabeth Mead
Department of Geriatric Medicine, University of Edinburgh, 51 Little France Crescent, Edinburgh EH16 4SA, UK

Abstract

Studies in non-stroke patients have shown an association between dysregulation of the hypothalamic–pituitary–adrenal axis and morbidity and mortality. We conducted a systematic review to evaluate cortisol levels in acute stroke and their associations with outcome. We searched MEDLINE and EMBASE for articles up to April 2013 and PsychINFO for articles up to July 2013, using the keywords “cortisol” and “stroke” and associated terms or synonyms. We included studies published in peer-reviewed journals that recruited 10 or more participants and measured cortisol at least once in the first year following stroke. Data were extracted regarding cortisol levels, including changes over time and their relationship to stroke severity, and outcome. Of 11,240 abstracts, 101 full texts were obtained and 48 fulfilled our inclusion criteria. Cortisol levels were high in the first week after stroke in the majority of studies (26 studies, n = 1,340). Higher

Correspondence to: Amanda Jayne Barugh.
a.j.barugh@sms.ed.ac.uk.

Conflicts of interest On behalf of all authors, the corresponding author states that there are no conflicts of interest.

Ethical standard This manuscript does not contain new clinical studies or patient data.

Europe PMC Funders Author Manuscripts

cortisol was associated with dependency (8/11 studies, *n* = 822), delirium (5/6 studies, *n* = 269) depression (3/5 studies *n* = 117) and mortality (8/10 studies, *n* = 856). Five studies adjusted for stroke severity; one found an association between higher cortisol and dependency, and three found an association between higher cortisol and mortality. Cortisol levels are high for at least 7 days after stroke. Elevated cortisol after stroke is associated with dependency, morbidity, and mortality; however, there is insufficient evidence to conclude that these relationships are independent of stroke severity.

Keywords

Cortisol; Stroke; Systematic review; Outcome

Introduction

Activation of the hypothalamic–pituitary–adrenal (HPA) axis in the context of acute, severe illness generally results in elevated cortisol levels. This has physiological benefits, including the mobilization of glucose from the liver and adipose tissue and the potentiation of cardiovascular output [1, 2]. More severe illness stimulates correspondingly higher cortisol concentrations [3, 4]. The HPA axis is entrained on the circadian cycle, and exhibits diurnal variation, with a characteristic peak of cortisol being produced in the early morning and a nadir occurring in the late afternoon. Some studies have found that greater severity of illness is associated with the loss of diurnal variation in cortisol [5].

Ageing is associated with a tendency towards dysregulation of the HPA axis [6], leading to higher and more prolonged elevations of cortisol following stress. Neurodegenerative disease is also associated with dysregulation of the HPA axis [7]. Following an acute stroke, prolonged HPA axis activation may also occur for reasons specific to stroke. These reasons include cytokine release following neuronal injury [8], and that the stroke lesion itself may destroy HPA inhibitory areas of the brain in the frontal or medial temporal lobes [9].

In conditions other than stroke there is some evidence that prolonged exposure to high cortisol levels is neurotoxic. For example, brain atrophy and cognitive impairments are often found in Cushing's disease (ACTH-secreting adenoma resulting in sustained high cortisol). Similarly, patients taking long-term oral corticosteroids (for a variety of chronic conditions) have been shown to have smaller hippocampal volumes compared with controls [10]. Prolonged activation of the HPA axis has also been associated with adverse clinical consequences including delirium [11, 12], dementia [13], and death [14].

Although several studies have investigated what happens to the HPA axis after stroke [9, 15, 16], there are no systematic reviews. It is important to know whether HPA axis activation, or indeed downregulation, is associated with adverse outcomes in patients with stroke because treatments that impact on the HPA axis may thus affect outcomes.

This systematic review was performed with three main goals. First, we aimed to document comprehensively the evidence on cortisol levels and changes over time following stroke. Second, we wished to determine if there are any associations between cortisol levels and

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

stroke severity. Third, we wanted to determine if there are associations between cortisol levels and stroke outcomes–specifically dependency [defined as the degree of functional impairment, measured by, for example, the Modified Rankin Scale (mRS), Barthel Index (BI), Katz Index (KI) or the Glasgow Outcome Scale (GOS)], morbidity, and mortality-independent of stroke severity.

Methods

Searches were conducted in MEDLINE (from 1966) and EMBASE (from 1980) in April 2013 and in PsychINFO in July 2013. Searches used the keywords “stroke” and “cortisol” and their synonyms and were not limited by language (Appendix 1). Well-validated search strings, including more than 50 terms, were used to perform the search. Where possible, translations of papers were obtained (possible for one Chinese, one Russian and two Spanish papers, not possible for one Polish, one Bosnian and one Serbian paper). Results were exported to EndNote X4 and duplicates removed. Every title and abstract was read and full texts for all potentially relevant papers were obtained. Inclusion and exclusion criteria were then applied. Reference lists of the included papers and relevant review articles were scrutinized for further references.

Inclusion criteria

1. Full text publication in peer-reviewed journal;
2. Recruited 10 or more participants after stroke [ischaemic, haemorrhagic or subarachnoid hemorrhage (SAH)], older than 18 years;
3. Reported cortisol levels [measured in blood, saliva, cerebrospinal fluid (CSF) or urine] at least once in the first year following stroke

Exclusion criteria

1. Published only in abstract form;
2. Contained no primary data (for example reviews, editorials);
3. Dissertations or case reports;
4. Did not report data for stroke participants separately from other participants

Quality assessment

We used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement to assess quality [17]. This consists of 22 items, with each item scoring one point, thus the maximum score is 22 points. One author (AB) rated all of the studies (Appendix 2).

Data extraction

Data were extracted using standardized data collection forms. Data concerning study design, participant characteristics, and outcome measures was extracted. AB and PG independently extracted data for the included studies. Any uncertainties were discussed with a third reviewer (GM).

Data synthesis

The data lacked homogeneity, in particular with respect to the timing and method of cortisol measurement, and so were not suitable for meta-analysis. We tabulated the results (Table 1) and provide summaries of each study below.

Results

We scrutinized 11,240 titles and abstracts, and retrieved 101 full texts (Fig. 1). Forty-eight studies recruiting 2,340 participants (median 36, range 10–281) met the inclusion criteria. The mean participant age range was from 47 years (absolute range 25–69) [18] to 80 years (absolute range 75–92) [19]. The proportion of males ranged from 13 [20] to 92 % [21]. Twenty-eight studies used a longitudinal methodology and the remaining 20 were cross-sectional studies.

Measurement of cortisol

Of the 48 included studies, 41 (n = 2,105) measured cortisol in blood (Table 1). Eleven studies (n = 428) used either the dexamethasone suppression test (DST) or short synacthen test (SST) (which included a random, pre-test measure of blood cortisol), 16 (n = 1,214) measured cortisol in blood in the early morning, and 13 (n = 532) measured diurnal cortisol levels. The remaining seven studies measured salivary (n = 146), urinary (=94) and/or cerebrospinal fluid (CSF) (n = 53) cortisol. There was variability in time from stroke to first sample being taken (median 1 day, interquartile range (IQR) 1–3 days, range 0–111 days).

