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METHODS

Methods of Evidence-Based Anatomy: a guide to conducting systematic reviews and meta-analysis of anatomical studies

Brandon Michael Henry[a,b,*,1], Krzysztof A. Tomaszewski[a,b,1], Jerzy A. Walocha[a,b]

[a] International Evidence-Based Anatomy Working Group, 12 Kopernika Street, 31-034 Krakow, Poland
[b] Department of Anatomy, Jagiellonian University Medical College, 12 Kopernika Street, 31-034 Krakow, Poland

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ABSTRACT

Evidence-Based Anatomy (EBA) is the concept of applying evidence-based principles and research methods to the anatomical sciences. While narrative reviews are common in the anatomical sciences, true systematic reviews (SR) and meta-analysis (MA) are only beginning to grow in popularity. In order to enhance the quality of future EBA studies, and ensure the clinical reliability of their results, a uniform methodology is needed. In this paper, we present a step-by-step methodological guide for performing SRs and MAs of anatomical studies. We address the EBA-specific challenges in each step of the SR and MA process, and discuss methods and strategies to overcome these difficulties. Furthermore, we discuss in detail the statistical methods used in MA of anatomical data, including multi-categorical and single-categorical pooled prevalence estimates, as well as pooled means of one group. Lastly, we discuss the major limitations of EBA, including the lack of a proper quality assessment tool for anatomical studies. The methods described in this paper present a uniform road map for future EBA studies.

1. Introduction

While many of the basic medical sciences have seen great advancements in the past century, the basic principles and methods of anatomical research have remained largely unchanged. Furthermore, as other medical sciences have progressed into the evidence-based era, the current foundation of clinical anatomy is still largely based on findings from single epidemiological-type studies. As such, the majority of current anatomical literature lacks the power allowing for conclusive findings on the population as a whole. This may leave clinicians partially in the dark on important variable anatomical characteristics, potentially leading to an increased risk of iatrogenic injury during procedures and misinterpretation of the results from diagnostic studies.

In a 2006 study analyzing surgical error in malpractice claims, 13% of injuries due to surgical errors were attributed to "abnormal or difficult" anatomy (Rogers et al., 2006). We suspect this may be in large part due to poor anatomical knowledge with respect to variations among practicing clinicians. This knowledge gap may be attributable to changes in undergraduate medical education, which have reduced the number of curriculum hours and faculty members devoted to gross anatomy (Cottam, 1999). However, irregardless the cause, as variant anatomy in part contributes to significant number of malpractice claims, there is a need to improve the basis of anatomical knowledge among practicing physicians by enhancing the methods through which anatomical information is synthesized and presented to the medical community.

Evidence-Based Anatomy (EBA), first proposed by Yammine (2014), is a concept which aims to apply the evidence-based principles and techniques which are commonly used in other medical sciences to the field of anatomy. Similarly, as in other fields of evidence-based medicine (EBM), EBA relies on systematic reviews (SR) and meta-analysis (MA) to provide a high-level overview of primary anatomical research. Although narrative literature reviews are quite common in anatomical writing, true SRs with a clear, detailed, and reproducible methodology allowing for synthesis of evidence-based data are few and far between.

The central process of an SR consists of identifying, selecting, and appraising high-quality studies on a focused review topic, followed by taking the obtained data, analyzing it, and constructing high-quality results which provide evidence-based information to clinicians (Uman, 2011). A SR may also contain an MA, which uses statistical techniques to pool data from several studies in order to obtain single quantitative effect size estimate (Uman, 2011). Through EBA, we can enhance our understanding of clinical anatomy and provide more accurate evidence-based data

* Corresponding author at: Department of Anatomy, Jagiellonian University Medical College, 12 Kopernika Street, 31-034 Krakow, Poland. Tel.: +48 795677090.
E-mail address: bmhenry55@gmail.com (K.A. Tomaszewski).
[1] These authors equally contributed to this work.

