Risk of prostate cancer in men with spinal cord injury: a systematic review and meta-analysis

Arcangelo Barbonetti¹, Settimio D’Andrea², Alessio Martorella², Giorgio Felzani¹, Sandro Francavilla², Felice Francavilla²

A lower risk of prostate cancer has been reported in men with spinal cord injury (SCI) as compared to that observed in able-bodied subjects. As injury-related consequences can have opposite effects on prostate pathophysiology, this meta-analysis aimed to (1) establish the existence/quantify the extent of decreased prostate cancer risk following SCI and (2) find out if there is any statistically significant difference in prostate-specific antigen (PSA) levels between SCI and able-bodied subjects. MEDLINE, Cochrane Library, Scopus, CINAHL, and ScienceDirect databases were used. Only studies reporting a prostate cancer diagnosis and/or PSA levels following SCI and in able-bodied controls were included. Five studies provided information about prostate cancer on 35,293 subjects with SCI and 158,140 controls. Six studies were included in PSA analysis which reported information on 391 men with SCI and 1921 controls. Pooled estimates indicated that SCI reduced the prostate cancer risk by approximately 50% as compared to controls, whereas differences in PSA levels were not statistically significant. Funnel plots suggested the presence of publication bias only in PSA analysis. Between-study heterogeneity was established and when, according to meta-regression models, analysis was restricted to studies including men with mean age over 55 years, prostate cancer risk in SCI decreased up to 65.0% than that in controls with no heterogeneity (P = 0.33, I² = 9%). In conclusion, in men over 55 years old, SCI decreases the prostate cancer risk up to 65.0% than that in controls. The large between-study heterogeneity on PSA confirms its poor reliability as a screening tool for prostate cancer in SCI.

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INTRODUCTION

Every year, spinal cord injury (SCI) occurs in 17,000 individuals in the United States and approximately 80% of these individuals are males.¹ Yet, with advancements in technology and routine checkups, the life expectancy for these patients has improved substantially and approached to that of the general population,² with the result that most patients with SCI are likely to go through age-related problems. Age, in particular, represents a well-known risk factor for prostate cancer, which is the most frequently diagnosed cancer among males aged 65–74 years; it is also the third leading cause of cancer-related death in the United States.³ Therefore, it is expected that a larger number of patients with SCI may develop prostate cancer later in their lives. Moreover, the techniques of management of neurogenic bladder, including catheterization, predispose the patients to recurrent urinary tract infections following SCI. The resultant chronic inflammation of the prostate may increase the risk of developing prostate cancer in these subjects, which can be concluded on the basis of an established association between prostatitis and prostate cancer, as documented by population-based case–control studies.⁴ Nevertheless, a lower prevalence of prostate cancer has been reported among individuals with SCI as compared to able-bodied age-matched individuals. The low levels of circulating androgens,⁵⁶ along with the loss of neurogenic stimulation of prostate growth and activity,⁷⁸⁹ peculiar to individuals with SCI, could prove to be protective to some extent, thus contributing to explaining a lower risk of prostate cancer, which, for all practical purposes, usually discourages screening programs in this population. In reality, the utility of enrolling men with SCI in screening programs is not clear because of the uncertainty in the efficiency of the use of prostate-specific antigen (PSA) as a screening tool for prostate cancer in these subjects. On the one hand, a low prostate volume, peculiar to males with chronic SCI,¹⁰¹¹ would be associated with lower levels of PSA when compared to age-specific reference ranges; on the other hand, chronic prostate inflammation, catheterization, and repeated manual bowel evacuation are expected to yield falsely elevated PSA levels. As a result, several case–control studies have produced conflicting results, reporting either lower, similar or higher serum PSA levels in males with SCI as compared to that in able-bodied age-matched subjects.¹² In this scenario, where the actual level of the decreased prevalence of prostate cancer in SCI has not yet been determined, the limited use of screening programs could be the reason why prostate cancer would be diagnosed at an advanced stage and grade in this population.¹³ In order to assess the relationship of SCI with prostate cancer and PSA levels comprehensively, we carried out a meta-analysis of the available case–control studies, aiming to answer the following

¹Spinal Unit, San Raffaele Sulmona Institute, Sulmona 67039, Italy; ²Andrology Unit, Department of Life, Health and Environmental Sciences, University of L’Aquila, L’Aquila 67100, Italy.
Correspondence: Dr. A Barbonetti (arcangelo.barbonetti@virgilio.it)
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questions: (1) “Does, and to what extent, the presence of SCI decrease the risk of prostate cancer with respect to the general population?” and (2) “Is there any statistically significant difference in PSA levels between males with SCI and their able-bodied age-matched controls?”

