

# World Journal of *Meta-Analysis*

*World J Meta-Anal* 2017 August 26; 5(4): 80-123





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*World Journal of Meta-Analysis*  
Volume 5 Number 4 August 26, 2017

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NAME OF JOURNAL  
*World Journal of Meta-Analysis*

ISSN  
ISSN 2308-3840 (online)

LAUNCH DATE  
May 26, 2013

FREQUENCY  
Bimonthly

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PUBLICATION DATE  
August 26, 2017

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## Assessing the quality of studies in meta-analyses: Advantages and limitations of the Newcastle Ottawa Scale

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**Author contributions:** Luchini C and Solmi M wrote the manuscript; Stubbs B and Veronese N critically evaluated the manuscript; all the authors approved the final form and the submission.

**Conflict-of-interest statement:** None to declare.

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**Manuscript source:** Invited manuscript

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**Received:** January 13, 2017  
**Peer-review started:** January 16, 2017  
**First decision:** February 17, 2017  
**Revised:** May 18, 2017  
**Accepted:** June 6, 2017  
**Article in press:** June 8, 2017  
**Published online:** August 26, 2017

### Abstract

One of the most important points in the meta-analyses is certainly represented by the assessment of the quality of the studies included in such research. The meta-analyses are considered the highest level of evidence in science. Also for this reason, the quality of the studies included should be accurately evaluated by standardized tools. The overall results of the meta-analysis depend indeed also on a rigorous evaluation of the studies quality. Among all the possible tools for this complex evaluation, the Newcastle Ottawa Scale (NOS) is one of the most used worldwide, above all for observational studies. In this review, we will discuss the strengths and limitation of the NOS, also on the basis of the branch of science in which it has been applied.

**Key words:** Quality; Meta-analysis; Newcastle Ottawa Scale

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**Core tip:** To assess the quality of a meta-analysis is a remarkable point. In this review, we summarize the current evidence regarding the use of the Newcastle Ottawa Scale, one of the most used tool for evaluating

quality in meta-analyses of observational studies. Taking also our works as example, we found that, even standardized and quick in its application, it suffers from some limitations, particularly when evaluating cross-sectional studies.

Luchini C, Stubbs B, Solmi M, Veronese N. Assessing the quality of studies in meta-analyses: Advantages and limitations of the Newcastle Ottawa Scale. *World J Meta-Anal* 2017; 5(4): 80-84 Available from: URL: <http://www.wjgnet.com/2308-3840/full/v5/i4/80.htm> DOI: <http://dx.doi.org/10.13105/wjma.v5.i4.80>

## INTRODUCTION

The quality assessment of studies included in systematic reviews and meta analyses is essential to enable a clear understanding of the evidence base. There are several sources of biases in meta-analyses including inaccurate selection of participants, data collection, analysis and selective reporting of study results<sup>[1]</sup>. Many of these biases derive directly from the studies which are included in the meta-analysis. However, since systematic reviews and meta-analyses are considered the highest level of evidence in science<sup>[2]</sup>, the quality of the studies included should be accurately evaluated by validated and standardized tools.

For randomized controlled trials (RCTs), numerous tools are available to assess the risk of bias and methodological quality. Among the most commonly used, the Cochrane Collaboration's tool<sup>[3]</sup> seems one of the most accurate, since it accounts for the main features of the RCTs. However, other tools (such as the Jadad's scale<sup>[4]</sup>) are commonly used.

There are less methodological quality assessment tools available for the meta-analyses of observational studies. Some authors (including our group<sup>[5,6]</sup>) have used reporting checklists for detailing the quality of included studies (such as STROBE<sup>[7-9]</sup>). Whilst this method has several strengths, it may be seen as a simple reporting checklist. Such tools are not validated for assessing the quality of studies included in meta-analyses<sup>[1]</sup>. For this reason, other tools are commonly used for assessing quality and risk of bias in observational (both cross-sectional and longitudinal) studies. Among these, the Newcastle Ottawa Scale (NOS)<sup>[10]</sup> is one of the most used worldwide.

Given the rising number of meta analyses of observational studies in the scientific literature, it is mandatory that the tools used to assess study quality in such endeavors are appraised. In this review, we will discuss the strengths and limitation of the NOS and its application, taking as example the branches of pathology and psychiatry, also with reference to some meta-analyses from our group of research.

## REVIEW AND DISCUSSION

### NOS: Definition

The NOS can be used for both case-control and longitudinal (prospective studies). Typically, cross-sectional studies are evaluated as case control studies. The NOS evaluates three quality parameters (selection, comparability, and outcome) divided across eight specific items, which slightly differ when scoring case control and longitudinal studies<sup>[10]</sup>. Each item on the scale is scored from one point, except for comparability, which can be adapted to the specific topic of interest to score up to two points. Thus, the maximum for each study is 9, with studies having less than 5 points being identified as representing at high risk of bias<sup>[11]</sup>.

In order to minimize the subjective interpretation of bias from scoring the NOS typically two independent authors should score each paper. However, in our opinion, the most important as well as critical point in the NOS scoring and filling in is certainly represented by the specific field in which the meta-analysis has been conducted. Each field of science has indeed intrinsic aspects with consequent implications: Here we present these differences and both the advantages and the limitations of NOS scale in some of the most important branches of science.

