Research plan/protocol example

Systematic review and effect size meta-analysis

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Original reference:

Detels, Roger; Beaglehole, Robert, Lansang, Mary Ann; Guildford, Martin. Oxford Textbook of Public Health, 5th edition. Oxford University Press.

Chapter 6.14

Systematic Reviews and Meta-analysis

Egger, M., Davey Smith, G. Sterne, J.

See Box 6.14.2 for a checklist of steps in conducting a systematic review.

* Study questions
  + How prevalent and severe is vitamin D deficiency in patients requiring critical care?
  + Is vitamin D deficiency associated with survival outcome in patients requiring critical care?
  + Do higher levels of vitamin D in critically ill patients associate with better prognosis, lower scores of organ failure, reduced length of stay, younger age or lower rates of infection?
  + Are patients with sepsis also affected?
* Study design
  + We planned, conducted and reported this systematic study and meta-analysis following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.
* Background
  + Vitamin D deficiency prevalence has recently been reported to be common and associated to higher risk of death in critically ill patients. Several studies have also looked at the degree of deficiency and association with clinical measures but more precise estimates and increased power are required to better understand this, particularly in patients suffering from sepsis syndrome.
* Objectives
  + To systematically review the prevalence and severity of vitamin D deficiency (plasma/serum 25(OH)D levels) in critically ill and septic patients;
  + To perform a systematic review and meta-analysis of the relationship between plasma/serum 25(OH)D levels and mortality in critically ill and septic patients;
  + To perform a systematic review and meta-analysis of the association between plasma/serum 25(OH)D levels with length of stay, prognostic scores, organ failure, age and infection status in critically ill and septic patients.
* Outcomes
  + Primary outcome: prevalence and severity of 25(OH)D deficiency;
  + Secondary outcomes: All cause mortality at each study endpoint(s) (e.g. at ICU discharge, 28 days from ICU admission, hospital discharge and 6 months and/or 1 year from ICU admission);
  + Tertiary outcomes: length of stay, SOFA score, APACHE or PRISM score, age (<18, 18-65 and >65 years) and infection status.
* Inclusion and exclusion criteria
  + Participants
    - All patients with acute conditions and/or treated in intensive care or emergency units admitted for acute conditions in whom serum or plasma vitamin D (25OHD2 or 25OHD3, measured just prior [<4 weeks] or during stay), survival, length of stay, APACHE and SOFA scores, age and/or infection data was collected.
  + Study designs and quality criteria
    - Observational studies including cross sectional, case control, cohort (including longitudinal) and trials measuring baseline levels of vitamin D (25(OH)D) in plasma or serum were included which reported (in print or by personal communication) either prevalence or odds ratios, or raw data to enable their calculation;
    - Articles were excluded if they were not original contributions; if they were reviews, case reports, experimental, in vitro or observations carried out in patients not identified as being treated in emergency or intensive care units or for acute conditions.
    - Selected studies were assessed using the Newcastle-Ottawa Scale.
  + Covariates, effect modifiers, and confounders
    - We noted and recorded any possible covariates, effect modifiers, and confounders (age, gender, diagnosis, duration of follow-up, risk of bias, fluid resuscitation, co-morbidity, length of hospital stay, chronic disease, ethnicity, geography, and platform of vitamin D measurements).
    - We listed known and potential confounders and assessed included studies for quality and bias according to these;
    - Consider weighting studies according to sample size for instance.
* Study selection
  + Data sources and limits
    - Pubmed, Pubmed Central, the International Clinical Trials Registry Platform (ICTRP) of the World Health Organisation (WHO) and Scopus were used searching with no prior date and up until 24/August/2012; original observational investigations and trials in humans, English language and with full text availability were included.
    - Consider including baseline values from clinical trials.
  + Search strategy
    - 1. Study selection was performed by one researcher and checked by two additional researchers according to above criteria. A log with reasons of excluded studies from the second stage onwards is available.
      2. Authors, institutions, and journals were not considered in study selection