Cortisol levels and changes over time following stroke

Cortisol after stroke

Cortisol levels in blood (n = 1,953) at baseline (i.e., at the time of recruitment) following admission to the hospital ranged from 200 [22] to 1,120 nmol/L [23]. The majority of studies (27 studies, n = 1,373) found that cortisol levels were high (outside of the reference range) within the first week after stroke onset. Eight studies compared baseline cortisol levels to those in controls. The majority of controls were healthy, age-matched individuals; one study included both healthy controls and controls admitted with nonstroke, acute medical conditions [24]. Three of these studies found no significant difference (n = 187) [25–27], four (n = 163) [24, 28, 29] found significantly higher cortisol levels in stroke patients, and one study (n = 25) found that male, but not female, stroke patients had significantly higher cortisol levels compared to controls [30].

Changes in cortisol over time

Twelve studies (n = 541) measured cortisol at two or more time points on different (non-consecutive) days and reported changes over time. Five studies (n = 264) reported that cortisol fell [18, 26, 31–33], with two of these (n = 106) [26, 32] reporting cortisol levels within the reference range at follow-up (4 days and 2 weeks, respectively) in all participants. One study (n = 22) reported low (below the reference range) serum cortisol in all subjects after stroke for the duration of the study period (9 days on average) [34]. Two studies found persistent elevation of cortisol over the duration of their study period, one of which studied participants up to day 5 after stroke (n = 23) and one up to 1 month after stroke (n = 111) [35, 36]. Four studies (n = 121) reported that cortisol was within the normal reference range over the entire study period (ranging from 7 days to 3 months).

Dexamethasone suppression test (DST) after stroke

Eight studies (n = 311) used the DST (median day of first test; day 5 post-stroke, IQR 2.8–5.8 days); all reported non-suppression of cortisol in stroke participants [21, 24, 25, 27, 37–40]. This persisted over time in the three studies that repeated the test (median day of second test; day 17.5 post-stroke, IQR 3.5–28 days).

Diurnal variation in cortisol after stroke

Ten studies (nine using blood and one using saliva) analyzed diurnal variation in cortisol. Five studies measured cortisol twice during a 24 h period (morning and evening) and the remainder took measurements four times during a 24 h period (generally early morning, mid-morning, early evening and just before bed). Five (n = 196) found that diurnal variation was lost in those with more severe strokes (as determined by a validated scoring scale, for example the Scandinavian Stroke Scale), but preserved in those with more minor strokes [18, 22, 29, 41, 42]. Two studies (n = 82) [43, 44] found that diurnal variation was lost in those with high baseline cortisol, but did not assess whether this was associated with stroke severity. One study (n = 22) [34] found that diurnal variation was lost between days 1 and 7 after stroke, and one study found that over half (17/22) of their participants had an abnormal diurnal variation in the first week after stroke, but at 1 month, this change persisted in only two participants [37]. Finally, one study that recruited only those with mild stroke (n = 17) [45] found that diurnal variation was preserved in all participants.

Associations between cortisol and stroke severity

Sixteen studies investigated the associations between cortisol and stroke severity (of these 16, four included only those with an SAH).

Ischaemic or haemorrhagic stroke

Stroke severity was measured using a variety of rating scales, however the most frequently used scales were the National Institutes of Health Stroke Scale (NIHSS) and the Scandinavian Stroke Scale (SSS). Eleven studies (n = 966) found a statistically significant correlation between elevated cortisol levels and more severe strokes [22, 27, 35, 36, 38, 39, 41, 44, 46–48] and one (n = 25) found an association (not statistically significant) [40] (Appendix 2). The remaining four (n = 204) found no association [24, 45, 49, 50].

Subarachnoid haemorrhage

Subarachnoid haemorrhage severity was measured using the Hunt–Hess score, the Fisher score or the Glasgow Coma Scale score. Of the four studies involving only participants with an SAH, one (n = 51) found a small correlation between higher morning cortisol levels and Glasgow Coma Scale [22], one (n = 60) found a correlation between higher cortisol and the Fisher scale [51], one (n = 25) found a negative correlation between cortisol concentrations and the Fisher CT grade [52], and one (n = 30) found no correlation between urinary cortisol and the Hunt-Hess score [53].

Associations between cortisol and stroke outcome (including dependency, morbidity, and mortality)

Cortisol, dependency, and length of stay

Eleven studies (n = 942) reported the association between cortisol and dependency, of which eight (n = 822) found that a higher cortisol level was associated with more dependency [26, 41, 43, 44, 46, 47, 54, 55], and three studies (n = 120) did not [34, 35, 38] (Table 1). Of the eight studies that found an association, seven measured cortisol within 24 h of stroke onset, as did two out of the three studies that found no association. Three studies reported the relationship between cortisol and length of stay; two (n = 38) reported that a higher cortisol level was associated with a longer length of intensive care unit stay [18, 20], and one of these also found an association between higher cortisol level and overall length of stay [20]. The third study (n = 25) found no relationship between cortisol and length of hospital stay, however, this study was in a rehabilitation hospital, and so cortisol was measured relatively late (mean of 37 days) after stroke [40].

Cortisol and morbidity

Five studies examined the relationship between cortisol and delirium. Three (n = 187) found a correlation between elevated cortisol and delirium [25–27], one (n = 20) found a non-significant trend towards this association [39] and one (n = 23) found that a high adrenocorticotrophic hormone level (ACTH) was associated with delirium [35] (see Table 1 for summary of effect sizes). Five studies examined the relationship between cortisol and depression. Three studies (n = 117) found a correlation between an abnormal DST and depression [38, 40, 45], one (n = 12) found a non-significant association between higher cortisol and depression [21], and one (n = 62) found no relationship [24]. Finally, one (n = 66) study investigated the relationship between cortisol and infection and found a positive correlation [50], two studies (n = 131) investigated the relationship between cortisol and blood pressure and also found a positive correlation [56], and one study (n = 44) found an association between electrocardiographic abnormalities after SAH and elevated morning cortisol levels [57].

Cortisol and mortality

Of the 10 studies (n = 895) [19, 20, 22, 26, 41, 44, 46, 47, 56, 58] that examined the relationship between cortisol and mortality, all found that elevated cortisol was associated

with increased mortality (see Table 1 for summary of effect sizes); this was not statistically significant in two of the studies ($n = 39$) [19, 20].