**MATERIALS AND METHODS**

The study was conducted according to the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement; it also complies with the guidelines for Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE). PRISMA and MOOSE Checklists have been presented as Supplementary Table 1 and 2. The International prospective register of systematic reviews (PROSPERO) registration number is CRD42017057672.

**Systematic search strategy**

We conducted a systematic search in MEDLINE, Cochrane Library, Scopus, CINAHL, and ScienceDirect to identify all relevant studies in English language with the terms: (“spinal cord injur*” OR “spine injur*” OR “spinal injur*” OR “paraplegia OR tetraplegia OR quadriplegia”) AND (prostate OR “prostate specific antigen” OR PSA OR “prostate tumour” OR “prostate neoplasm” OR “prostate adenocarcinoma”). If it was not clear from title and abstract whether the paper contained relevant data, the full paper was retrieved. The references cited in all full-text articles were also hand-searched in an effort to obtain additional studies for inclusion.

**Inclusion and exclusion criteria**

The primary outcome of interest was the relationship between SCI and prostate cancer. The secondary outcome was the difference in serum PSA levels between males with SCI and able-bodied subjects. The eligibility criteria used for the study were: (1) observational case–control studies, enrolling individuals aged 18 years or older having SCI and an able-bodied control group; (2) availability of odds ratios (ORs) for prostate cancer or data for its calculation and/or mean ± standard deviation (s.d.) of PSA levels in both groups. Two independent reviewers (AB and SDA) assessed the eligibility of each selected paper; any disagreement was resolved via discussion involving a third reviewer (FF).

**Data extraction**

Data were extracted from the selected articles by including the first author, publication year, geographic region, and mean age of participants. From the studies evaluating prostate cancer, we extracted the number of events (prostate cancer) and the total number of participants in cases (males with SCI) and controls (age-matched able-bodied subjects); from the studies reporting PSA levels, we obtained mean ± s.d. of PSA measurement along with the total number of participants in cases and controls. Where data were missing or inconsistent, the authors were contacted to obtain the necessary information.

**Quality assessment**

The quality of studies was assessed through the “star system” of the Newcastle–Ottawa Quality Assessment Scale (NOS). The minimum number of stars was 0 and the maximum that could be awarded was 9 stars. Those getting scores ≥7 were regarded as high-quality studies.

**Statistical analysis**

The relationship between SCI and prostate cancer was assessed using OR and 95% confidence interval (95% CI) as well as by Mantel–Haenszel estimates. The differences in PSA levels were assessed by calculating the standardized mean difference (SMD). In the presence of significant heterogeneity, data were combined using random effects models, which assumed that the included studies have varying effect sizes, thus providing a conservative estimate of the overall effect. For nonsignificant heterogeneity, the results were pooled in a fixed effects model.

**RESULTS**

**Study selection and quality assessment**

The electronic search yielded 1159 studies. Three articles were retrieved from the manual search. After removal of duplicate, 839 studies were left, 802 of which were excluded as they were irrelevant on the basis of titles and abstracts. Hence, as shown in Figure 1, a total of 37 studies were identified; however, only 9 of them met the inclusion criteria.

Five studies evaluated the difference in the prevalence of prostate cancer between males with SCI and able-bodied controls. In all the studies, the included males were diagnosed with prostate cancer
after they sustained SCI. Six studies reported serum PSA levels between the two groups of subjects.13,16,17,23–25

Quality rating of the studies, based on the NOS score, is outlined in Table 2. Quality scores ranged from 5 to 8. Eight articles were considered to be of high quality,12,15,16–18,24–26 scoring ≥7; one article was assessed to be moderate. In the study by Lynne et al., a selection bias could not be ruled out since that study enrolled only volunteers and comparability could not be ensured by adjusting either on age or other variables.