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that can improve everyday clinical practice. Such information can also be incorporated into the anatomical education curriculum, as evidence-based synthesis of anatomical data may be especially beneficial for highlighting the most dangerous variants for both medical students and young surgeons. In EBA, we can probe associations between anatomy and variables such as race or gender in detail, and thus form conclusions not possible from single studies with small sample sizes. Furthermore, EBA allows us to recognize areas of anatomy that still require additional basic laboratory research and can allow us to explore the connections between anatomy and pathology in depth.

While evidence-based methods are commonplace to clinical researchers, for many anatomists and other basic science researchers it is a relatively new and unexplored concept. The aim of this paper is to provide a step-by-step guide for performing SRs and MAs of anatomical studies as well as to provide a uniform methodology for conduction of EBA. Additionally, we share tips and advices from our own experience with EBA (Henry et al., 2015a,b; Ramakrishnan et al., 2015; Roy et al., 2015a,b). Lastly, we address the lack of uniform statistical methods currently used in EBA, which can lead to misinterpretation of data and production of inaccurate clinical information.

2. Before you begin

Before starting an EBA project, we highly suggest authors familiarize themselves with the basic techniques and procedures of MA and SR, as well as of EBM. While many resources are available, we highly recommend authors read the Cochrane Handbook of Systematic Reviews of Interventions (The Cochrane Collaboration, 2011). Although it is focused on interventional studies, it nonetheless provides a very comprehensive source of information on performing SR and MA. Additionally, we recommend reading "How to Read a Systematic Review and Meta-analysis and Apply the Results to Patient Care: Users' Guides to the Medical Literature" by Murad et al. (2014).

3. Step 1: Determine the review topic and set objectives

An overview of the EBA process is presented in Fig. 1. The first step in EBA, as in all systematic reviews, is determining the topic of the review. However, unlike clinical systematic reviews which often center on a focused question, reviews in EBA can be either focused or on a broader topic, encompassing the entirety of anatomical characteristics of a specific structure. As such, setting specific primary and secondary objectives for the review are essential in the EBA process. When setting objectives, we recommend the authors strongly consider the clinical relevance of the anatomical characteristics of the study and how synthesizing evidence-based data could improve clinical practice.

Once the authors have determined the topic for review, a clear, short, and descriptive title for the project should be developed, which in a straightforward manner identifies the study as an MA or SR. Furthermore, we would recommend the registration of the review on PROSPERO, an international register of prospective systematic reviews (http://www.crd.york.ac.uk/PROSPERO/). This prevents duplication of ongoing studies, and helps identify potential reporting bias in MAs and SRs, which is a bias that may have influenced the identification of relevant studies (Sedgwick, 2015). Reporting bias can occur in MA/SR in several circumstances, and includes forms of bias such as (Sedgwick, 2015):

- Citation bias—the tendency for articles more commonly cited than others to be identified and included in the MA,