Cortisol and outcome, independent of stroke severity

Only five studies adjusted for stroke severity when examining the relationship between cortisol and outcome. Three studies ($n = 504$) [22, 46, 47] found that cortisol was independently associated with death after stroke, and two out of three ($n = 453$) also found higher cortisol to be independently associated with poorer functional outcome [46, 47]. The remaining two studies ($n = 215$) found that cortisol was not an independent predictor of outcome after adjusting for stroke severity [31, 36].

Methodological quality

The STROBE score [59] ranged from 6 to 21, with a median score of 18 (Appendix 2). The lower quality studies (particularly those with a STROBE score of <10) did not report the relationship between cortisol and stroke outcome, and so these papers have had little influence on the main conclusions of this review.

Discussion

This is the first systematic review of studies of cortisol levels in relation to stroke severity and outcomes. Forty-eight studies met our inclusion criteria. The methodological quality of these studies was generally high. Cortisol levels were high (above the reference range) in the first 7 days after stroke onset. Those studies including participants with less severe strokes (not requiring critical care) found a decrease in cortisol over the first week following a stroke. By 3 months, cortisol levels were generally in the normal reference range. We are not able to conclude what the trajectory of cortisol is between these two time points (7 days and 3 months), as few studies investigated this aspect. Diurnal variation in cortisol appears to be lost in those with more severe strokes, but is preserved in those with more minor strokes. Elevated cortisol levels were correlated with increased stroke severity in the majority of studies that explored this association. Studies tended to find that elevated cortisol levels were associated with higher dependency, length of hospital stay, depression, delirium, and mortality.

There are some limitations in the included studies: none of the included studies reported sample size calculations and several studies only measured cortisol on one occasion rather than exploring changes over time, meaning that short-term physiological stressors such as acute illness may have contributed significantly to the cortisol levels reported. Furthermore, all the studies recruited participants from a hospital setting, meaning that results may not be applicable to those with minor strokes. Ten studies [19, 31, 37, 40, 42, 43, 45, 46, 60–62] included only those able to provide informed consent, meaning that those with aphasia or delirium would have been excluded. This could have reduced the generalizability of the findings, especially since delirium has been found to be associated with higher cortisol levels [25]. Finally, we must consider the possibility that the results presented are confounded by unmeasured variables, for example an association between cortisol and

stroke may reflect a causal relationship with a hormone, neurotransmitter, or other physiological parameter that was not measured in any of the included studies.

Our systematic review has several strengths. Our protocol had pre-defined inclusion and exclusion criteria. Screening and data extraction were performed independently by two authors, reducing the risk of transcription and data extraction error or omission. Systematic search strategies were used, and so it is unlikely that relevant articles were missed.

Some limitations of this review should be acknowledged. We did not search conference proceedings; however, this was deliberate, as we have found that crucial details are often missing from these publications. Only six abstracts of conference proceedings would have met our inclusion criteria. Interestingly, from the limited information available in these proceedings, it would appear than none of them reported negative findings, with four out of six reporting abnormalities in cortisol levels after SAH [63–66], one reporting evening cortisol levels above the reference range after ischaemic stroke [67], and one reporting an association between high cortisol and stroke severity [68]. We included ischaemic and haemorrhagic strokes, including SAH. It could be argued that as SAH has a different aetiology and risk factor profile than ischaemic and haemorrhagic stroke, it should have been excluded; however, we have taken care to report the findings from those studies including SAH separately. Furthermore, SAH does have several factors in common with other stroke types, for example, sudden onset of disease and long-term neurological sequelae. We were not able to perform a meta-analysis because the studies were too heterogeneous, particularly with respect to the timing and method of cortisol sampling. Finally, publication bias may have favored publication of those papers showing a positive association between cortisol and stroke, leading us to overestimate the strength of the association.

Previous non-systematic, narrative reviews have found a correlation between cortisol and functional impairment and mortality after stroke [9, 15, 16], however, two of these previous papers included discussions about cortisol after stroke only as part of a broader review of endocrine or of cognitive changes [15, 16], and the third, while providing a more extensive overview, was published in 1997, and consequently includes only 17 studies [9]. Our systematic review provides a more comprehensive overview of all studies to date and synthesizes the evidence.

Overall, if cortisol dysregulation was shown to be an independent predictor of poor outcome after stroke, even after correcting for stroke severity, this would provide justification for further investigation of this mechanism. While we have found some evidence of an independent association between cortisol and functional outcome, and between cortisol and mortality after stroke, we do not know what the direction of causality is (no studies were able to measure cortisol pre-stroke, and so it is possible that those with poorer outcomes may have had higher cortisol levels before stroke onset, for example). Additional larger studies designed to examine the complex relationship between the HPA axis and stroke would be required before trials to target cortisol dysregulation after stroke could be justified.

Europe PMC Funders Author Manuscripts

Conclusions

Cortisol levels are high for at least 7 days after stroke and are within the normal range in the majority of people by 3 months. Elevated cortisol after stroke is associated with greater dependency, morbidity, and mortality. However, there is currently insufficient evidence to conclude that these relationships are independent of stroke severity. Understanding the mechanism underlying these relationships may allow the development of therapeutic interventions to improve outcomes after stroke and merits further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

A.J.B was funded by a Research Training Fellowship from the Dunhill Medical Trust (grant number: RTF17/0111). A.J.B, S.D.S and A.M.J.M are members of the University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross-council Lifelong Health and Wellbeing (LLHW) initiative. Funding from the BBSRC, EPSRC, ESRC and MRC is gratefully acknowledged.

Appendix 1

Search strategies

Part A: stroke search strings (Cochrane stroke group)

1. Cerebrovascular disorders/
2. Exp basal ganglia cerebrovascular disease/
3. Exp brain ischemia/
4. Exp carotid artery diseases/
5. Cerebrovascular accident/
6. Exp brain infarction/
7. Exp cerebrovascular trauma/
8. Exp hypoxia–ischemia, brain/
9. Exp intracranial arterial diseases/
10. Intracranial arteriovenous malformations/
11. Exp “Intracranial Embolism and Thrombosis”/
12. Exp intracranial hemorrhages/
13. Vasospasm, intracranial/
14. Vertebral artery dissection/
15. Aneurysm, ruptured/
16. Brain injuries/

17. Brain injury, chronic/

18. Exp carotid arteries/

19. Endarterectomy, carotid/or endarterectomy/

20. *Heart septal defects, atrial/

21. *Atrial fibrillation/

22. (Stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or isch?emi$ attack$ or tia$1 or neurologic$ deficit$ or SAH or AVM).tw.

23. [(Brain$ or cerebr$ or cerebell$ or cortical or vertebrobasilar or hemispher $ or intracran$ or intracerebral or infratentorial or supratentorial or MCA or anterior circulation or posterior circulation or basal ganglia) adj10 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypox$ or vasospasm or obstruction or vasculopathy)].tw.

24. [(Lacunar or cortical) adj5 infarct$].tw.

25. [(Brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or subarachnoid or putaminal or putamen or posterior fossa) adj10 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed $)].tw.