Synthesis of results

Overall, five studies evaluating the risk of prostate cancer12,16–18,26 provided information on 35,293 males with SCI and 158,140 able-bodied controls. As shown in Figure 2a, pooled OR suggested that the presence of SCI reduces the risk of prostate cancer by almost one-half as compared to that in able-bodied males (OR = 0.47, 95% CI: 0.27 to 0.83, P = 0.009). Between-study heterogeneity was revealed by I² value >50% (I² for heterogeneity = 56%).

The six studies that reported PSA levels13,16,17,23–25 provided information on 391 males with SCI and 1921 able-bodied controls. As shown in Figure 2b, the overall difference between the two groups was not found to be statistically significant (pooled SMD: 0.11, 95% CI: −0.46 to 0.68, P = 0.7; I² for heterogeneity < 0.00001, F = 95%).

Publication bias and heterogeneity evaluation

As shown in Figure 3a, the reasonably symmetrical shape of funnel plot suggested the absence of obvious publication bias among studies investigating the risk of prostate cancer. On the contrary, a clear asymmetry was observed in the funnel plot of studies analyzing PSA levels (Figure 3b).

As between-study heterogeneity in the pooled analyses was found (Figure 2), linear meta-regression analyses were performed in order to detect possible covariates responsible for this variability.

It was observed that only the mean age of study population contributed significantly to the source of heterogeneity in the analysis of prostate cancer: the older age of the participants was significantly associated with a higher decrease in OR for prostate cancer in SCI as compared to the controls (β = −0.10; 95% CI: −0.19 to −0.01; P = 0.02). Accordingly, in a subgroup analysis (Figure 4a), where we excluded the study by Torricelli et al. and the largest study by Lee et al.12 both reporting a mean age of participants to be <55 years, the pooled OR for the association between SCI and prostate cancer further decreased up to 0.35 (95% CI: 0.22 to 0.56, P < 0.0001) with no heterogeneity (P for heterogeneity = 0.33, F = 9%).

As far as PSA levels were concerned, in the linear meta-regression models, both sample size and NOS quality score of the studies contributed significantly to heterogeneity: lower values of SMD, indicative of lower PSA levels in SCI as compared to that in controls, were associated with a higher decrease in OR for prostate cancer in SCI as compared to the controls (β = −0.48; 95% CI: −1.92 to −1.04; P < 0.0001) and a larger sample size of the study population (β = −0.03; 95% CI: −0.06 to −0.001; P = 0.03). In a subgroup analysis (Figure 4b), where we excluded the study by

| Study          | Geographic region | Endpoints of interest | Endpoint assessment | Age of SCI group (year) | Age of control group (year) | SCI level |
|----------------|-------------------|-----------------------|---------------------|-------------------------|-----------------------------|-----------|
| Lynne et al. 1999 | USA               | PSA                   | EIA                 | ≥24                     | ≥19                         | C: 38%; T: 52%; LS: 5%; Unknown: 5% |
| Konety et al. 2000 | USA               | PSA                   | EIA                 | >40                     | >40                         | NA        |
| Pannek et al. 2003 | Germany          | PSA                   | EIA                 | ≥35                     | ≥35                         | NA        |
| Alexandro et al. 2004 | Brazil           | PSA                   | EIA                 | ≥18                     | ≥18                         | C: 17%; T: 80%; LS: 3% |
| Scott et al. 2004 | USA               | PSA and prostate cancer | Cancer registry and clinic databases | >50                     | >50                         | NA        |
| Bartoletti et al. 2009 | Italy            | PSA and prostate cancer | PSA: EIA; prostate cancer; biopsy | ≥52                     | ≥58                         | T12 and above: 80.5%; L1 and below: 19.5% |
| Patel et al. 2011 | USA               | Prostate cancer       | Hospital registry   | ≥40                     | ≥40                         | C: 48%; T: 43%; LS: 9% |
| Torricelli et al. 2011 | Brazil           | PSA and prostate cancer | PSA: NA; prostate cancer; biopsy | ≥33                     | ≥36                         | NA        |
| Lee et al. 2014  | China             | Prostate cancer       | Histological diagnosis on illness registry | ≥20                     | ≥20                         | NA        |