      3. Searches were performed for terms appearing in the title, abstract or keywords using the details below. Two stages were performed for each source: first, articles were scanned for exclusion criteria appearing in titles; second, remaining articles were searched for inclusion and exclusion criteria abstracts and full texts.
      4. For Pubmed, we derived a list of 44 articles for further inspection and a final list of xxx were included.
      5. For Pubmed Central we searched in titles and abstracts for the first 100 results ordered by relevance and included 3 articles that fulfilled our criteria.
      6. For Scopus, all language types were accepted and the document type ‘article’ was further refined using the details below (219 articles). For these, all downloadable articles with abstract or full text availability were considered after excluding documents that did not fulfil the study design and participant criteria for inclusion as above from searching the titles. Abstracts of the remaining 37 articles were searched and a further xxx were excluded at the second stage. All document types other than ‘article’ included in Scopus were excluded in the first stage of selection.
      7. Additionally, reference lists of relevant articles were manually searched for additional citations not included above.
    - Search details were:
      1. PUBMED (130 articles): ((vitamin d) AND (critical care OR intensive care OR critically ill OR emergency) NOT ("case reports"[Publication Type] OR "editorial"[Publication Type] OR review[Publication Type]));
      2. PUBMED CENTRAL (4170 articles): ((vitamin d) AND (critical care OR intensive care OR critically ill OR emergency));
      3. PUBMED (106 articles): ‘hospitalized’, ‘vitamin d’.; Filters activated: Full text available, Humans, English.
      4. Scopus (454 results): (TITLE-ABS-KEY(vitamin d) AND TITLE-ABS-KEY(critical care) OR TITLE-ABS-KEY(emergency) OR TITLE-ABS-KEY(intensive care) OR TITLE-ABS-KEY(critically ill)) AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal); Limited to: document type (article, letter, undefined, conference paper, short survey, article in press and note);
      5. The search in (d) for document type ‘article’ was further refined using the following details (219 articles): (TITLE-ABS-KEY(vitamin d) AND TITLE-ABS-KEY(critical care) OR TITLE-ABS-KEY(emergency) OR TITLE-ABS-KEY(intensive care) OR TITLE-ABS-KEY(critically ill)) AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal) AND (LIMIT-TO(DOCTYPE, "ar")) AND (EXCLUDE(SUBJAREA, "AGRI") OR EXCLUDE(SUBJAREA, "VETE") OR EXCLUDE(SUBJAREA, "AGRI") OR EXCLUDE(SUBJAREA, "VETE") OR EXCLUDE(SUBJAREA, "SOCI") OR EXCLUDE(SUBJAREA, "ARTS") OR EXCLUDE(SUBJAREA, "PHYS") OR EXCLUDE(SUBJAREA, "PSYC") OR EXCLUDE(SUBJAREA, "BUSI") OR EXCLUDE(SUBJAREA, "ENGI") OR EXCLUDE(SUBJAREA, "MATH")) AND (EXCLUDE(EXACTKEYWORD, "Case report")) AND (LIMIT-TO(EXACTKEYWORD, "Human")).
      6. International Clinical Trials Registry Platform (ICTRP) (1 article): the search terms ‘vitamin d’, ‘calcitriol’, critical\*’, ‘sepsis’ were used in the title, condition and intervention boxes in various combinations. Results for children included one trial which was excluded at the first stage of selection. For adults, four trials are registered but none are in recruiting phase or have available data. Published trials with data were included in the above searches.
* Quality assessment of selected studies
  + Assessment was performed by one observer and checked by another. The quality of each study was rated according to the Newcastle-Ottawa Scale (http://www.ohri.ca/programs/clinical\_epidemiology/oxford.asp)
* Data extraction
  + Data required:
    - Primary outcome, prevalence and severity of vitamin D deficiency in sepsis and critically ill patients:
      1. Total number of patients within each category of 25(OH)D (0 – 25, 26 – 50, 51 – 75, >75 nmol/L) divided by diagnosis (‘sepsis’ and ‘other’).
      2. Create table with study characteristics (e.g. study type, place, sample size, bins (e.g. serum levels of VD), individuals by diagnosis, estimates of effect size.
    - Secondary outcome, association of vitamin D levels with survival:
      1. Diagnosis (‘sepsis’ and ‘other’);
      2. Survival endpoints: days to death, mortality in-ICU, at 28 days (or nearest) from ICU admission, in-hospital, at 6 months (or nearest) and at 1 year (or nearest) from ICU admission;
      3. 25(OH)D categories (as above);
      4. Number of patients alive and dead for each 25(OH)D category (as above), survival measure and diagnosis;
      5. Mean and standard deviation of days to death of patients for each 25(OH)D category and diagnosis.
    - Tertiary outcome, mean and standard deviation at each 25(OH)D category of:
      1. Length of stay (in days)
      2. APACHE or PRISM (score)
      3. SOFA (score)
      4. Infection status (positive or negative)
      5. Age (under 65 or 65 and over years)
  + A data extraction form was designed and pilot tested.