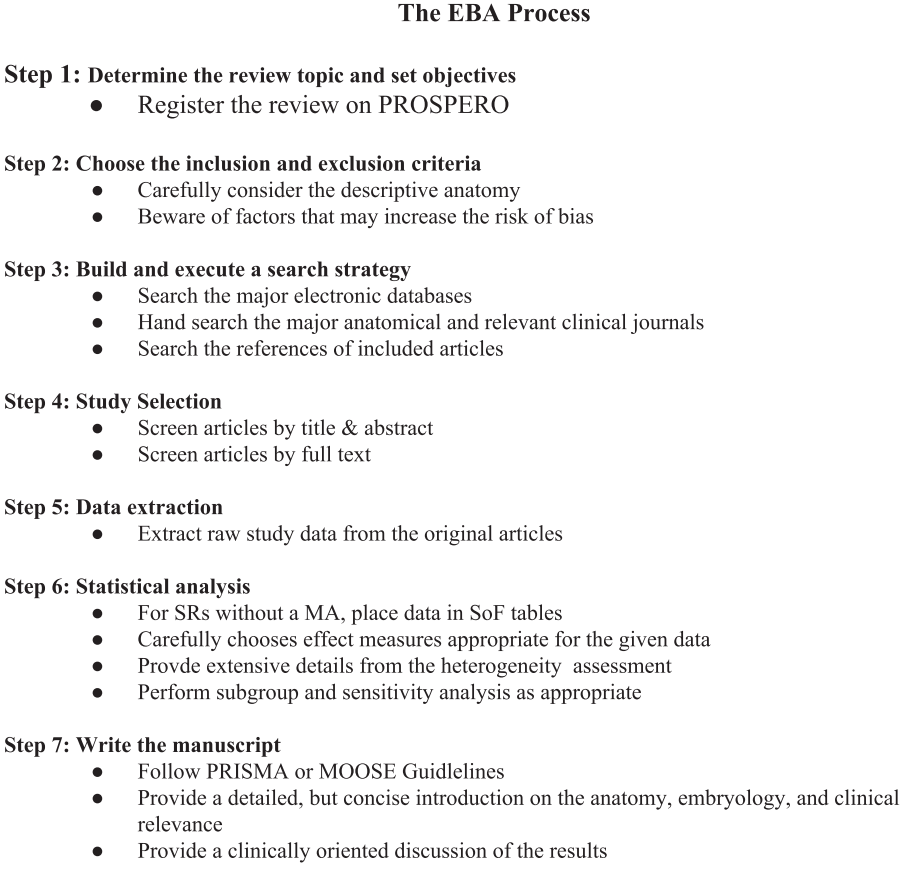

Fig. 1. The EBA process. SR—systematic review; MA—meta-analysis; SoF—summary of findings.

- Location bias—failure to identify articles in less accessible journals or databases,
- Language bias—inclusion of articles only in accessible languages,
- Publication bias—omission of unpublished studies, which are often not published due to the lack of significant results; for example, if a study found no significant differences in the prevalence of anatomic variation in a diseased group versus a healthy control group,
- Time-lag bias—rushed or delayed publication of a study, which may have influenced its inclusion in the MA,
- Multiple publication bias—inclusion of multiple articles reporting data and results of the same study.

In the steps below, we provide tips on avoiding reporting bias, as well as other forms of bias, in anatomical MA/SRs.

4. Step 2: Choosing inclusion and exclusion criteria

The next step in the EBA process is to determine the eligibility criteria for article inclusion, the MA/SR. Choosing the inclusion and exclusion criteria for the review requires careful evaluation to maintain the integrity of the SR/MA and reduce the risk of bias in the study. The first and simplest inclusion factor for any SR or MA is as follows: Does the study address the objective(s) of the review? Next, it is important to consider which patient demographics (age, sex, race, health status, etc.) are appropriate for the study. Authors should pay special attention to patient demographics, especially disease status, as it may increase the risk of bias by inclusion in the analysis. For example, patients with migraine headaches have been demonstrated to be at an increased risk for variations in the Circle of Willis as compared to healthy individuals (Henry et al., 2015a). Therefore, in an MA or SR on the variations in the cerebral circulation, data from studies that assessed migraine patients should not be included in full, as that would introduce selection bias (bias introduced by inappropriate collection and inclusion of data thus altering the statistical outcome) into the review. Nevertheless, such studies are not completely useless to the project, as they may still include healthy control groups whose data can be included in the SR/MA.

Another important factor to consider in setting inclusion criteria is the modality used by the original studies. While dissection and imaging modalities make up the majority of anatomical studies, other methods such as electrophysiological or intraoperative studies also contain valuable anatomical data. When judging which modalities to include, it is important to consider whether the modality itself may introduce selection bias into the review. Occasionally, certain specific criteria can be set for a modality to reduce bias, instead of completely rejecting the modality. For example, older methods of imaging may not have been very accurate for the assessment of the anatomical structure in question, and as such, could affect the reported prevalence rate or the reported characteristics of the structure.

It is also important to consider study design when assessing the modality. For example, in our recent SR and MA on the anatomical variations of the median nerve (Henry et al., 2015b), we decided to exclude retrospective intraoperative studies. These studies relied upon a review of medical records from carpal tunnel release surgeries to report prevalence data on median nerve variations, thus introducing a high risk of interviewer bias (also known as recorder bias). Interviewer bias occurs when there are systematic differences in the recording and/or interpretation of data in a study. Thus, in studies which rely upon patient chart review for anatomical data, we recommend careful evaluation to determine whether inclusion of such studies is appropriate in the SR/MA.

