Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis


CRD summary
This review concluded that there was no evidence that the serotonin transporter genotype alone, or in interaction with stressful life events, was associated with an elevated risk of depression. The conclusions accurately reflected the results of this review of a large number of individuals, but a number of shortcomings in the review process mean that their reliability is unclear.

Authors’ objectives
To assess the relationship between the serotonin transporter gene (5-HTTLPR) and risk of depression. The authors also assessed the interaction between stressful life events and depression but this lies outside the scope of this abstract.

Searching
The databases PubMed, EMBASE and PsycINFO were searched up to March 2009. Search terms were reported. The references of identified studies were also checked. Only published studies were eligible for inclusion in the review.

Study selection
Studies that reported data on the association between the serotonin transporter linked polymorphic region (5-HTTLPR) genotype (either short-short (SS), short-long (SL) or long-long (LL)), number of stressful life events and a categorical measure of depression (as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, (DSM-IV) or the International Statistical Classification of Diseases, 10th Revision (ICD-10)) were eligible for inclusion. Studies which allowed the use of a cut point to define depression from standardised rating scales were also eligible for inclusion.

Included studies were cross-sectional or prospective cohort studies. The majority of the studies used a structured interview (DSM-IV or ICD-10) to diagnose depression; the remainder used scales such as the Beck Depression Inventory. Participants in the majority of studies were white. Mean ages of participants ranged from 16 to 65 years or over, and most studies contained a majority of women.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Original data were requested from the authors of all studies which appeared to meet inclusion criteria and were published prior to 2008. 5-HTTLPR genotype was coded as 0, 1 or 2 based on the number of S-alleles. Major depression was coded as a dichotomous outcome when based on diagnostic interviews, or as above the 85th percentile of score distribution on dimensional scale measures. Odds ratios with 95% confidence intervals (CI) were calculated for the presence of S alleles in those with and without depression.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
The studies were combined in a random-effects meta-analysis with logistic regression to assess the relationship between the number of S alleles and the incidence of major depression. Pooled odds ratios with 95% CIs were calculated for the presence of S alleles in those with and without depression. A second meta-analysis using individual-level data was used to assess sex-specific relationships between the variables. Further analyses assessing the impact of stressful life events

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and interactions between the variables, and subsequent logistic regression analyses, lie outside the scope of this abstract. Heterogeneity was assessed using the \( \chi^2 \) statistic.

**Results of the review**

Fourteen studies (n=14,250 participants, of which 1,769 were classified as having depression) were included in the review, with original data available for 10 of these (n=10,943 participants). Sample sizes ranged from 118 to 4,175.

There was no significant difference in \( S \) allele frequency between those with and without depression in any single study or in the meta-analysis (odds ratio 1.05, 95% CI: 0.98, 1.13, 14 studies). The subgroup analysis based on individual level data (10 studies) also found no significant differences in S allele frequency between those with and without depression in men, women or overall. There was no evidence of statistically significant heterogeneity between studies.

Results for the relationship between stressful life events and depression and the interaction of life events and allelic frequency were also reported.

**Authors’ conclusions**

There was no evidence that the serotonin transporter genotype alone, or in interaction with stressful life events, associated with an elevated risk of depression in men alone, women alone, or in both sexes combined.

**CRD commentary**

The review assessed a clear question supported by clear inclusion criteria with the exception of participant definition. The search was adequate but the decision to restrict the review to published studies may have led to the exclusion of some relevant studies and the introduction of publication bias. The authors did not report conducting a validity assessment of the published data and did not report checking of the individual patient data obtained for some studies. They also did not report using methods designed to reduce reviewer bias and error in the selection of studies or in the extraction of data. The decision to employ meta-analysis and the use of subgroups for the analysis of individual-level data appeared appropriate.

The authors’ conclusions accurately reflected the results of this review which included a large number of individuals. In the absence of a validity assessment, and given poor reporting of aspects of the review process and the possibility of publication bias, it is not clear how reliable the conclusions are.

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

Practice: The authors stated that it is crucial that the importance of replicating research findings relating to genetic associations with behavioural outcomes be recognised before they are used as indicators of disease risk or translated into clinical and public health practice.

Research: The authors did not state any implications for further research.

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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.