1The PSA values reported by Scott et al. were not included in the meta-analysis as they were measured only in men with a diagnosis of prostate cancer. EIA: enzyme immunoassay; NA: not available; PSA: prostate-specific antigen; SCI: spinal cord injury; C: cervical; T: thoracic; LS: lumbosacral; T12: twelfth thoracic vertebra; L1: first lumbar vertebra

Table 2: Newcastle-Ottawa Quality Assessment Scale for case-control studies

| Study          | Definition of exposure | Representativeness | Selection of controls | Definition of controls | On other risk factors | On assessment of exposure | Same methods of ascertainment for cases and controls | Non-response rate | Total |
|----------------|------------------------|--------------------|-----------------------|------------------------|-----------------------|--------------------------|-----------------------------------------------------|-----------------|-------|
| Lynne et al. 1999 | 1                      | 0                  | 1                     | 1                      | 0                     | 0                        | 1                                                  | 1               | 5     |
| Konety et al. 2000 | 1                      | 0                  | 1                     | 1                      | 1                     | 1                        | 1                                                  | 1               | 7     |
| Pannek et al. 2003 | 1                      | 1                  | 1                     | 1                      | 1                     | 0                        | 1                                                  | 1               | 7     |
| Alexandro et al. 2004 | 1                     | 1                  | 1                     | 1                      | 1                     | 0                        | 1                                                  | 1               | 7     |
| Scott et al. 2004 | 1                      | 1                  | 1                     | 1                      | 1                     | 0                        | 1                                                  | 1               | 7     |
| Bartoletti et al. 2009 | 1                     | 1                  | 1                     | 1                      | 1                     | 0                        | 1                                                  | 1               | 8     |
| Patel et al. 2011 | 1                      | 1                  | 1                     | 1                      | 1                     | 0                        | 0                                                  | 1               | 7     |
| Torricelli et al. 2011 | 1                     | 1                  | 1                     | 1                      | 1                     | 0                        | 1                                                  | 1               | 7     |
| Lee et al. 2014  | 0                      | 1                  | 1                     | 1                      | 1                     | 1                        | 1                                                  | 1               | 8     |
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Lynne et al., exhibiting both the lowest NOS score (Table 1) and the smallest sample size, the pooled SMD indicated lower PSA levels in SCI, which, however, were not statistically significant (SMD: -0.36; 95% CI: -0.74 to 0.02, \(P\) = 0.07) and associated with the persistence of large heterogeneity (\(P\) for heterogeneity < 0.00001, \(I^2\) = 89%).

**DISCUSSION**

Although a lower risk of prostate cancer has been reported among males with SCI as compared to the able-bodied age-matched individuals, the actual decrease in its prevalence within this population has not yet been determined. The results from the present meta-analysis of five carefully selected observational case–control studies suggest that the presence of SCI reduces the risk of prostate cancer by almost one-half as compared to their able-bodied age-matched subjects.

Indeed, according to the results of the meta-regression models, when the analysis was restricted to males of mean age over 55 years, the risk decreased up to 65% than that in the controls, with a true population effect size between 44% and 78% (\(P\) < 0.0001), indicating that, as the prevalence of prostate cancer increases with an increase in the age of the general population, the "protective" effect of SCI becomes more evident.

The interruption of neural pathways to the prostate has been suggested to be a possible mechanism underlying the lower risk of prostate cancer in individuals with SCI. In rats, where autonomic nervous system plays a key role in the growth of the prostate gland, spinal denervation promotes changes in the cellular morphology, growth, and functions of the gland. However, in humans, the influence of neurologic factors on the physiology/pathophysiology of the prostate remains largely unknown. Nevertheless, an increased risk of prostate cancer in paraplegic male subjects as compared to that in tetraplegic patients has been reported in two studies, which supports the role of denervation in lowering the incidence of prostate cancer after SCI. A further and even more relevant role would be played by androgen deficiency, peculiar to this population. High rates of biochemical androgen deficiency, ranging from approximately 33% to 46%, have been reported in males having chronic SCI.