Case reports, conference abstracts, and letters to the editor should always be excluded. While data from unpublished studies can technically be used, we recommended caution and careful evaluation of all non-peer reviewed studies. Published studies reporting missing, unclear, or incomplete results should always be excluded if an attempt to contact the authors of the original study for clarification is not possible, unsuccessful, or does not resolve the issue. Furthermore, we highly recommend the careful evaluation of all studies that do not clearly define (by text or figures) the descriptive anatomy used in the study, as they may introduce bias. In accordance with the above, we recommend clear anatomical definitions be stated in the inclusion criteria of the MA/SR.

For example, in our MA and SR on the median nerve and its thenar motor branch (TMB) (Henry et al., 2015b), our inclusion criteria were as follows:

(1) the study reported extractable prevalence data related to Lanz's classification type 1, 2, 3, or 4 or data on side of branching of the TMB,
(2) the study had clearly defined descriptions of TMB variations, and
(3) it was a cadaveric or a prospective intraoperative study.

5. Step 3: Build and execute a search strategy

Due to the characteristics of anatomical studies, as well as the multitude of different study types which contain anatomical data, developing an effective search strategy for EBA is particularly tricky compared to many other fields of EBM. A broad search strategy should be used to minimize location bias. Authors should begin with developing a comprehensive list of keywords for the search. During the keyword building process, authors should review the National Library of Medicine, Medical Subject Headlines (MeSH, http://www.ncbi.nlm.nih.gov/mesh). Anatomical structures often have several names or eponyms that require inclusion.

In order to be as comprehensive as possible, authors should take the time to search several electronic databases during the search process, using a search strategy that is tailored individually to each. At minimum, we would suggest searching PubMed, Embase, Web of Science, and ScienceDirect. Due to the long history of anatomical studies, we recommend not setting a date limit. Additionally, in order to obtain globally applicable data, we do not suggest applying any language restrictions to the search. When building a search strategy, the key is to balance sensitivity (identifying a high proportion of relevant articles) with specificity (retrieving a low proportion of irrelevant articles; Uman, 2011). We would urge caution when using restrictive terms or filters (such as "humans") during database searching. From our experience, we have noticed the tendency to lose viable articles when such terms or filters are applied. Moreover, we would strongly advise authors to seek advice when building a search strategy by consulting a librarian or a colleague who has extensive experience with SR and MA. Authors may also consult and cooperate with the International Evidence-Based Anatomy Working Group (iEBA-WG, www.eba.cm.uj.edu.pl/), the coordinators of which are the authors of this guide. The iEBA-WG is always open to assisting, helping, and collaborating with all those interested in EBA.

In addition to database searching, we recommend a hand search of the major anatomical journals (e.g., Annals of Anatomy, Journal of Anatomy, Anatomical Record, Clinical Anatomy, Surgical and Radiologic Anatomy, Anatomical Science International, Folia Morphologica, etc.), as well as the relevant clinical journals related to the anatomical structure of the study. Lastly, authors should search the references of all included studies for additional articles eligible for inclusion in the meta-analysis. This is particularly important

in EBA, as many of the older or foreign studies may be difficult to identify during database searches.

6. Step 4: Study selection

Identifying articles eligible for inclusion should begin with screening and excluding articles by title and abstract. After this initial screening, full-text articles should be used to assess the eligibility of articles for inclusion in the meta-analysis.

Assessment of study eligibility for inclusion in the meta-analysis should be preferably performed independently by two separate reviewers. In the event of disagreement between two reviewers during the eligibility process, we suggest that it should be resolved by forming a consensus among the entire review team, meanwhile consulting with the author of the original study when necessary and possible.

Translators should be used whenever accessible, limiting exclusion of studies with valuable data in languages not spoken by the authors and thus reducing language bias. Studies with unclear anatomical descriptions and incomplete or missing results require careful evaluation. The decision to exclude a study due to any of the above should only be made after attempting to seek clarification from the author(s) of the original study, whenever possible.

