**HIV infection and diverse physical health outcomes: an umbrella review of meta-analyses of observational studies**

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Key Points: The present umbrella review captures the complexities and variety of physical outcomes associated with HIV. It reports on 55 unique outcomes. Three (higher prevalence of cough, higher incidence of pregnancy related mortality and ischemic heart disease) outcomes had strong evidence.

**Abstract**

**Introduction:** Our aim was to assess both the credibility and strength of evidence arising from systematic reviews with meta-analyses of observational studies and non-ADIS defining physical health outcomes associated with HIV.

**Methods:** We performed an umbrella review of observational studies. Evidence was graded as convincing, highly suggestive, suggestive, weak and non-significant.

**Results:** From 3413 studies returned, 20 were included covering 55 health outcomes. Median number of participants was 18,743 (range: 403 to 225,000,000). Overall, 45 (81.8%) of the 55 unique outcomes reported nominally significant summary results (p<0.05). Only five outcomes (9.0%; higher likelihood of presence of breathlessness and COPD prevalence, maternal sepsis, higher risk of anemia and all fractures among PLWHIV) showed suggestive evidence with P values < 10-3 and three (5.5%; higher prevalence of cough in cross-sectional studies and higher incidence of pregnancy related mortality and ischemic heart disease among PLWHIV in cohort studies) outcomes showed a stronger evidence using a stringent P value (<10-6). None of the unique outcomes presented convincing evidence (class I), yet three outcomes presented highly suggestive evidence, five outcomes presented suggestive evidence and 37 outcomes presented a weak evidence.

**Discussion:** Results show highly suggestive and suggestive evidence for HIV and presence of cough, prevalence of COPD, ischemic heart disease, pregnancy mortality and sepsis, and bone fractures. Public health policies should reflect and accommodate these changes, especially in light of the increases in life expectancy and incidence of comorbidities in this population.

**Key Words**: HIV, Human Immunodeficiency Virus, Health Outcomes, Comorbid, Umbrella Review

**Introduction**

Incidence rates of human immunodeficiency virus (HIV) infection are showing a slow but steady decline over the two past decades. Despite this decline, 1.8 million people globally are newly infected with HIV every year, which maintains HIV’s status as one of the top global health issues1.

Globally the most common cause of death in people living with HIV (PLWHIV) is tuberculosis2. However, in developed countries where tuberculosis is rare and there is high access to antiretroviral treatment (ART), non-AIDS related diseases (including but not limited to diabetes mellitus, kidney and liver disease, hypertension and cardiovascular disease, hypertension, non-AIDS related malignancies) are a leading cause of death among PLWHIV who receive treatment3. Correspondingly, the importance of non-AIDS related comorbidities, their complications and mortality has increased over the last decade4.

Reasons for the rise in non-AIDS related morbidity is a question of some debate. In general, the availability of ART led to a substantial rise in life expectancy of PLWHIV, now almost comparable to that of the general seronegative population, which may be accompanied by more non-AIDS related morbidity5. Studies have, however, reported greater prevalence of age-associated diseases in PLWHIV. This may be explained by the persistent immunodeficiency, immune activation and chronic infection associated inflammation connected with infection6. Additionally, the ART itself may act directly, with reported adverse effects including hyperlipidaemia, insulin resistance and the proinflammatory effect of some nucleoside analogues7 8. Lastly, PLWHIV in developed countries, as a population, often exhibit greater risk factors associated with incidence of non-AIDS related illnesses such as smoking, drug use and alcohol use5 7 9 10.

Given the incidence, morbidity and mortality associated with HIV, numerous systematic reviews and meta analyses have attempted to quantify this disparate literature. To date, most systematic reviews have focused on a single disease end point and there has not been a systematic evaluation on the relationship between HIV and diverse physical health outcomes. Moreover, the strength and reliability of the literature is unclear.

In order to address the breadth of the literature of complex health behaviors and outcomes, an increasing emphasis has been placed on “umbrella reviews”11, (i.e., the syntheses of existing systematic reviews with meta-analyses, to capture the breadth of outcomes associated with a given exposure). In this study, we undertook an umbrella review of existing systematic reviews with meta-analyses of HIV and all physical health outcomes in order to systematically assess the quality and strength of the evidence across all health outcomes, and identify those with the strongest evidence.

**Materials and Methods**

The protocol for the present umbrella review was preregistered with PROSPERO (registration number: CRD42018107336).

An umbrella review was carried out following standardized procedures11 12. Electronic databases were systematically searched via MEDLINE/PubMed, PsycINFO, Embase from inception to 25th August 2018. The following search terms were used in MEDLINE/PubMed “(meta-analysis or meta-anal\* or systematic review) and (HIV or LAV or HTLV III or HTLV-III or AIDS or human immunodeficiency virus or human T-lymphotropic virus III or acquired immunodeficiency)”. In addition, we hand-searched the reference lists of eligible articles and other narrative overview of systematic reviews/meta-analyses.