  + Data was requested to corresponding authors by email if not available in the publication in the required format or scale, and/or extracted using an electronic collection spreadsheet by one researcher and tested for accuracy by another.
* Analysis and presentation of results
  + Show a flow diagram for study selection and a table with a summary table of study characteristics (i.e. Figure 1). Make list of excluded studies available to interested readers.
  + Perform statistics for each age group:
    - Weight studies according to N-O Scale, sample size, etc.?
    - Perform sensitivity analyses (tests if the results are sensitive to restrictions on the data included (exclude systematically certain types of studies and test again, if results are consistent it provides stronger evidence of an effect and of generalizability):
      1. Examine funnel plots (graph designed to check the existence of publication bias).
      2. Explore other possible sources of heterogeneity (check Higgins 2003 test).
      3. Consider correcting for publication bias (caution as there is no real way of knowing what the bias actually is). See Macaskill Stat Med 2001 and others:
         1. <http://www.bmj.com/content/343/bmj.d4002.abstract>
         2. <http://bmcmedresmethodol.biomedcentral.com/articles/10.1186/1471-2288-14-70>
         3. <https://www.ncbi.nlm.nih.gov/pubmed/11223905>
         4. <https://www.ncbi.nlm.nih.gov/pubmed/21784880>
  + Perform statistics for each objective and subgroup (diagnosis) analysis:
    - Tabulate results from individual studies for each objective and subgroup analysis: tabulate according to effect modifier (i.e. latitude, main ethnicity, etc.).
    - Primary: e.g. From PMID: 22377290: We calculated prevalence rates by extracting raw proportions with 95% CIs calculated with the Wilson method.39 We calculated pooled proportions with a random effects model (DerSimonian and Laird method40) and stabilised the variances of the raw proportions before pooling of data.41 [reference 39= R Newcombe. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med, 17 (1998), pp. 857–872; Reference 40= R DerSimonian, N Laird. Meta-analysis in clinical trials. Control Clin Trials, 7 (1986), pp. 177–188; Reference 41= A Stuart, JK Ord. Kendall's advanced theory of statistics (6th edn.)Edward Arnold, London (1994)].
    - Secondary and tertiary:
      1. Examine forest plot: graphical display designed to illustrate the relative strength of treatment effects in multiple quantitative scientific studies addressing the same question.
    - Test for adjusted p-values given in regression analysis in papers?
  + Random effects v. fixed effects model, or run both; results should be similar if heterogeneity is low.
  + Consider Bayesian meta-analysis methods even though these make an a priori assumption of effect.
  + Stats methods blurb: We calculated pooled odds ratios (ORs) with 95% CIs for the risk of xxx compared with xxx controls with a xxx model. We did analyses with xxx (version xxx). We used the I2 statistic to estimate heterogeneity in pooled studies. We used the Egger and Begg-Mazumdar tests to estimate risk of bias. Forest plots were generated to show either prevalence proportions or ORs with corresponding CIs for each study and the overall random effects pooled estimate. We further explored potential sources of heterogeneity by visual inspection of the data and forest plots, and through meta-regression analysis. We did univariate analyses with xxx (version xxx) to test the individual association of several covariates with pooled estimates: geographical region (USA vs rest of the world); sex (mixed vs female; male vs female); sample size (n<200 vs n≥200 for prevalence studies; n<1000 vs n≥1000 for risk studies); and quality assessment score.
  + Examine changes in results after exclusion of specific studies (low quality, small sample size, etc.).
  + Carry out meta-regression analysis to try to determine source of between study heterogeneity (sample size, quality, funding source, location, etc.).
* Interpretation of results
  + Consider limitations, including publication and related biases
  + Consider strength of evidence
  + Consider applicability
  + Consider implications for future research
  + Remember: for meta-analysis of observational studies it is more important to gain insight from understanding effects and sources of heterogeneity than from obtaining a possibly spurious summary calculation of effect.
  + Consider an analysis of the strength of causality using Bradford Hill criteria
  + Compare to the magnitude of other similar/comparable studies
  + Discuss direction of effect, low power of heterogeneity tests and results of trials and animal studies models for direction of effect for example.
* Manuscript:
  + Write according to reporting guidelines depending on study type (MOOSE, STROBE, QUORUM, etc.).