26. [(Brain or cerebral or intracranial or communicating or giant or basilar or vertebral artery or berry or saccular or ruptured) adj10 aneurysm$].tw.

27. (Vertebral artery dissection or cerebral art$ disease$).tw.

28. ((Brain or intracranial or basal ganglia or lenticulostriate) adj10 [vascular adj5 (disease$ or disorder or accident or injur$ or trauma$ or insult or event)]).tw.

29. [(Isch?emic or apoplectic) adj5 (event or events or insult or attack$)].tw.

30. [(Cerebral vein or cerebral venous or sinus or sagittal) adj5 thrombo$].tw.

31. (CVDST or CVT).tw.

32. [(Intracranial or cerebral art$ or basilar art$ or vertebral art$ or vertebrobasilar or vertebral basilar) adj5 (stenosis or isch?emia or insufficiency or arteriosclero$ or atherosclero$ or occlus$)].tw.

33. [(Venous or arteriovenous or brain vasc$) adj5 malformation$].tw.

34. [(Brain or cerebral) adj5 (angioma$ or hemangioma$ or haemangioma $)].tw.

35. Carotid$.tw.

36. (Patent foramen ovale or PFO).tw.

Europe PMC Funders Author Manuscripts

37. [(Atrial or atrium or auricular) adj fibrillation].tw.

38. Asymptomatic cervical bruit.tw.

39. Exp aphasia/or anomia/or hemiplegia/or hemianopsia/or exp paresis/or deglutition disorders/or dysarthria/or pseudobulbar palsy/or muscle spasticity/

40. (Aphasi$ or apraxi$ or dysphasi$ or dysphagi$ or deglutition disorder$ or swallow$ disorder$ or dysarthri$ or hemipleg$ or hemipar$ or paresis or paretic or hemianop$ or hemineglect or spasticity or anomi$ or dysnomi$ or acquired brain injur$ or hemiball$).tw.

41. [(unilateral or visual or hemispatial or attentional or spatial) adj10 neglect].tw.

42. or/1-41

Part B: Cortisol search strings

43. Hydrocortisone/

44. Cortisol.tw.

45. S-cortisol.tw.

46. S?cortisol.tw.

47. Serum-cortisol.tw.

48. Cortisone.tw.

49. Corticosteroid.tw.

50. Glucocorticoid*.tw.

51. Epicortisol.tw.

52. Stress response.tw.

53. Hypercortisol?emia.tw.

54. or/43-53

Appendix 2

See Appendix 2, Table 2

References

1. Sorrells S, RM Sapolsky. An inflammatory review of glucocorticoid action in the CNS. Brain Behav Immun. 2007; 21:259–272. [PubMed: 17194565]
2. Munck A, Naray-Fejes-Toth A. Glucocorticoids and stress: permissive and supressive actions. Ann N Y Acad Sci. 1994; 30(746):115–130. [PubMed: 7825870]
3. Jurney TH, Cockrell JL Jr, Lindberg JS, Lamiell JM, Wade CE. Spectrum of serum cortisol response to ACTH in ICU patients—correlation with degree of illness and mortality. Chest. 1987; 92(2):292–295. [PubMed: 3038477]

4. Wade CE, Lindberg JS, Cockrell JL, Lamiell JM, Hunt MM, Ducey J, Jurney TH. Upon-admission adrenal steroidogenesis is adapted to the degree of illness in intensive care unit patients. J Clin Endocrinol Metab. 1988; 67:223–227. [PubMed: 2839534]
5. Reincke M, Lehmann R, Karl M, Magiakou A, Chrousos GP, Allolio B. Severe illness neuroendocrinology. Ann N Y Acad Sci. 1995; 29(771):556–559. [PubMed: 8597431]
6. Otte C, Hart S, Neylan TC, Marmar CR, Yaffe K, Mohr DC. A meta-analysis of cortisol response to challenge in human aging: importance of gender. Psychoneuroendocrinology. 2005; 30:80–91. [PubMed: 15358445]
7. MacLullich A, Deary IJ, Starr JM, Ferguson KJ, Wardlaw JM, Seckl JR. Plasma cortisol levels, brain volumes and cognition in healthy elderly men. Psychoneuroendocrinology. 2005; 30(5):505–515. [PubMed: 15721061]
8. Miller AH, Spencer RL, McEwen BS, Stein M. Depression, adrenal steroids and the immune system. Ann Intern Med. 1993; 25(5):481–487.
9. Mitchell A. Clinical implications of poststroke hypothalamo-pituitary adrenal axis dysfunction: a critical literature review. J Stroke Cerebrovascular Dis. 1997; 6(6):377–388.
10. Brown E, Woolston D, Frol A, Bobadilla L, Khan DA, Hanczyc M, Rush AJ, Fleckenstein J, Babcock E, Cullum CM. Hippocampal volume, spectroscopy, cognition, and mood in patients receiving corticosteroid therapy. Biol Psychiatry. 2004; 55:538–545. [PubMed: 15023583]
11. van Munster B, Bisschop PH, Zwinderman AH, Korevaar JC, Endert E, Wiersinga WJ, van Oosten HE, Goslings JC, de Rooij SE. Cortisol, interleukins and S100B in delirium in the elderly. Brain Cogn. 2010; 74:18–23. [PubMed: 20580479]
12. Pearson A, de Vries A, Middleton SD, Gillies F, White TO, Armstrong IR, Andrew R, Seckl JR, MacLullich AM. Cerebrospinal fluid cortisol levels are higher in patients with delirium versus controls. BMC Res Notes. 2010; 3:33. [PubMed: 20181121]
13. Lee B, Thomas AG, McAtee MJ. Associations of salivary cortisol with cognitive function in the Baltimore memory study. Arch Gen Psychiatry. 2007; 64:810–818. [PubMed: 17606815]
14. Kumari M, et al. Association of diurnal patterns in salivary cortisol with all-cause and cardiovascular mortality: findings from the Whitehall II study. J Clin Endocrinol Metab. 2011; 96(5):1478–1485. [PubMed: 21346074]
15. Franceschini R, et al. Endocrine abnormalities and outcome of ischaemic stroke. Biomed Pharmacother. 2001; 55(8):458–465. [PubMed: 11686580]
16. Olsson T. Activity in the hypothalamic-pituitary-adrenal axis and delirium. Dement Geriatr Cogn Disord. 1999; 10(5):345–349. [PubMed: 10473937]
17. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. STROBE initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008; 61:344–349. [PubMed: 18313558]
18. Poll EM, et al. Cortisol dynamics in the acute phase of aneurysmal subarachnoid hemorrhage: associations with disease severity and outcome. J Neurotrauma. 2010; 27(1):189–195. [PubMed: 19772477]
19. O'Neill PA, et al. Stress hormone and blood glucose response following acute stroke in the elderly. Stroke. 1991; 22(7):842–847. [PubMed: 1853403]
20. Weant KA, et al. Acute relative adrenal insufficiency after aneurysmal subarachnoid hemorrhage. Neurosurgery. 2008; 63(4):645–649. [PubMed: 18824943]
21. Harney JH, et al. Dexamethasone suppression test and onset of poststroke depression in patients with ischemic infarction. J Clin Psychiatry. 1993; 54(9):343–348. [PubMed: 8407853]
22. Anne M, et al. Neurohormonal activation in ischemic stroke: effects of acute phase disturbances on long-term mortality. Curr Neurovasc Res. 2007; 4(3):170–175. [PubMed: 17691970]
23. Zhao Y, Liu ZM, Zhai CH. Changes in peripheral leukocytic glucocorticoid receptor in patients with ischemic and hemorrhagic stroke [Chinese]. Zhonghua nei ke za zhi [Chin J Intern Med]. 1989; 28(8):479–481. 510.
24. Olsson T, et al. Hypercortisolism revealed by the dexamethasone suppression test with acute ischemic stroke. Stroke. 1989; 20(12):1685–1690. [PubMed: 2595730]