The primary screening was carried out by two authors (IG and LY) and any disagreements were resolved via screening of the disagreed title/ abstract by a third author (NV). Full texts were sourced for all potential eligible articles, and screened by two investigators (IG and LY) who determined the final references to be included.

We included systematic reviews with meta-analyses of observational studies (cross sectional, case control or retrospective and prospective cohort studies), which investigated the relationship between HIV and any physical health outcomes. Specific inclusion criteria include: 1) Systematic reviews with meta analyses reporting data on HIV (diagnosed through self-report or laboratory confirmation); 2) Meta-analyses of cross sectional or cohort studies that investigated the association of HIV with any health outcome (e.g. cardiovascular disease, cancer, obesity/overweight, diabetes or metabolic diseases). Studies had to report these outcomes as odds ratio (OR), relative risk (RR), hazard ratio (HR) or continuous data (standardized mean difference, SMD; weighted mean difference, WMD or mean difference, MD). 4) Studies published in any language. Studies were excluded if they were related to immunosuppression or related to correlates of HIV infection.

**Data Extraction**

The following information were extracted from each article by two independent investigators: (1) first author name; (2) year of publication; (3) journal; (4) the number of included studies and the total number of people included in the review; (5) the inclusion criteria for studied population; ( (6) the effect size(s) used in the review; (7) subgrouping used in the meta-analysis (with or without antiretroviral therapy); (8) study design (case-control, retrospective, prospective); (9) number of cases (i.e. those having the outcome of interest, e.g. cancer) and controls (i.e. those not having the outcome of interest, e.g. no cancer) for each study. We then extracted the study-specific estimated relative risk for health outcome (RR, OR, HR, SMD, WMD, MD), along with the 95% confidence interval (CI). If two meta-analyses are available for the same association, we included the largest in terms of number of studies.

**Risk of bias (quality) assessment**

Two authors independently rated the methodological quality of the included meta-analyses using the AMSTAR 2 tool13 (see supplementary Table 1 for a full list of questions asked).

**Data analysis and credibility assessment**

For each meta-analysis we estimated the summary effect size and 95% CI, through random-effects models14. In cases where the summary effect size of a meta-analysis was reported as MD, we transformed the metric to RR with an established formula15. We also estimated the prediction interval and its 95% CI, which further accounts for between-study effects, and estimates the certainty of the association if a new study addresses that same association16-18. For the largest dataset of each meta-analysis, we calculated the standard error (SE) of the effect size. If the SE was less than 0.10 then the 95% CI would be lower than 0.20 (which is less than the magnitude of a small effect size). We also considered whether the largest study was significant (i.e. p-value <0.05). Between-study association was estimated with the I2 metric; values > 50% were indicative of high heterogeneity, while values above 75% suggest very high heterogeneity19 20.

In addition, we calculated the evidence of small-study effects (i.e., whether small studies would have inflated effect sizes compared to larger ones). To this end, we used the regression asymmetry test developed by Egger and coworkers21. A *p* value <0.10 with more conservative effects in larger studies than in random-effects meta-analysis was considered as indicative of small-study effects22.

Finally, we applied the excess significance test23 which evaluates whether the number of studies with nominally significant results (i.e. with p<0.05) among those included in a meta-analysis is too large based on the power that these data sets have to detect effects at α=0.05. For this analysis, the power estimate for each data set was calculated. The sum of the power estimates of each study provides the expected (E) number of data sets with nominal statistical significance. As described elsewhere, the number of expected ‘positive’ (i.e., statistically significant data sets) studies can be compared with the observed (O) number of statistically significant studies through a χ2-based test23. The larger the difference between O and E, the higher the degree of excess of significance bias. The true effect size of a meta-analysis is unknown. We considered the effect size of the largest study for each meta-analysis (i.e., with the lower SE), and based on this, we estimated the effect sizes of each constituent study with an algorithm using a non-central *t* distribution. Excess significance for single meta-analysis was considered whenever p<0.10.

We used credibility assessment criteria, which are based on established tools for observational evidence as summarized previously24 25, classifying the evidence of significant outcomes (p-value in random effect model <0.05) in four classes (class I, convincing; class II, highly suggestive; class III, suggestive; class IV, weak). Full details are given in Table 1.

**Results**

As shown in **Figure 1**, the review of the literature identified 3413 unique papers across three major databases. After applying the inclusion/exclusion criteria, 103 papers were identified and of them, 20 were eligible. A total of 55 unique health outcomes were assessed across the 20 meta-analyses included in our umbrella review.

