**Supplemental Digital Content 2.** **Risk of bias**

**Bias assessment of included papers**

Risk of bias for the included papers was assessed using tools specific to the type of study. The 59 observational papers were categorised into Cohort (n=55), Case Series (n=1) and Case Control (n=3) studies and assessed using their respective Newcastle-Ottawa scoring tool\*.1 These tools were domain-based evaluations, where critical assessments are made separately for individual domains. The Newcastle-Ottawa Score has 3 domains; ‘selection’, ‘comparability’ and ‘outcome/exposure’, and awards ‘stars’ based upon meeting criteria in each domain.2 The total number of stars in each domain is used to convert the Newcastle-Ottawa Score to AHRQ standards: good, fair, and poor.

Two reviewers (RH, AR) assessed each paper independently after agreement of the criteria. Any disparities were resolved through discussion, with the input of a third reviewer (AV) if required. The majority (86%) of papers were assessed to be fair-good.



**Supplemental Digital Content 2, Figure 1**: AHRQ Assessment of Observational Papers (n=59)



**Supplemental Digital Content 2, Figure 2**: Summary of Newcastle-Ottawa score for cohort studies



**Supplemental Digital Content 2, Figure 3**: Summary of Newcastle-Ottawa score for case-control/case series studies

**Supplemental Digital Content 2, Table 1:** Summary of Newcastle-Ottawa score for cohort studies

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Cohort (n=56)** | **2 stars** | **1 star** | **No star** | **Total** |
| Representativeness of the exposed cohort |  | 21 | 34 | 55 |
| Selection of Non-Exposed Cohort |  | 49 | 6 | 55 |
| Ascertainment of exposure |  | 54 | 1 | 55 |
| Demonstration that outcome of interest was not present at the start of the study |  | 13 | 42 | 55 |
| Comparability of cohorts on the basis of the design or analysis | 25 | 27 | 3 | 55 |
| Assessment of outcome |  | 31 | 24 | 55 |
| Was follow-up long enough for outcomes to occur? |  | 54 | 1 | 55 |
| Adequacy of follow up of cohorts |  | 47 | 8 | 55 |

**Supplemental Digital Content 2, Table 2:** Summary of Newcastle-Ottawa score for case-control/case series studies

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Case control/case studies (n=4)** | **2 stars** | **1 star** | **No star** | **Total** |
| Is the case definition adequate? |   | 3 | 1 | 4 |
| Representativeness of cases |   | 2 | 2 | 4 |
| Selection of controls |   | 2 | 2 | 4 |
| Definition of controls |   | 1 | 3 | 4 |
| Comparability of cohorts on the basis of the design or analysis controlled for confounders | 2 | 2 | 0 | 4 |
| Ascertainment of exposure |   | 4 | 0 | 4 |
| Same method of ascertainment for cases and control |   | 3 | 1 | 4 |