25. Gustafson Y, Olsson T, Asplund K, Hagg E. Acute confusional state (delirium) soon after stroke is associated with hypercortisolism. Cerebrovasc Dis. 1993; 3:33–38.
26. Marklund N, et al. Low and high circulating cortisol levels predict mortality and cognitive dysfunction early after stroke. J Intern Med. 2004; 256(1):15–21. [PubMed: 15189361]
27. Olsson T, et al. Abnormalities at different levels of the hypothalamic-pituitary-adrenocortical axis early after stroke. Stroke. 1992; 23(11):1573–1576. [PubMed: 1332219]
28. Burd GS, Sergeeva NA. Functional state of the pituitary-adrenal system in stroke patients [Russian]. Zh Nevropatol Psikhiatr Im S S Korsakova. 1952; 81(1):60–64. [PubMed: 6261493]
29. Atanassova PA, Terzieva DD, Dimitrov BD. Impaired nocturnal melatonin in acute phase of ischaemic stroke: cross-sectional matched case-control analysis. J Neuroendocrinol. 2009; 21(7): 657–663. [PubMed: 19453822]
30. Elwan O, et al. Hormonal changes in cerebral infarction in the young and elderly. J Neurol Sci. 1990; 98(2–3):235–243. [PubMed: 2243231]
31. Davalos A, et al. Effect of malnutrition after acute stroke on clinical outcome. Stroke. 1996; 27(6): 1028–1032. [PubMed: 8650709]
32. Espiner EA, et al. The neuro-cardio-endocrine response to acute subarachnoid haemorrhage. Clin Endocrinol. 2002; 56(5):629–635.
33. Giordano G, Aimaretti G, Ghigo E. Variations of pituitary function over time after brain injuries: the lesson from a prospective study. Pituitary. 2005; 8(3–4):227–231. [PubMed: 16508713]
34. Schwartz S, Schwab S, Klinga K, Maser-Gluth C, Bettendorf M. Neuroendocrine changes in patients with acute space occupying ischaemic stroke. J Neurol Neurosurg Psychiatry. 2003; 74(6): 725–727. [PubMed: 12754339]
35. Fassbender K, et al. Pattern of activation of the hypothalamic-pituitary-adrenal axis in acute stroke: relation to acute confusional state, extent of brain damage, and clinical outcome. Stroke. 1994; 25(6):1105–1108. [PubMed: 8202965]
36. Zierath D, et al. Plasma alpha-melanocyte stimulating hormone predicts outcome in ischemic stroke. Stroke. 2011; 42(12):3415–3420. [PubMed: 21960572]
37. Jenkins JS, et al. Hypothalamic-pituitary-adrenal function after subarachnoid haemorrhage. Br Med J. 1969; 4(5685):707–709. [PubMed: 5354872]
38. Reding M, Orto L, Willensky P. The dexamethasone suppression test. An indicator of depression in stroke but not a predictor of rehabilitation outcome. Arch Neurol. 1985; 42(3):209–212. [PubMed: 3977650]
39. Olsson T. Urinary free cortisol excretion shortly after ischaemic stroke. J Intern Med. 1990; 228(2): 177–181. [PubMed: 2394969]
40. Finklestein S, et al. Mood, vegetative disturbance, and dexamethasone suppression test after stroke. Ann Neurol. 1982; 12(5):463–468. [PubMed: 6960804]
41. Murros K, et al. Serum cortisol and outcome in ischemic brain infarction. J Neurol Sci. 1993; 116(1):12–17. [PubMed: 8509800]
42. Szczudlik A, et al. Serum interleukin-6 predicts cortisol release in acute stroke patients. J Endocrinol Invest. 2004; 27(1):37–41. [PubMed: 15053241]
43. Johansson A, et al. Cortisol axis abnormalities early after stroke-relationships to cytokines and leptin. J Intern Med. 2000; 247(2):179–187. [PubMed: 10692080]
44. Slowik A, et al. Hypercortisolemia in acute stroke is related to the inflammatory response. J Neurol Sci. 2002; 196(1–2):27–32. [PubMed: 11959152]
45. Theodoropoulou A, et al. Prolactin, cortisol secretion and thyroid function in patients with stroke of mild severity. Horm Metab Res. 2006; 38(9):587–591. [PubMed: 16981141]
46. Christensen H, Boysen G, Johannesen HH. Serum-cortisol reflects severity and mortality in acute stroke. J Neurol Sci. 2004; 217(2):175–180. [PubMed: 14706221]
47. Neidert S, et al. Anterior pituitary axis hormones and outcome in acute ischaemic stroke. J Intern Med. 2011; 269(4):420–432. [PubMed: 21205022]
48. Urra X, et al. Harms and benefits of lymphocyte subpopulations in patients with acute stroke. Neuroscience. 2009; 158(3):1174–1183. [PubMed: 18619524]

