

Figure S3. Quality of included studies

Methodological quality of included studies using the SIGN checklist, by study.

Cohort studies

Section 1: Studies conception

Section 2: Global evaluation of the paper

+ Yes
NA Not applicable
? Can't say
- No
 - Low quality
 + Acceptable
 ++ High quality

	Section 1: Studies conception													Section 2: Global evaluation of the paper				
	Appropriate and clearly focused question	Comparable groups	Participation rate i.e flow chart	Performance bias	Number of dropped outs (%)	Characteristics of dropped outs	Clearly defined outcomes	Blind assessments	Compared process measures of not blind	Reliable assessment of exposure	Reliable assessment of outcomes	More than one assessment of exposure	Confusion bias	Presence of confidence intervals	Minimise the risk of bias and to establish a causal relationship	Clear evidence of an association between exposure and outcome	Results directly applicable	General level of evidence
Burggraaf 2001	+	-	-	-	+	-	+	-	+	+	+	-	-	+	+	+	+	+
Cacciatori 1996	+	+	-	NA	+	-	+	-	-	+	+	+	-	+	+	+	+	+
Cai 2018	+	+	-	NA	+	-	+	-	-	+	+	+	+	+	++	+	+	+
Chen 2006	+	+	-	NA	+	-	+	-	-	+	+	+	+	+	+	+	+	+
Falcone 2014	+	+	+	NA	NA	+	+	-	-	+	+	+	+	-	+	+	+	+
Kabir 2009	+	+	-	NA	NA	+	+	-	-	+	+	+	+	+	+	+	+	+
Kaminski 2012	+	NA	NA	NA	NA	+	+	NA	-	+	+	+	+	+	+	+	+	+
Osman 2004	+	+	+	NA	+	-	+	-	-	+	+	+	+	+	+	+	+	+
Wustmann 2008	+	NA	NA	NA	+	NA	+	NA	-	+	+	+	-	-	-	+	+	+

Randomized controlled studies

Selection bias

Comparability bias

Outcome bias

	Selection bias			Comparability bias			Outcome bias			Results are comparable for all sites	General level of evidence
	Appropriate and clearly focused question	Assignment of subjects is randomised	Adequate concealment method is used	Subjects and investigators blind about treatment	Treatment and control groups are similar	Only difference between group is treatment	Standard and valid outcomes	Number of dropped outs (%)	Analyses in randomly allocated groups		
Eustatia-Rutten 2008	+	+	?	+	+	+	+	+	+	NA	+
Yönm 2002	+	+	?	-	+	+	+	?	+	NA	+

SIGN checklist for cohort studies

 SIGN		Methodology Checklist 3: Cohort studies	
Study identification <i>(Include author, title, year of publication, journal title, pages)</i>			
Guideline topic:		Key Question No:	Reviewer:
<p>Before completing this checklist, consider:</p> <ol style="list-style-type: none"> 1. Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist. 2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist.. 			
Reason for rejection: 1. Paper not relevant to key question <input type="checkbox"/> 2. Other reason <input type="checkbox"/> (please specify): Please note that a retrospective study (ie a database or chart study) cannot be rated higher than +.			
Section 1: Internal validity			
<i>In a well conducted cohort study:</i>		<i>Does this study do it?</i>	
1.1	The study addresses an appropriate and clearly focused question	Yes <input type="checkbox"/> No <input type="checkbox"/> Can't say <input type="checkbox"/>	
SELECTION OF SUBJECTS			
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	Yes <input type="checkbox"/> No <input type="checkbox"/> Can't say <input type="checkbox"/> Does not apply <input type="checkbox"/>	
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	Yes <input type="checkbox"/> No <input type="checkbox"/> Does not apply <input type="checkbox"/>	

1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	Yes <input type="checkbox"/> No <input type="checkbox"/> Can't say <input type="checkbox"/> Does not apply <input type="checkbox"/>
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.	
1.6	Comparison is made between full participants and those lost to follow up, by exposure status.	Yes <input type="checkbox"/> No <input type="checkbox"/> Can't say <input type="checkbox"/> Does not apply <input type="checkbox"/>