### NOS for meta-analyses in pathology

The pathologists' role in the era of modern medicine is based on performing an accurate as well as precise diagnosis, using standardized parameters, fixed cut-offs and thresholds. This standard strategy should be applied from the gross sampling to the pathology report<sup>[12,13]</sup>. The perfect tool for modern surgical pathologists to reach a consensus on the parameters to be reported in the diagnosis (when, how and why) is certainly represented by meta-analysis. With this statistical method the best standard and significant parameters, that can guide the pathologists during the diagnostic activity, can be documented. The meta-analysis can be thus applied to three of the main aspects of surgical pathology: (1) the prognostic impact of the mutation status of particular genes in cancer<sup>[14,15]</sup>; (2) the prognostic role of macro- or microscopic features of cancers<sup>[16-25]</sup>; and (3) the diagnostic utility of some morphological, immunohistochemical and/or molecular parameters<sup>[26]</sup>. Regarding the specific points of NOS scale for pathologists, an important topic is represented by the selection of the right method for ascertainment of exposure. If the meta-analysis regards a morphological aspect or an immunohistochemical staining, the classical microscopic exam should be preferred. Conversely, if the investigation regards a molecular aspect, the best standard molecular approach for the specific parameter should be applied, knowing that two of the most important are Sanger Sequencing<sup>[27]</sup>

**Table 1** Strengths and weaknesses of the Newcastle Ottawa Scale

Strengths	Weaknesses
Quick and adaptable	Not validation for cross-sectional studies
Validated	Poor agreement
Moderator	Lack of comprehensive manuals

and Next Generation Sequencing<sup>[28-30]</sup>. For the outcome of interest, it is important specifying that this point is very subjective and may vary more than other points among different meta-analyses. In prognostic meta-analyses, however, we suggest to consider the disease-specific survival or the recurrence-free survival as the right parameter, being the overall survival the most common parameter in prognostic studies and thus not an index of quality. The point of NOS scale represented by the control for important factor or additional factor is obviously very important, since it can give two stars, determining a significant part of the quality's evaluation. In this case the choice of the right parameters it is even more important. Knowing that data from multivariate analysis are more reliable, this merit should be acknowledge using this index, for example giving a star to a study that presents hazard ratios and an additional star if this data are obtained considering at least two or more potential confounders. For meta-analysis in pathology, at last, it has to be highlighted that a standard length for the follow-up of patients is 60 mo (5 years). A point of strength of this scale is that these parameters are not fixed and adaptable on the basis of the specific analysis. For example, a meta-analysis on the survival of patients with glioblastomas, a tumor with a very poor prognosis generally no longer than 2 years, will reach a star for smaller period (18 mo for example) than the classical 60 mo. The adaptability of NOS scale in this sense represents surely a point of strength. A limitation of this scale in pathology is that it may be very difficult, or even impossible, considering every possible source of bias in this scale, or highlighting every point of strength of the analyzed studies with this multi-stars system. The expertise and a consensus meeting among the authors is the best way to choose the right parameters for this scale.

### NOS for meta-analyses in psychiatry

Psychiatry is different from pathology and other branches of medicine, since diagnoses, response, and remission are defined exclusively on clinical evaluation. Thus, the selection and exposure or outcome NOS items, which assess whether cases are diagnosed through reliable and independent validation or through self-report instead, is fundamental in establishing research quality. Moreover, among the main diagnostic systems, namely DSM-V<sup>[31]</sup> and ICD, some differences are evident<sup>[32]</sup> and there remains a great debate about diagnosis in general. Also, a control group defined as free from a specific mental disease in the

general population, has a lower odds of having other psychiatric comorbidity compared to a control population of inpatients, due to frequent medical comorbidity among patients with severe psychiatric conditions<sup>[33,34]</sup>. Furthermore, remission and response definitions need specific psychopathologic scales' cut-offs to be defined, and self-report or no description of such criteria need to be accounted for from a quality assessment scale, which is the case of NOS. Finally, treatment adherence is a substantial problem in psychiatry, and results are often affected by rates of completers and subjects lost at follow-up; again outcome NOS items account for such a variable. Thus authors encourage the use of NOS scale in the field of psychiatry, as has already been done in both observational<sup>[35,36]</sup> and interventional<sup>[37]</sup> studies' meta-analyses.

### Strengths of the NOS

The NOS is one of the most known scale for assessing quality and risk of bias in observational studies for several reasons<sup>[38]</sup>, as reported in Table 1. The first one is that this tool is relatively quick to do, although it requires the right attention. Second, as already explained, the adaptability of its indexes on the basis of the investigated topic is very important. Furthermore, differently from other checklists and tools, it is validated for case-control and longitudinal studies<sup>[10]</sup>. Finally, differently from other tools, NOS gives a score between 0 and 9 and so it is possible to use it as potential moderator in meta-regression analyses<sup>[11,39]</sup>.

### Weaknesses of the NOS

The NOS suffers from several weaknesses, however (Table 1). First, some domains are not univocal and one author should usually adapt this scale modifying some items. It is particularly true for cross-sectional studies for which the NOS should be adapted from the scheme of the case-control studies. Regarding the longitudinal investigations, the points usually adapted by the authors are the number and type of adjustments in the multivariate analyses, the duration of follow-up (not univocal follow-up is in fact given) and the outcome of interest not present at the baseline.

Another point of weakness is the low agreement between two independent reviewers in making the NOS. In the work proposed by Hartling *et al.*<sup>[40]</sup>, the agreement between the two reviewers was moderate/poor as shown by the *k*-value ( $< 0.50$  for eight of the nine questions on the NOS). This is particularly true in case of low experience by the authors in meta-analysis/systematic reviews<sup>[41]</sup> suggesting that a training with a more expert author is needed.

Finally, the lack of comprehensive manuals could be interpreted as another limitation<sup>[42]</sup>.

## CONCLUSION

The NOS is a tool commonly used in medicine for

the assessment of quality. Although it is a validated instrument and with a long history of reliability it suffers from several limitations. Other tools (tailored for cross-sectional studies and with more univocal items for other observational studies) are probably needed.

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