49. Dziedzic T, et al. Serum albumin as a determinant of cortisol release in patients with acute ischemic stroke. Atherosclerosis. 2012; 221(1):212–214. [PubMed: 22245038]
50. Harms H, et al. Influence of stroke localization on autonomic activation, immunodepression, and post-stroke infection. Cerebrovasc Dis. 2011; 32(6):552–560. [PubMed: 22104620]
51. Parenti G, et al. Evaluation of the anterior pituitary function in the acute phase after spontaneous subarachnoid hemorrhage. J Endocrinol Invest. 2011; 34(5):361–365. [PubMed: 20811167]
52. Shin IY, et al. Abnormal diurnal pattern of cortisol secretion in patients after aneurysmal subarachnoid hemorrhage. Stress. 2011; 14(2):156–165. [PubMed: 21034298]
53. Bendel S, et al. Pituitary-adrenal function in patients with acute subarachnoid haemorrhage: a prospective cohort study. Crit Care. 2008; 12(5):R126. [PubMed: 18851750]
54. Dimopoulou I, et al. Endocrine alterations in critically ill patients with stroke during the early recovery period. Neurocrit Care. 2005; 3(3):224–229. [PubMed: 16377833]
55. Feibel JH, et al. Prognostic value of the stress response following stroke. JAMA. 1977; 238(13): 1374–1376. [PubMed: 578192]
56. Fiebel J, Hardy PM, Campbell RG, Goldstein MN, Joynt RJ. Prognostic value of the stress response following stroke. JAMA. 1977; 238:1374–1376. [PubMed: 578192]
57. July J, As'ad S, Suhadi FXB, Islam AA. Cortisol dynamics are associated with electrocardiographic abnormalities following the aneurysmal subarachnoid haemorrhage. J Cardiovasc Dis Res. 2012; 3:315–318. [PubMed: 23233777]
58. Korsic M, et al. Some aspects of adrenocortical stress response following stroke. Acta med Iugosl. 1990; 44(2):137–145. [PubMed: 2112824]
59. Vandenbroucke JP, von Elm E, Altman DG, Gotzsche C, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elabouration. Ann Intern Med. 2007; 147:163–194.
60. Christensen H, et al. Serum cardiac troponin I in acute stroke is related to serum cortisol and TNF-alpha. Cerebrovasc Dis. 2004; 18(3):194–199. [PubMed: 15273434]
61. Lueken U, et al. Altered tonic and phasic cortisol secretion following unilateral stroke. Psychoneuroendocrinology. 2009; 34(3):402–412. [PubMed: 18996647]
62. Michalaki M, et al. Hypothalamic-pituitary-adrenal axis response to the severity of illness in non-critically ill patients: does relative corticosteroid insufficiency exist. Eur J Endocrinol. 2010; 162(2):341–347. [PubMed: 19903798]
63. Djurdjevic SP, Jovanovic V, Stojanovic M, et al. Screening for neuroendocrine dysfunction in patients after spontaneous subarachnoid hemorrhage. BioScientifica. 2009; 20:554. In: 11th European Congress of Endocrinology (2010) Istanbul, Turkey.
64. Takala, R.; Laukka, D.; Polonen, T., et al. Acute hormonal changes after aneurysmal subarachnoid haemorrhage. congress of the Scandanavian Society of Anaesthesiology and Intensive Care Medicine. Blackwell munksgaard; Turku: 2013. p. 30
65. Hannonl, MJ.; Behan, LA.; O'Brien, MM., et al. Aneurysmal subarachnoid hemorrhage is a rare cause of acute glucocorticoid deficiency and long-term hypopituitarism. 94th annual meeting and expo of the Endocrine Society; Endocrine Society, Houston. 2012.
66. Tolli, A.; Bellander, BM.; Hoybye, C.; Hulting, A.; Lund, S.; Borg, J. Identification of pituitary insufficiency in patients with traumatic brain injury (TBI) or subarachnoid haemorrhage (SAH). Informa Healthcare; 8th world congress on brain injury of the International Brain Injury Association; Washington. 2010. p. 314-315.
67. Lee S, et al. Increase in salivary cortisol in the evening correlates with sleep duration and quality in stroke patients. Int J Cardiol. 2011; 152:S14. conference world hypertension league regional congress, Beijing, China, 3–6 Nov 2011.
68. Hall CE, et al. Cortisol concentration is related to stroke severity: results from the GRASP trial. Stroke. 2010; 41(4):e321. 2010 international stroke conference, San Antonio, 23–26 Feb 2010.
69. Selakovic VM, Jovanovic MD, Jovicic A. Changes of cortisol levels and index of lipid peroxidation in cerebrospinal fluid of patients in the acute phase of completed stroke. Vojnosanitetski Pregled, Military, Medical and Pharmaceutical Review. 2002; 59(5):458–491.
70. Zetterling M, et al. Cortisol and adrenocorticotrophic hormone dynamics in the acute phase of subarachnoid haemorrhage. Br J Neurosurg. 2011; 25(6):684–692. [PubMed: 22115015]

71. Mangieri P, et al. Evaluation of pituitary and thyroid hormones in patients with subarachnoid hemorrhage due to ruptured intracranial aneurysm. Arquivos de Neuro-Psiquiatria. 2003; 61(1): 14–19. [PubMed: 12715013]

72. Ahmed N, de la Torre B, Wahlgren NG. Salivary cortisol, a biological marker of stress, is positively associated with 24-hour systolic blood pressure in patients with acute ischaemic stroke. Cerebrovasc Dis. 2004; 18(3):206–213. [PubMed: 15273436]

73. Huttner HB, Kiphuth I-C, Teuber L, et al. Neuroendocrine changes in patients with spontaneous supratentorial intracerebral haemorrhage. Neurocrit care. 2013; 18(1):39–44. [PubMed: 21837535]

74. Laures-Gore JS. Aphasia severity and salivary cortisol over time. J Clin Exp Neuropsychol. 2012; 34(5):489–496. [PubMed: 22352852]

