Late-night salivary cortisol for the diagnosis of Cushing syndrome: a meta-analysis

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CRD summary
This review assessed the performance of late-night salivary cortisol as an initial screening and diagnostic test for Cushing's syndrome and concluded that it was a robust and convenient test. Despite some limitations in the data and analysis, this conclusion is likely to be reliable.

Authors' objectives
To assess the accuracy of late-night salivary cortisol for the diagnosis of Cushing's syndrome.

Searching
MEDLINE and EMBASE were searched to December 2007 and search terms were reported. Major textbooks, review articles, and the bibliographies of included studies were screened for additional articles. Missing articles and unpublished data were also sought from experts in the field.

Study selection
Studies assessing the performance of late-night salivary cortisol in adults (over 18 years old) who were referred for investigation of possible Cushing's syndrome were eligible for inclusion. The diagnosis of Cushing's syndrome had to be based on clinical and other biochemical data (not late-night salivary cortisol) and confirmed by pathology or clinical and biochemical remission after therapy or both. The exclusion of Cushing's syndrome was confirmed by other biochemical testing and a lack of clinical progression during follow-up. Included studies were required to report sufficient data for the calculation of the sensitivity and specificity of late-night salivary cortisol.

The prevalence of Cushing's syndrome, in included studies, ranged from 14% to 67%. The methods used to measure salivary cortisol varied between studies and the cut-off threshold for a diagnosis of Cushing's syndrome ranged from 0.13 to 0.55 μg per dL of salivary cortisol (one study did not report the cut-off).

Two reviewers independently assessed titles and abstracts, and reviewed the full text of all relevant articles, for inclusion.

Assessment of study quality
The methodological quality of the included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool, which assesses aspects of reporting quality, patient spectrum, blinding, verification biases, disease progression bias, and handling of indeterminate results and drop-outs.

Two reviewers independently assessed study quality and disagreements were resolved by discussion with a third reviewer.

Data extraction
For each included study, the data were extracted on the cut-off threshold for a positive diagnosis, the reference standard used to confirm diagnosis, and the numbers of true positive, false negative, false positive, and true negative results. The sensitivity, specificity, positive and negative likelihood ratios (LRs), and diagnostic odds ratio (DOR), with 95% confidence intervals (CIs) were calculated for each study.

Two reviewers independently extracted the data and disagreements were resolved by discussion with a third reviewer.

Methods of synthesis
Pooled estimates of sensitivity, specificity, positive and negative LRs, and DOR were calculated using a random-effects model. The I² test was used to assess between study heterogeneity. A symmetric summary receiver operating
characteristic curve was fitted, using the Moses-Shapiro-Littenberg model, and used to assess the threshold effect (changes in the DOR caused by variation in the diagnostic cut-off).

**Results of the review**

Seven studies, with a total of 947 participants, were included. These studies generally met the majority of QUADAS criteria, but only two studies reported blinded interpretation of test results and the time elapsing between index test and confirmation of diagnosis was often unclear. There was also variation in the methods used to confirm the exclusion of Cushing's syndrome as a diagnosis.

The pooled estimate of sensitivity was 92% (95% CI 88 to 94) and the pooled estimate of specificity was 96% (95% CI 94 to 97). The pooled estimate of positive LR was 21 (95% CI 10 to 43) and the pooled estimate of negative LR was 0.08 (95% CI 0.02 to 0.32). The pooled estimate of DOR was 311 (95% CI 92 to 1,059). The $I^2$ test indicated high heterogeneity for sensitivity and negative LR, and moderate heterogeneity for all other parameters; there was one apparent outlier with a reported sensitivity of 45%, where all other sensitivity and specificity estimates were over 90%. The summary receiver operating characteristic curve indicated that variation in the cut-off values between studies did not affect test performance.

**Authors' conclusions**

The authors concluded that the results of their meta-analysis supported the use of late-night salivary cortisol as an initial screening and diagnostic test for Cushing's syndrome.

**CRD commentary**

This review clearly stated its objective and defined appropriate inclusion criteria. A number of sources were searched for relevant studies and attempts were made to identify unpublished data. No language restrictions were reported. Measures to avoid error and bias were taken throughout the review process and the methodological quality of included studies was assessed and reported in full. The use of heterogeneous data sets to generate pooled estimates of test performance is generally not recommended, but heterogeneity appears to have been generated by a single study and greater exploration of this, including sensitivity analysis, would have been useful.

Overall, the test performance data, though limited, supported the authors' conclusions.

**Implications of the review for practice and research**

**Practice:** The authors stated that late-night salivary cortisol was a robust and convenient test, which could be used in initial screening and diagnostic testing for Cushing's syndrome.

**Research:** The authors made no recommendations for research.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.