During the study selection process, the review team should be vigilant of any duplicate publications of the same study data. From our experience in EBA, we have noticed two common types of duplicate publications. The first is multiple publication of the same study data in multiple languages. The second type, slightly more difficult to detect, is that some time following the publication of a study, a second study by the same author(s) on the same topic, with a larger sample size, is published. When this occurs, it is often difficult to determine if the second study was in fact a completely new sample or an expansion of the original sample. This situation requires careful evaluation of the studies to minimize risk of multiple publication bias, and the review team should make every effort possible to contact the authors of the original study for clarification. If the review team strongly suspects or confirms sample expansion of a previous study, we recommend excluding the older study, and using only the most recent study, with the largest sample.

7. Step 5: Data extraction

Data extraction should preferably be performed independently by two different reviewers. In the event that only one reviewer performs data extraction, we highly recommend that it is checked for errors by a second or even a third reviewer whenever possible. For ease of use, we recommend that data be extracted into tables using software such as Microsoft Excel. The extracted data should always include: author, year, country, study design, population, modality, and sample size/number of structures assessed. As a general rule, we recommend the extraction of as much raw anatomical data as possible. Whenever possible, subgroup data [such as anatomical data with respect to gender, laterality, side (left vs. right), age, etc.] should be extracted.

When anatomical definitions vary between studies, careful evaluation of each article should be performed by the entire review team. During the extraction process, inaccuracies in the reported results of the individual studies are inevitable. When they do occur, we recommend that authors of the original studies be contacted, and further data sought after, if necessary.

Additional raw study data obtained directly from the authors of the published study should be carefully evaluated for any inconsistencies before inclusion in the meta-analysis. However, such additional data may be helpful in several circumstances, and not only in cases of data discrepancies. For example, a study may have reported that no significant differences were found in the prevalence of a variable with respect to gender or side (left vs. right), but did not report the actual proportion value. In such a situation, access to the raw study data set would allow for the extraction and analysis of additional anatomical data. Thus, we would encourage reviewers to seek out additional raw data from the study authors when it may potentially be both useful and available.

One issue that requires specific attention during extraction for an EBA manuscript is how the rate for an anatomical characteristic is presented with respect to the sample. For example, if a structure is present bilaterally in humans, as with the median nerve, it may be presented in original studies as a rate per limb or per person. It is important to clarify in the inclusion criteria which rate they will extract, and how (if appropriate and possible) they will convert one rate to the other for the purposes of the analysis. If the need for conversion arises, we highly recommend contacting the authors of the original studies to inquire about additional data.

Lastly, when extracting for prevalence rates, if rare anomalies are reported in the study, we suggest two ways to preserve the statistical integrity of the data. Option one is to subtract the number of patients with rare anomalies from the total sample size, and thus not include them in the analysis. The excluded anomalies along with detailed explanations and rationale for exclusion should be clarified in the MA/SR. Option two is to create a rare anomalies category to incorporate the anomalies, thus creating a prevalence rate for this category. The choice should be made after carefully evaluating the data and considering the clinical implications. When a decision is reached, the rationale for the decision should be fully explained in the manuscript.

8. Step 6: Statistical analysis

When performing an MA of anatomical data, it is important to consider how to analyze the data in order to present results which can be easily understood and applied to the clinical setting. In an SR that does not include an MA, we highly recommend the use of Summary of Findings (SoF) tables to present data in a clear, comprehensible format (Langendam et al., 2013).

First, due to multiple statistical issues, we highly recommend authors avoid simple pooling of raw data, a relatively poor procedure as compared to an MA (Bravata and Olkin, 2001). Simple pooling refers to the process of analyzing all the data as if it was obtained from the same sample, without proper weighting. Meta-analysis allows for weighting of individual studies before incorporation into the final analysis, which avoids several of the issues with simple data pooling (Bravata and Olkin, 2001). Furthermore, MA allows for assessment of heterogeneity (any form of variability) between studies and the use of various statistical models to improve the accuracy of a pooled effect measure estimate (the statistical result of the meta-analysis). We recommend consultation with a biostatistician who has experience in MA for expert advice on properly analyzing data.