Whether and to what extent it can result in clinical hypogonadism is still unclear, because in the presence of SCI, the sexual symptoms, along with other putative clinical features of hypogonadism (e.g., changes in body composition, osteoporosis, anemia, and mood disorders), overlap with direct or indirect consequences of neurological damage and disability. However, regardless of other putative clinical reflections, androgen deficiency could prove to be protective to some extent, resulting in a lower incidence of prostate cancer. Evidence shows that both the occurrence and progression of prostate cancer are influenced by androgens as (1) prolonged administration of high dosages of testosterone induces prostate cancer in rats, (2) malignancies of the prostate rarely occur in dogs and men castrated prior to puberty, and (3) androgen-ablative therapy inhibits the growth of prostate tumor.

In keeping with the notion of a major role of androgens in prostate cancer, meta-analyses indicate that shorter polymorphic cytosine-adenine-guanine (CAG) repeat sequences in the androgen receptor gene, which promote both a higher receptor binding affinity for androgens and a higher transactivation activity, are associated with an increased risk of prostate cancer.

In the present analysis, a poor value of serum PSA levels as a screening tool for prostate cancer following SCI resulted from the large

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**Table 1**

| Study or subgroup | SCI | Control | Odds ratio M–H, random (95% CI) | Odds ratio M–H, random (95% CI) |
|------------------|-----|---------|---------------------------------|---------------------------------|
| Barbonetti et al., 2009 | 0   | 113     | 10 109 5.9% 0.04 (0.00; 0.72) | 0.04 (0.00; 0.72) |
| Lee et al., 2014 | 107 | 34 173 | 7671 136 922 42.8% 0.64 (0.52, 0.78) | 0.64 (0.52, 0.78) |
| Patel et al., 2011 | 350 | 18 344 | 21.1% 0.37 (0.15, 0.90) | 0.37 (0.15, 0.90) |
| Scott et al., 2004 | 11  636 | 919 | 20 949 29.8% 0.38 (0.21, 0.70) | 0.38 (0.21, 0.70) |
| Torricelli et al., 2011 | 1  21 | 0  46 | 2.8% 6.80 (0.27, 17.41) | 6.80 (0.27, 17.41) |
| Total (95% CI) | 35 293 | 155 140 | 100.0% 0.47 (0.27, 0.83) | 0.47 (0.27, 0.83) |

**Figure 2:** Forest plots depicting (a) the odds ratios for prostate cancer in men with SCI and able-bodied controls, and (b) standardized mean difference in the serum levels of PSA between men with SCI and able-bodied controls. Diamonds indicate the overall summary estimates for the analysis (the width of the diamonds represents the 95% CI); boxes indicate the weight of the individual study in the pooled analysis. The serum PSA levels are reported with ng ml\(^{-1}\). CI: confidence interval; df: degrees of freedom; IV: inverse variance; M–H: Mantel–Haenszel; s.d.: standard deviation; std.: standardized; PSA: prostate-specific antigen; SCI: spinal cord injury.

**Figure 3:** Funnel plots of an overall analysis of the relationship of spinal cord injury with (a) prostate cancer risk and (b) serum prostate-specific antigen (PSA) levels.
Figure 4: Forest plots depicting the results of the subgroup analyses on the relationship of SCI with (a) prostate cancer risk and (b) serum prostate-specific antigen (PSA) levels. After evaluation of heterogeneity, only studies carried out on samples with mean age >55 years were included in (a) the analysis of prostate cancer risk and the study from Lynne et al,23 exhibiting both the lowest quality score at the Newcastle–Ottawa scale and the smallest sample size was excluded from (b) the analysis of serum PSA levels. The PSA levels are reported in ng ml−1. CI: confidence interval; df: degrees of freedom; IV: inverse variance; M–H: Mantel–Haenszel; s.d.: standard deviation; std.: standardized; SCI: spinal cord injury.