ASSESSMENT		
1.7	The outcomes are clearly defined.	Yes <input type="checkbox"/> No <input type="checkbox"/> Can't say <input type="checkbox"/>
1.8	The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	Yes <input type="checkbox"/> No <input type="checkbox"/> Can't say <input type="checkbox"/> Does not apply <input type="checkbox"/>
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	Yes <input type="checkbox"/> No <input type="checkbox"/> Can't say <input type="checkbox"/>
1.10	The method of assessment of exposure is reliable.	Yes <input type="checkbox"/> No <input type="checkbox"/> Can't say <input type="checkbox"/>
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	Yes <input type="checkbox"/> No <input type="checkbox"/> Can't say <input type="checkbox"/> Does not apply <input type="checkbox"/>
1.12	Exposure level or prognostic factor is assessed more than once.	Yes <input type="checkbox"/> No <input type="checkbox"/> Can't say <input type="checkbox"/> Does not apply <input type="checkbox"/>
CONFOUNDING		
1.13	The main potential confounders are identified and taken into account in the design and analysis.	Yes <input type="checkbox"/> No <input type="checkbox"/> Can't say <input type="checkbox"/>
STATISTICAL ANALYSIS		
1.14	Have confidence intervals been provided?	Yes <input type="checkbox"/> No <input type="checkbox"/>
SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	How well was the study done to minimise the risk of bias or confounding?	High quality (++) <input type="checkbox"/> Acceptable (+) <input type="checkbox"/>

		Unacceptable – reject 0	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	Yes <input type="checkbox"/> Can't say <input type="checkbox"/>	No <input type="checkbox"/>
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
2.4	Notes. Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above.		

SIGN checklist for controlled trials studies

		Methodology Checklist 2: Controlled Trials	
Study identification (Include author, title, year of publication, journal title, pages)			
Guideline topic:		Key Question No:	Reviewer:
<p>Before completing this checklist, consider:</p> <ol style="list-style-type: none"> 1. Is the paper a randomised controlled trial or a controlled clinical trial? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist. If it is a controlled clinical trial questions 1.2, 1.3, and 1.4 are not relevant, and the study cannot be rated higher than 1+ 2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist. 			
Reason for rejection: 1. Paper not relevant to key question <input type="checkbox"/> 2. Other reason <input type="checkbox"/> (please specify):			
Section 1: Internal validity			
<i>In a well conducted RCT study...</i>		<i>Does this study do it?</i>	
1.1	The study addresses an appropriate and clearly focused question	Yes <input type="checkbox"/>	No <input type="checkbox"/> Can't say <input type="checkbox"/>
1.2	The assignment of subjects to treatment groups is randomised.	Yes <input type="checkbox"/>	No <input type="checkbox"/> Can't say <input type="checkbox"/>
1.3	<i>An adequate concealment method is used.</i>	Yes <input type="checkbox"/>	No <input type="checkbox"/> Can't say <input type="checkbox"/>
1.4	The design keeps subjects and investigators 'blind' about treatment allocation.	Yes <input type="checkbox"/>	No <input type="checkbox"/> Can't say <input type="checkbox"/>
1.5	The treatment and control groups are similar at the start of the trial.	Yes <input type="checkbox"/>	No <input type="checkbox"/> Can't say <input type="checkbox"/>
1.6	The only difference between groups is the treatment under investigation.	Yes <input type="checkbox"/>	No <input type="checkbox"/> Can't say <input type="checkbox"/>
1.7	All relevant outcomes are measured in a standard, valid and reliable way.	Yes <input type="checkbox"/>	No <input type="checkbox"/> Can't say <input type="checkbox"/>
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?		

1.9	<i>All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).</i>	Yes <input type="checkbox"/> Can't say <input type="checkbox"/>	No <input type="checkbox"/> Does not apply <input type="checkbox"/>
1.10	Where the study is carried out at more than one site, results are comparable for all sites.	Yes <input type="checkbox"/> Can't say <input type="checkbox"/>	No <input type="checkbox"/> Does not apply <input type="checkbox"/>

SECTION 2: OVERALL ASSESSMENT OF THE STUDY

2.1	How well was the study done to minimise bias? <i>Code as follows:</i>	High quality (++) <input type="checkbox"/> Acceptable (+) <input type="checkbox"/> Low quality (-) <input type="checkbox"/> Unacceptable – reject 0 <input type="checkbox"/>
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	
2.4	Notes. Summarise the authors' conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above.	

Methodological quality of included studies using the STROBE and CONSORT checklist, by study

Studies included	STROBE score	CONSORT score
Burgraaf, 2001	52%	-
Cacciatori, 1996	61%	-
Cai, 2018	70%	-
Chen, 2006	66%	-
Eustatia-Rutten, 2008	-	60%
Falcone, 2014	61%	-
Kabir, 2009	56%	-
Kaminski, 2012	64%	-
Osman, 2004	47%	-
Wustmann, 2008	55%	-
Yönem, 2002	-	54%