**Supplemental Digital Content 2, Table 3:** Newcastle-Ottawa score breakdown for each cohort study.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author (first) and year** | Representativeness of the exposed cohort  | Selection of Non-Exposed Cohort  | Ascertainment of exposure | Demonstration that outcome of interest was not present at the start of the study | **Selection Total**  | **Comparability** of cohorts on the basis of the design or analysis | Assessment of outcome  | Was follow-up long enough for outcomes to occur? | Was follow-up complete? | Outcome Total  | **Rating**  |
| Abbasi M, *2004*3 | 1 | 1 | 1 | 0 | 3 | 1 | 1 | 1 | 1 | 3 | **Good**  |
| Al Nimer F, *2015* (e)4 | 0 | 1 | 1 | 0 | 2 | 0 | 0 | 1 | 1 | 2 | **Poor**  |
| Bogoslovsky T, *2017*5 | 0 | 1 | 1 | 0 | 2 | 1 | 1 | 1 | 1 | 3 | **Fair**  |
| Carabias CS, 20206 | 1 | 0 | 1 | 1 | 3 | 1 | 1 | 1 | 1 | 3 | **Good** |
| Castello LM, *2018*7 | 1 | 0 | 1 | 1 | 3 | 2 | 1 | 1 | 1 | 3 | **Good**  |
| De Oliveira CO, *2007*8 | 0 | 0 | 1 | 1 | 2 | 2 | 1 | 1 | 0 | 2 | **Fair**  |
| Dickens AM, *2018*9 | 1 | 1 | 1 | 1 | 4 | 1 | 1 | 1 | 1 | 3 | **Good**  |
| Egea-Guerrero JJ, *2012*10 | 0 | 1 | 1 | 1 | 3 | 2 | 1 | 1 | 1 | 3 | **Good**  |
| Egea-Guerrero JJ, *2018*11 | 0 | 1 | 1 | 0 | 2 | 2 | 1 | 1 | 1 | 3 | **Fair**  |
| Faulkinberry S, *2019*12 | 0 | 0 | 1 | 0 | 1 | 2 | 0 | 1 | 0 | 1 | **Poor**  |
| Ghonemi MO, *2013*13 | 1 | 1 | 1 | 0 | 3 | 2 | 1 | 1 | 1 | 3 | **Good**  |
| Guzel A, *2008*14 | 1 | 1 | 1 | 1 | 4 | 2 | 0 | 1 | 1 | 2 | **Good**  |
| Hatefi M, *2016*15 | 1 | 1 | 1 | 0 | 3 | 1 | 0 | 1 | 1 | 2 | **Good**  |
| Heidari K, *2015*16 | 1 | 1 | 1 | 1 | 4 | 2 | 0 | 1 | 1 | 2 | **Good**  |
| Herrmann M, *2000*17 | 1 | 1 | 1 | 0 | 3 | 1 | 1 | 1 | 1 | 3 | **Good**  |
| Ingebrigtsen T, *1999* (b)18 | 0 | 1 | 1 | 0 | 2 | 2 | 1 | 1 | 0 | 2 | **Fair**  |
| Kelmendi FM, *2018*19 | 0 | 1 | 1 | 0 | 2 | 2 | 1 | 1 | 1 | 3 | **Fair**  |
| Korfias S, *2007*20 | 1 | 1 | 1 | 0 | 3 | 2 | 1 | 1 | 1 | 3 | **Good**  |
| Kou Z, 201321 | 0 | 0 | 1 | 1 | 2 | 2 | 1 | 0 | 1 | 2 | **Fair**  |
| Langness S, *2018*22 | 1 | 1 | 1 | 0 | 3 | 1 | 1 | 1 | 1 | 3 | **Good**  |
| Li Q, *2017*23 | 0 | 1 | 1 | 1 | 3 | 1 | 1 | 1 | 1 | 3 | **Good**  |
| Lo TY, *2009*24 | 1 | 1 | 1 | 0 | 3 | 0 | 0 | 1 | 1 | 2 | **Poor**  |
| McMahon PJ, *2015*  (a)25 | 0 | 1 | 1 | 0 | 2 | 2 | 1 | 1 | 1 | 3 | **Fair**  |
| Metting Z, *2012*26 | 1 | 1 | 1 | 0 | 3 | 1 | 1 | 1 | 1 | 3 | **Good**  |
| Mondello S, *2012* (c)27 | 0 | 1 | 1 | 0 | 2 | 1 | 1 | 1 | 1 | 3 | **Fair**  |
| Mondello S, *2016*28 | 0 | 1 | 1 | 0 | 2 | 2 | 1 | 1 | 1 | 3 | **Fair**  |
| Muller K, *2007*29 | 0 | 1 | 1 | 0 | 2 | 2 | 0 | 1 | 1 | 2 | **Fair**  |
| Naeimi ZS, *2006*30 | 0 | 1 | 1 | 0 | 2 | 1 | 1 | 1 | 1 | 3 | **Fair**  |
| Okonkwo DO, *2013* (a)31 | 0 | 1 | 1 | 0 | 2 | 1 | 1 | 1 | 0 | 2 | **Fair**  |
| Pandey S, *2017*32 | 0 | 1 | 1 | 1 | 3 | 1 | 0 | 1 | 1 | 2 | **Good**  |
| Papa L, *2017*33 | 0 | 1 | 1 | 0 | 2 | 1 | 1 | 1 | 1 | 3 | **Fair**  |
| Papa L, *2014*34 | 0 | 1 | 1 | 0 | 2 | 1 | 1 | 1 | 1 | 3 | **Fair**  |
| Pelinka LE, *2004* (d)35 | 0 | 1 | 1 | 0 | 2 | 2 | 0 | 1 | 1 | 2 | **Fair**  |