Some limitations of this meta-analysis have been recognized. Firstly, the inclusion of a limited number of studies. This, however, resulted from a strict screening and selection of the literature. Although only five studies were included in the quantitative analysis of prostate cancer, as a whole, they provided information on a very large number of males with SCI and their age-matched able-bodied controls. The study by Lee et al,12 accounted for the largest proportion of the global study population; nevertheless, when this study, where the mean age was below 55 years, was excluded, according to the results of the meta-regression models, the pooled estimate remained statistically significant, with a further decrease (up to 65%) in the risk of prostate cancer in males with SCI as compared to that in able-bodied controls. Secondly, for instance, only the study by Bartoletti et al,16 reported testosterone levels in 113 males with SCI and 109 age-matched able-bodied subjects; although the SCI group showed significantly lower testosterone levels, PSA values, prostate sizes, and prostate cancer prevalence, the independent association of testosterone with prostate endpoints was not investigated by multivariable regression models.

On the basis of the present study, it can be concluded that, in older males, chronic SCI represents a condition which reduces the risk of prostate cancer up to 65% as compared to that in able-bodied controls. The large between-study heterogeneity on serum PSA levels makes this marker a poor reliable screening tool for prostate cancer following SCI. This was mainly due to the interaction of opposite effects exerted by clinical variables peculiar to this population. These findings should be considered in defining more appropriate screening strategies for prostate cancer in males with SCI.

AUTHOR CONTRIBUTIONS
AB conceived the study, performed the systematic search to identify all relevant studies, assessed the eligibility of each selected study, assessed the quality of the studies, and performed data extraction and statistical analysis; SDA performed the systematic search to identify all relevant studies, assessed the eligibility of the full-text papers of the selected studies, and performed data extraction; AM participated in the systematic search and helped draft the manuscript; GF helped draft the manuscript; SF assessed the quality of the studies and critically revised the manuscript; FF conceived the study, evaluated for eligibility of the full text of the selected studies, assessed the quality of the studies, and wrote the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS
All authors declared no competing interests.
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Supplementary Table 1: PRISMA Checklist

| Section/topic                       | # | Checklist item                                                                 | Reported section               |
|-------------------------------------|---|-------------------------------------------------------------------------------|--------------------------------|
| **TITLE**                           |   |                                                                               |                                |
| Title                               | 1 | Identify the report as a systematic review, meta-analysis, or both.            | Title page                     |
| ABSTRACT                            |   |                                                                               |                                |
| Structured summary                  | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | Abstract                       |
| **INTRODUCTION**                    |   |                                                                               |                                |
| Rationale                           | 3 | Describe the rationale for the review in the context of what is already known. | Introduction                   |
| Objectives                          | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | Introduction                   |
| **METHODS**                         |   |                                                                               |                                |
| Protocol and registration           | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | Material and methods           |
| Eligibility criteria                | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | Inclusion and exclusion criteria |
| Information sources                 | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | Systematic search strategy     |
| Search                              | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Figure 1                       |
| Study selection                     | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | Inclusion and exclusion criteria |
| Data collection process             | 10| Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | Data extraction                |
| Data items                          | 11| List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | Systematic search strategy     |
| Risk of bias in individual studies  | 12| Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | Quality assessment             |
| Summary measures                    | 13| State the principal summary measures (e.g., risk ratio, difference in means). | Statistical analysis           |
| Synthesis of results                | 14| Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis. | Statistical analysis           |
| Risk of bias across studies         | 15| Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | Statistical analysis           |
| Additional analyses                 | 16| Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | Statistical analysis           |
| **RESULTS**                         |   |                                                                               |                                |
| Study selection                     | 17| Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | Results: Figure 1              |
| Study characteristics               | 18| For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | Results: Table 1               |
| Risk of bias within studies         | 19| Present data on risk of bias of each study and, if available, any outcome level assessment (see Item 12). | Results: Table 2               |
| Results of individual studies       | 20| For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Results: Figure 2              |
| Synthesis of results                | 21| Present results of each meta-analysis done, including confidence intervals and measures of consistency. | Results: Figure 2              |
| Risk of bias across studies         | 22| Present results of any assessment of risk of bias across studies (see Item 15). | Results: Figure 3              |
| Additional analysis                 | 23| Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression (see Item 16)). | Results: meta-regression analyses and subgroup analysis (Figure 4) |
| **DISCUSSION**                      |   |                                                                               |                                |
| Summary of evidence                 | 24| Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | Discussion                     |
| Limitations                         | 25| Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). | Discussion                     |
| Conclusions                         | 26| Provide a general interpretation of the results in the context of other evidence, and implications for future research. | Discussion                     |
| **FUNDING**                         |   |                                                                               |                                |
| Funding                             | 27| Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | Not available                  |