In MA, effect sizes are given with their 95% confidence intervals (CIs) and can be presented in both quantitative format and graphical representation (forest plots; Uman, 2011). In anatomical MA, which contains many variables and/or subgroups, we recommend to present data in highly detailed tables for the purpose of improving readability (Roy et al., 2015a) .

The results of anatomical studies generally consist of two main types of data—proportions (e.g., prevalence rates of variations, duplication, etc.) and means (e.g., mean nerve length, mean vessel diameter, mean number of nerve fibers, etc.). Depending on the type of data, a proper effect measure can be chosen. For data of proportions, the effect measure used is pooled prevalence estimate (PPE), which provides an estimate of the prevalence of an

anatomical variable in a chosen population. For PPE, we recommend the use of the free software MetaXL version 2.0 by EpiGear International Pty Ltd. (Wilston, Queensland, Australia). MetaXL is a plugin for Microsoft Excel which allows for the calculation of PPE for both single category (i.e., simple prevalence) or multiple category MA. The multiple category MA is especially useful for calculating the prevalence of different types of variations at once; for example, the PPE of each type of variation in a classification. MetaXL implements a double arcsine transformation with a back-transformation to report the PPE (Barendregt et al., 2013). The double arcsine transformation stabilizes the variance in a multi-categorical prevalence MA by making variance dependent only on the population size (Barendregt et al., 2013). This type of transformation has been shown to be preferential to logit transformations in multi-categorical prevalence MA (Barendregt et al., 2013). The PPE should always be presented with its 95% CI.

For calculating a pooled mean in an MA for anatomical data reported as means, we recommend the use of the Comprehensive Meta Analysis software by Biostat Inc. (Englewood, NJ, USA). This software allows for easy MA of means in one group. It requires the input of sample size, mean, and the standard deviation from each study to calculate a pooled mean value with a 95% CI.

In both types of MA, heterogeneity among the studies should always be assessed, preferentially using both the Chi-squared test and I-squared statistic. For the Chi-squared test, the *p*-value of Cochran's *Q* should be reported, with a value of <0.10 considered to indicate statistically significant heterogeneity between studies (The Cochrane Collaboration, 2011). The I-squared statistic, an overall measure of heterogeneity, should be reported with its 95% CI. The I-squared statistic should be interpreted as follows: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% may represent considerable heterogeneity, in accordance with the guidelines in the current version of the Cochrane Handbook of Systematic Reviews of Interventions (The Cochrane Collaboration, 2011).

From our own experience, we found that the heterogeneity in anatomical MAs is almost always high. As such, due to intrinsic heterogeneity in anatomical studies, and to maximize the validity of the results, we recommend only the use of a random-effects model in anatomical MA. Unlike a fixed-effects model which assumes that the difference between the results of studies are due solely to chance, a random effects model assumes that the effects being estimated (i.e., the measurements of the anatomical variables) in the different studies are not identical (The Cochrane Collaboration, 2011). The implementation of random-effects meta-analysis is as simple as selecting the random-effects results tab in Comprehensive Meta Analysis or choosing to use the random-effects formula in MetaXL.

The sources of heterogeneity in the MA should always be explored. To probe them, subgroup analysis and sensitivity analysis should be performed. Subgroup analysis by geographical distribution of the studies and by the modality of the study (e.g., dissection vs. imaging studies) should almost always be performed. Other subgroup analyses, such as by gender, age, laterality, and side (left vs. right) should be performed whenever data are available. For comparing subgroups, we recommend that the same measures used for the main analysis (PPE or pooled mean) be used for the subgroup analysis. Thus, we recommend the use of CIs to assess for statistically significant differences between two or more subgroups. If the CIs between two subgroups overlap, the differences can be considered insignificant, while if there is no overlap between CIs, we can consider the differences between the groups to be statistically significant. In our experience, because of the high heterogeneity in anatomical MA, it is common to have wide confidence intervals, thus making it difficult to detect statistically significant differences. However, the use of effect size estimate CIs for comparing subgroup differences allows the readers to interpret for themselves clinically significant differences, regardless of the width of the CIs or statistical significance.