| Pelinka LE, *2004* (d)36 | 0 | 1 | 1 | 0 | 2 | 2 | 1 | 1 | 1 | 3 | **Fair**  |
| Posti JP, *2016*37 | 1 | 1 | 1 | 0 | 3 | 1 | 0 | 1 | 1 | 2 | **Good**  |
| Raabe A, *1998*38 | 0 | 1 | 1 | 0 | 2 | 1 | 0 | 1 | 1 | 2 | **Fair**  |
| Radwan W, *2013*39 | 0 | 1 | 1 | 0 | 2 | 0 | 0 | 1 | 0 | 1 | **Poor**  |
| Romner B, *2000* (b)40 | 0 | 1 | 1 | 1 | 3 | 2 | 0 | 1 | 1 | 2 | **Good**  |
| Rubenstein R, *2017* (a)41 | 0 | 1 | 1 | 0 | 2 | 1 | 0 | 1 | 1 | 2 | **Fair**  |
| Sandsmark DK, *2019*42 | 0 | 1 | 1 | 0 | 2 | 2 | 1 | 1 | 0 | 2 | **Fair**  |
| Shakeri M, *2014*43 | 0 | 1 | 1 | 1 | 3 | 2 | 1 | 1 | 1 | 3 | **Good**  |
| Skandsen T, *2018*44 | 0 | 0 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 2 | **Poor**  |
| Skogseid IM, 199245 | 0 | 1 | 1 | 0 | 2 | 1 | 0 | 1 | 1 | 2 | **Fair**  |
| Thelin EP, *2019* (e,f)46 | 0 | 1 | 1 | 0 | 2 | 1 | 0 | 1 | 1 | 2 | **Fair**  |
| Thelin EP, *2016* (e,f)47 | 1 | 1 | 1 | 0 | 3 | 2 | 0 | 1 | 1 | 2 | **Good**  |
| Thelin EP, *2013* (e)48 | 0 | 1 | 1 | 0 | 2 | 1 | 1 | 1 | 1 | 3 | **Fair**  |
| Thelin EP, *2016* (f)49  | **1** | 1 | 1 | 0 | 3 | 1 | 0 | 1 | 1 | 2 | **Fair**  |
| Tomita K, *2019*50 | 1 | 1 | 1 | 1 | 4 | 1 | 1 | 1 | 1 | 3 | **Good**  |
| Vervliet B, *2012*51 | 1 | 1 | 1 | 0 | 3 | 1 | 0 | 1 | 0 | 1 | **Poor**  |
| Vos PE, *2004*52 | 0 | 1 | 1 | 0 | 2 | 2 | 0 | 1 | 1 | 2 | **Fair**  |
| Wolf H, *2015*53  | 1 | 1 | 1 | 0 | 3 | 2 | 0 | 1 | 1 | 2 | **Good**  |
| Yue JK, *2019* (a)54 | **0** | 1 | 1 | 0 | 2 | 2 | 1 | 1 | 1 | 3 | **Fair**  |
| Zurek J, *2011* (g)55  | 1 | 1 | 1 | 0 | 3 | 1 | 0 | 1 | 1 | 2 | **Good**  |
| Zurek J, *2010* (g)56  | 1 | 1 | 1 | 0 | 3 | 1 | 0 | 1 | 1 | 2 | **Good**  |
| Zurek J, *2011* (g)57  | 0 | 1 | 1 | 0 | 2 | 2 | 1 | 1 | 1 | 3 | **Fair**  |

The itemised domain scores of papers according to Newcastle-Ottawa Quality Assessment Form for Cohort Studies. Note: A study can be given a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

**Supplemental Digital Content 2, Table 4:** Newcastle-Ottawa score breakdown for each case-control/case series study

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Authors** | Is the case definition adequate? | Representativeness of cases  | Selections of controls  | Definition of controls  | **Selection Total**  | Comparability of cohorts on the basis of the design or analysis controlled for confounders  | Ascertainment of exposure  | Same method of ascertainment for cases and control  | Non-Response Rate  | Outcome Total  | **Ratings** |
| Honda M, *2010*58 | 1 | 1 | 1 | 1 | 4 | 2 | 1 | 1 | 1 | 3 | **Good**  |
| Ljungqvist J, *2017*59 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 2 | **Poor**  |
| Mondello S, *2011* (c)60 | 0 | 1 | 1 | 0 | 2 | 2 | 1 | 1 | 1 | 3 | **Fair**  |
| Pleines, UE *2001*61 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 2 | **Poor**  |

The itemised domain scores of papers according to Newcastle-Ottawa Quality Assessment Form for Case Control/Case Series studies. Note: A study can be given a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

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