From: Moher et al. 20
### Supplementary Table 2: MOOSE Checklist for Meta-analyses of Observational Studies

| Item No | Recommendation                                                                 | Reported section                                      |
|---------|---------------------------------------------------------------------------------|--------------------------------------------------------|
|         | **Reporting of background should include**                                      |                                                        |
| 1       | Problem definition                                                              | Introduction                                           |
| 2       | Hypothesis statement                                                             | Introduction                                           |
| 3       | Description of study outcome(s)                                                  | Introduction/Material and methods                      |
| 4       | Type of exposure or intervention used                                            | Material and methods                                   |
| 5       | Type of study designs used                                                       | Material and methods                                   |
| 6       | Study population                                                                | Material and methods: Inclusion and exclusion criteria |
|         | **Reporting of search strategy should include**                                 |                                                        |
| 7       | Qualifications of searchers (e.g., librarians and investigators)                  | Material and methods                                   |
| 8       | Search strategy, including time period included in the synthesis and key words   | Material and methods: Systematic search strategy        |
| 9       | Effort to include all available studies, including contact with authors          | Material and methods                                   |
| 10      | Databases and registries searched                                                | Material and methods                                   |
| 11      | Search software used, name and version, including special features used (e.g., explosion) | Statistical analysis                                   |
| 12      | Use of hand searching (e.g., reference lists of obtained articles)              | Figure 1                                               |
| 13      | List of citations located and those excluded, including justification             | Study selection and Figure 1                          |
| 14      | Method of addressing articles published in languages other than English          | Not available                                           |
| 15      | Method of handling abstracts and unpublished studies                             | Not available                                           |
| 16      | Description of any contact with authors                                          | Data extraction                                         |
|         | **Reporting of methods should include**                                          |                                                        |
| 17      | Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested | Material and methods: Quality assessment               |
| 18      | Rationale for the selection and coding of data (e.g., sound clinical principles or convenience) | Material and methods: Inclusion and exclusion criteria |
| 19      | Documentation of how data were classified and coded (e.g., multiple raters, blinding and interrater reliability) | Material and methods: Quality assessment               |
| 20      | Assessment of confounding (e.g., comparability of cases and controls in studies where appropriate) | Material and methods: Quality assessment               |
| 21      | Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results | Material and methods: Quality assessment               |
| 22      | Assessment of heterogeneity                                                      | Material and methods: Statistical analysis             |
| 23      | Description of statistical methods (e.g., complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated | Material and methods: Statistical analysis             |
| 24      | Provision of appropriate tables and graphics                                     | Table 1, Table 2, Figures 1, 2, 3, 4                  |
|         | **Reporting of results should include**                                          |                                                        |
| 25      | Graphic summarizing individual study estimates and overall estimate              | Synthesis of results: Figure 2, Figure 4               |
| 26      | Table giving descriptive information for each study included                      | Table 1                                                |
| 27      | Results of sensitivity testing (e.g., subgroup analysis)                         | Figure 4                                               |
| 28      | Indication of statistical uncertainty of findings                                | Table 1                                                |
|         | **Reporting of discussion should include**                                       |                                                        |
| 29      | Quantitative assessment of bias (e.g., publication bias)                         | Publication bias [Figure 3] and heterogeneity evaluation |
| 30      | Justification for exclusion (e.g., exclusion of non-English language citations) | Figure 1                                               |
| 31      | Assessment of quality of included studies                                       | Quality of included studies: Table 2                  |
|         | **Reporting of conclusions should include**                                     |                                                        |
| 32      | Consideration of alternative explanations for observed results                   | Discussion                                             |
| 33      | Generalization of the conclusions (i.e., appropriate for the data presented and within the domain of the literature review) | Discussion                                             |
| 34      | Guidelines for future research                                                    | Discussion                                             |
| 35      | Disclosure of funding source                                                     | Not available                                           |

From: Stroup et al.20