Although the effect measures of odds ratio (OR; the measure of association between two variables) or mean difference (MD; the absolute difference in means between two groups) can also be used to compare statistical differences between subgroups, we recommend authors avoid these for the general reporting of the data, as they are often considered difficult to interpret by clinicians and lack the ease of instant clinical application that pooled mean or pooled prevalence estimates provide (The Cochrane Collaboration, 2011). This does not mean OR and MD do not have a place in EBA. We recommend their use when studying a specific association; for example, between a variation and a pathology, such as a link between migraine and Circle of Willis variations (Henry et al., 2015a).

Lastly, a sensitivity analysis should almost always be performed to help explore the sources of heterogeneity in the MA. A sensitivity analysis assesses whether the findings of the analysis are robust to decisions made in the process of performing the meta-analysis (The Cochrane Collaboration, 2011). It is performed by repeating the analysis, after substituting an alternative decision (e.g., changing the minimum sample size, excluding a particular study), and looking for significant differences between the obtained results and the primary analysis. (The Cochrane Collaboration, 2011). In general, we recommend performing a sensitivity analysis by limiting inclusion to studies with a sample size of ≥ 100. However, the inclusion sample size should be determined based on the range of data available in the MA. Additionally, authors can try a leave-one-out analysis, performed by removing one study at a time, and then repeating the analysis to probe if a single study significantly drove the results of the primary analysis.

9. Step 7: Write the manuscript

When preparing the manuscript, we highly recommend that authors always follow specific guidelines for the reporting of SR and MA. We suggest the use of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009) or the Meta-Analysis Of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000). It should be noted that it is becoming more common for journals to have specific guidelines for submission of SR and MA, and may specifically require PRISMA or MOOSE. As such, we highly suggest that when preparing the manuscript, the authors check the guidelines of the journal for which they plan to submit the manuscript.

In addition to the requirements above, we recommend a few EBA-specific additional items for the introduction and discussion to ensure quality of the manuscript. The introduction of the manuscript should contain a detailed, but concise review of the relevant anatomy, embryology, and clinical significance of the structure and its variations. Images of the relevant anatomical structure and its variations should be also included whenever possible. Additionally, the introduction should also include the anatomical and clinical rationale for the review, as well as the aims and objectives of the review. We recommend that the discussion section be a clinically focused review of the results, and should address the practical implications of the data and the need for, or the direction of further research.

10. Limitations of EBA

A few limitations of EBA should be mentioned, especially with respect to MA. One of the major limitations of EBA is the lack of an objective study quality and risk of bias assessment tool for

anatomical studies. Generally, in EBM, studies with poor methodological quality or at high risk of introducing bias into the MA/SR are excluded. From our own experience in EBA, we have found that many anatomical studies raise serious questions with respect to methodological quality and the reporting of results. Similar findings of poor reporting in anatomical studies have been reported by others (Yammine, 2014). To limit such bias as much as possible, we strongly recommend contacting the authors of original studies whenever encountering any inconsistencies.

We are currently engaged in the development of a tool to assess the methodological quality and risk of bias in anatomical studies. In addition, we are developing a checklist to improve the reporting of methods and results in original anatomical studies.

Lastly, assessment of publication bias is a standard part of MA in EBM. However, the current tools for assessment of publication bias are designed primarily for MA of interventional studies. Thus, for MA of multi-categorical PPE and one group pooled mean, the lack of a proper assessment of publication bias remains a limitation.

11. Conclusions

Evidence-based anatomy represents the next frontier in the advancement of clinical anatomy, and its exploration will improve clinical practice across the expanse of medical and surgical specialties. Through the methods and techniques described in this paper, a uniform strategy for SR and MA in anatomy is presented, which will improve the quality and clinical applicability of evidence derived from EBA.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.aanat.2015.12.002.

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