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

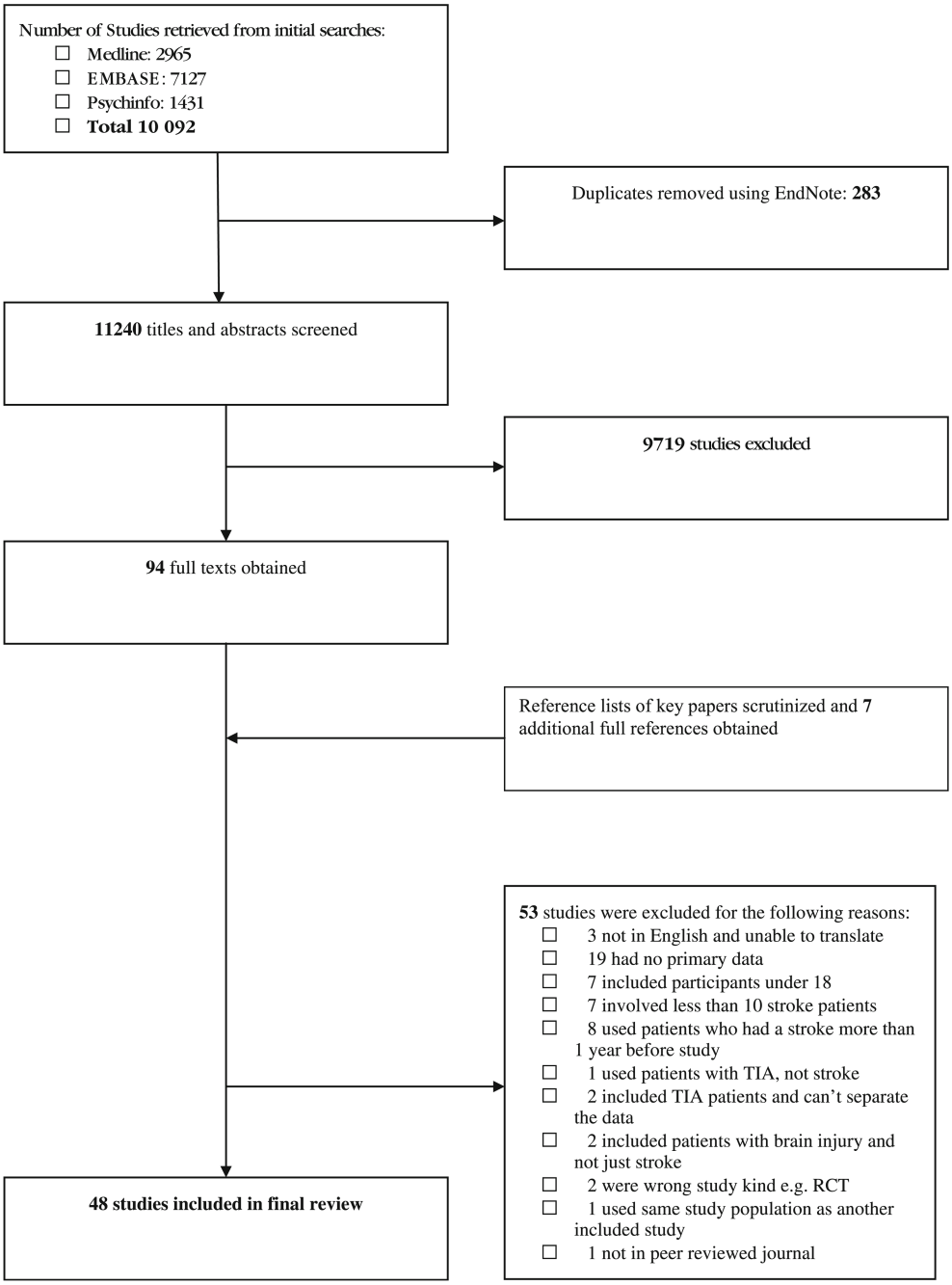

Fig. 1. Schema of systematic review

Europe PMC Funders Author Manuscripts

J Neurol. Author manuscript; available in PMC 2016 June 30.

Table 1

Table of characteristics of studies included in systematic review (listed alphabetically)

First author and country of origin	Number of participants	Mean age (Years)	Type of stroke	Cortisol measurement	Mean blood cortisol level at baseline, ± SD* (nmol/l)	Association between cortisol and outcome	Correlation coefficient, between cortisol and outcome (when available)	Study quality (STROBE 0–22)
Longitudinal studies								
Anne [22], Finland	51	67	Cerebral infarction	Blood	600 ± 200 if dead at 6 months 400 ± 200 if alive at 6 months	Mean cortisol on day 2 and 7 significantly correlated to stroke severity, mRS, and mortality	Severity $r = 0.44$ mRS $r = 0.37$ Mortality RR = 5.4 am and 5.8 pm	20
Bendel [53], Finland	30	52	Subarachnoid haemorrhage	Blood (SST)	790 ± 300	Serum cortisol not associated with bleeding severity	NR	20
Christensen [60], Denmark	172	74	Cerebral infarction (90 %) and haemorrhage (10 %)	Blood	550	Serum cortisol associated with stroke severity and positive correlation with higher mRS and mortality	Severity $r = 0.45$ mRS $r = 0.18$ Mortality OR = 1.9	21
Davalos [31], Spain	104	66	Cerebral infarction and haemorrhage	Blood and urine	Figures not stated	High free urinary cortisol predicted poor outcome, independent of age, sex, and nutritional status at admission	NR	18
Espiner [32], New Zealand	18	54	Subarachnoid haemorrhage	Blood	520	No data	NR	19
Fassbender [35], Germany	23	72	Cerebral infarction	Blood	Figures not stated	Cortisol not correlated with stroke severity or with delirium	NR	18
Feibel [55], USA	65	62	Cerebral infarction, brainstem infarction and subarachnoid haemorrhage	Blood	440 CI 340 BI 717 SAH	High cortisol correlated with hypertension and disability	NR	17
Giordano [33], Italy	32	52	Subarachnoid haemorrhage	Blood	Figures not stated	No data	NR	12
Gustafson [25], Sweden	83	75	Cerebral infarction	Blood (DST)	450	High cortisol correlated with delirium	NR	21
Harney [21], USA	12	61	Cerebral infarction	Blood (DST)	Figures not stated	Abnormal DST associated with depression at 1 week	Depression $r = 0.49$	17
Huttner [73], Germany	20	68	Cerebral haemorrhage	Blood	483	No data	NR	19

Europe PMC Funders Author Manuscripts

First author and country of origin	Number of participants	Mean age (Years)	Type of stroke	Cortisol measurement	Mean blood cortisol level at baseline, ± SD* (nmol/l)	Association between cortisol and outcome	Correlation coefficient, between cortisol and outcome (when available)	Study quality (STROBE 0–22)
Jenkins [37], UK	18	52	Subarachnoid haemorrhage	Blood	535	No data	NR	12
Johansson [43], Sweden	12	74	Cerebral infarction	Blood	500	Cortisol levels correlated significantly to the severity of paresis	Severity $r = 0.68$ to −0.73	18
July [57], Indonesia	44	52	Subarachnoid haemorrhage	Blood	632 normal ECG 803 abnormal ECG	High morning cortisol levels are associated with ECG abnormalities	ECG abnormality (day 2) OR = 2.56 ECG abnormality (day 4) OR = 1.08	14
Laures-Gore [74], USA	31	57	Cerebral infarction	Saliva	Not applicable	No relationship between cortisol levels and aphasia severity	Aphasia $r = 0.26$	17
Marklund [26], Sweden	88	71	Cerebral infarction	Blood	450	High cortisol levels correlated with severe functional impairment, disorientation, and mortality	NR	20
Michalaki [62], Greece	10	69	Cerebral infarction	Blood (SST)	760	No data	NR	18
Murros [41], Finland	101	61	Cerebral infarction	Blood	590	Cortisol levels correlated significantly to the severity of paresis (on day 1 and at 3 months) and to the mRS	Severity $r = 0.41$ (day 1), $r = 0.22$ (3 months) mRS $r = 0.25$	18
Neidert [47], Switzerland	281	68	Cerebral infarction	Blood	480	Cortisol levels correlated positively with functional outcome functional outcome and mortality	Functional outcome OR = 1.0 Mortality OR = 1.62	21
O'Neill [19], UK	23	80		Blood	306 good outcome 752 poor outcome	Cortisol levels independently related to outcome	NR	20
Poll [18], Germany	22	47	Subarachnoid haemorrhage	Blood	540	Abnormal cortisol (elevated baseline and loss of diurnal rhythm) correlated with lower GCS, longer ICU stay and less favorable outcome	GCS $r = -0.56$ LOS (ICU) $r = 0.65$ Outcome $r = -0.67$	19

Europe PMC Funders Author Manuscripts

First author and country of origin	Number of participants	Mean age (Years)	Type of stroke	Cortisol measurement	Mean blood cortisol level at baseline, ± SD* (nmol/l)	Association between cortisol and outcome	Correlation coefficient, between cortisol and outcome (when available)	Study quality (STROBE 0–22)
Reding [38], USA	75	68	Cerebral infarction	Blood (DST)	Figures not stated	Abnormal DST associated with higher depression scores and more severe strokes	NR	16
Schwartz [34], Germany	22	58	Cerebral infarction	Blood	270	Cortisol not related to outcome	NR	17
Slowik [44], Poland	70	69	Cerebral infarction	Blood	Figures not stated	Cortisol correlated with stroke severity (−0.42), and associated with higher mortality rates	Severity r = −0.42	18
Theodoropoulou [45],Greece	17	No data	Cerebral infarction	Blood	230	No correlation between cortisol and stroke severity or outcome	NR	15
Urra [48], Spain	46	74	Cerebral infarction and haemorrhage	Blood	Figures not stated	Cortisol was positively correlated with the NIHSS score (0.31)	NIHSS r = 0.31	19
Zetterling [70], Sweden	55	59	Subarachnoid haemorrhage	Blood	1,119 (Median)	Cortisol not related to outcome	NR	18
Zierrath [36], USA	111	57	Cerebral infarction	Blood	Figures not stated	Cortisol positively correlated with stroke severity (0.72)	Severity r = 0.72	21
Cross-sectional cohort studies (listed alphabetically)								
Ahmed [72], Sweden	53	66	Cerebral infarction	Saliva	Not applicable	Mean cortisol positively correlated with blood pressure	NR	21
Atanassova [29], Bulgaria	33	58	Cerebral infarction	Blood	484	No data	NR	18
Burd [28], Russia	31	NA	Cerebral infarction and haemorrhage	Blood	Not stated	No data	NR	7
Dimopoulou [54], Greece	33	57	Cerebral infarction and haemorrhage	Blood (SST)	410	No data	NR	17
Dziedzic [49], Poland	59	58	Cerebral infarction	Blood	590 lower tertile 590 middle tertile 550 upper tertile	High cortisol associated with low serum albumin	NR	15
Elwan [30], Egypt	51	55	Cerebral infarction	Blood and CSF	12.29 μg %	No data	NR	6
Finklestein [40], USA	25	72	Cerebral infarction and haemorrhage	Blood (DST)	Not applicable	Abnormal DST associated with depression	NR	14

Europe PMC Funders Author Manuscripts

First author and country of origin	Number of participants	Mean age (Years)	Type of stroke	Cortisol measurement	Mean blood cortisol level at baseline, ± SD* (nmol/l)	Association between cortisol and outcome	Correlation coefficient, between cortisol and outcome (when available)	Study quality (STROBE 0–22)
Harms [50], Germany	66	72	Cerebral infarction	24 h urine	Not applicable	Cortisol positively correlated with stroke volume but not severity	Stroke volume r = 0.32	21
Korsic [58], Croatia	28	68	Cerebral infarction and haemorrhage	24 h urine	Not applicable	Cortisol positively associated with mortality	NR	13
Lueken [61], Germany	32	57	Cerebral infarction	Saliva	Not applicable	No data	NR	20
Mangieri [71], Brazil	35	52	Subarachnoid haemorrhage	Blood	870	No data	NR	14
Olsson [24], Sweden	62	75	Cerebral infarction	Blood (DST)	440	High cortisol post-DST associated with disorientation but not associated with limb paresis or depression	NR	18
Olsson [39], Sweden	20	78	Cerebral infarction	Blood (DST) and 24 h urine	Figures not stated	Cortisol predicted functional outcome and correlated with presence of limb, paresis and disorientation	Paresis r = 0.59 Disorientation r = 0.41	19
Olsson [27], Sweden	16	71	Cerebral infarction	Blood (SST and DST)	390	Abnormal DST correlated with presence of limb paresis and delirium	Paresis r = 0.62 Delirium r = 0.66	18
Parenti [51], Italy	60	60	Subarachnoid haemorrhage	Blood	660	Cortisol positively correlated with Fisher's scale	Severity r = 0.43	19
Selakovic [69], Yugoslavia	53	No data	Cerebral infarction	CSF	Not applicable	No data	NR	16
Shin [52], Korea	25	56	Subarachnoid haemorrhage	Saliva	Not applicable	Nighttime cortisol negatively correlated with Fisher CT grade	NR	17
Szczudlik [42], Poland	22	61	Cerebral infarction	Blood	Figures not stated	Cortisol positively correlated with stroke severity	Severity r = −0.63	16
Weant [20], USA	16	58	Subarachnoid haemorrhage	Blood (SST)	620 (median)	Cortisol positively correlated with length of hospital stay and length of ICU stay	NR	20

Europe PMC Funders Author Manuscripts

First author and country of origin	Number of participants	Mean age (Years)	Type of stroke	Cortisol measurement	Mean blood cortisol level at baseline, ± SD* (nmol/l)	Association between cortisol and outcome	Correlation coefficient, between cortisol and outcome (when available)	Study quality (STROBE 0–22)
Zhao [23], China	37	66	Cerebral infarction and cerebral haemorrhage	Blood	1,120 (haemorrhagic) 900 (ischemic)	No data	NR	13

BI brainstem infarction, CI cerebral infarction, DST dexamethasone suppression test, GCS glasgow coma scale, ICU intensive care unit, LOS length of stay, mRS modified Rankin scale, NIHSS National Institutes of Health Stroke Scale, NR not reported, RR risk ratio, SST short Synacthen test, SD standard deviation, UK United Kingdom, USA United States of America

*Baseline cortisol refers to the first random cortisol sample taken after stroke

Europe PMC Funders Author Manuscripts

Table 2

Results of quality assessment

#	Criteria	Number (%) of papers meeting criteria
1	Title and abstract	18 (38)
Introduction		
2	Backround/rationale	48 (100)
3	Objectives	41 (85)
Methods		
4	Study design	47 (98)
5	Setting	41 (81)
6	Participants	43 (90)
7	Variables	44 (92)
8	Data sources/measurement	48 (100)
9	Bias	36 (75)
10	Study size	1 (2)
11	Quantitative variables	42 (88)
12	Statistical methods	42 (88)
Results		
13	Participants	40 (83)
14	Descriptive data	40 (83)
15	Outcome data	46 (96)
16	Main results	41 (85)
17	Other analyses	42 (88)
Discussion		
18	Key results	47 (98)
19	Limitations	23 (48)
20	Interpretation	46 (96)
21	Generalizability	36 (75)
Other information		
22	Funding	24 (50)