**Meta-analyses of observational studies**

As reported in Supplementary Table 2, the median number of studies of meta-analyses for each outcome was 8 (range 2 to 42), the median number of participants was 18,743 (range: 403 to 225,000,000), and the median number of cases was 847 (range: 7- 627,199). The diverse comorbidity outcomes included metabolic disorders, respiratory conditions, mortality, cardiovascular conditions, cancer, and maternal and newborn outcomes.

Overall, for 45 (81.8%) of the 55 unique outcomes there were nominally significant summary results (p<0.05); among which five outcomes (9.0%) showed suggestive evidence with P values < 10-3 and three (5.5%) outcomes showed stronger evidence using a stringent P value (<10-6).

Heterogeneity among studies was generally high: 39/55 outcomes (70.9%) had an estimated I2 consistent with large heterogeneity (>50%), with 26 showing very large heterogeneity (>75%). Five outcomes presented 95% prediction intervals excluding the null value. The evidence for excess statistical significance (i.e., whether smaller studies tend to give substantially larger estimates of effect size compared with larger studies) was present in 17 outcomes (30.9%) and small-study effects were also seen in 16 of the outcomes (29.1%). Studies with the largest sample size for each outcome maintained their statistical significance in 38/55 outcomes (69.1%). Further, the largest study for 15/55 outcomes (27.3%) had a more conservative effect compared to the random-effects model.

Based on the above criteria, no outcome presented convincing evidence (class I). Three outcomes presented highly suggestive evidence (class II: higher prevalence of cough in cross-sectional studies and higher incidence of pregnancy related mortality and ischemic heart disease among PLWHIV in cohort studies), five outcomes presented suggestive evidence (class III: higher likelihood of presence of breathlessness and higher COPD prevalence, maternal sepsis, higher risk of anemia and all fractures among PLWHIV) (Table 1 and Table 2) and 37 outcomes presented a weak evidence. The three outcomes in class II scored low or critically low according to the AMSTAR 2 evaluation (Supplementary Table 1).

The majority of meta-analyses scored critically low (n=15) on AMSTAR 2 and 4 scored low. (Supplementary Table 1).

**Discussion**

In this study, which included 20 meta-analyses and 55 different outcomes that are associated with HIV infection, we found highly suggestive evidence that HIV infection is associated with higher presence of coughing in cross-sectional studies and higher risk of pregnancy related mortality and ischemic heart disease in cohort studies. Suggestive evidence was found for higher likelihood of presence of breathlessness and COPD prevalence, maternal sepsis, higher risk of anemia and all fractures among PLWHIV. These conclusions are based on the evaluation of epidemiological evidence credibility, which is a common approach used in a variety of research. Such critical appraisals of literature are necessary, as the widely used nominal significance level of *p*<0.05 is widely used to claim new associations in literature. However, emerging evidence shows that results based on this criterion constitute weak evidence, as also confirmed by our umbrella review, where 45 outcomes were statistically significant (p < 0.05), but no convincing evidence was evident and highly suggestive evidence were observed for only three outcomes.

We found highly suggestive evidence that HIV infection is associated with presence of coughing and suggestive evidence for presence of breathlessness and prevalence of chronic obstructive pulmonary disease (COPD). These results indicate that even with high availability of ART, PLWHIV experience disproportionally more chronic respiratory illness in comparison to seronegative populations26. This may be linked to the exponential rise in life expectancy27 28, bringing about a population of aging PLWHIV that have higher prevalence of comorbidity and respiratory illness. Additionally, PLWHIV in resource rich settings have higher prevalence of smoking and illicit drug use than seronegative people 9 10 29 30, both of which are linked to a higher respiratory and cardiovascular disease incidence31.

Our analysis also showed highly suggestive evidence of the association between HIV infection with ischemic heart disease. Reasons for this include the aforementioned high prevalence of smoking and illicit drug use within this population, but may also be related to the underlying chronic inflammation and immune activation combined with coagulation abnormalities and atherosclerosis32. Overall, following the advent of ART, mortality of PLWHIV attributable to cardiovascular disease (CVD) is considerable33. Studies indicate that PLWHIV have higher risk of CVD incidence in comparison to seronegative people with some earlier studies indicating an even higher risk among PLWHIV receiving protease inhibitors in comparison to therapy naïve PLHWHIV34 35. Reasons for this may be linked to “inflamm-aging”, which describes a chronic low-grade inflammation characteristic of biological aging that shares similarities with persistent immune activation observed in PLWHIV36-39. The resulting immunosenesence coupled with “inflamm-aging” may predispose PLWHIV to comorbid conditions such as cardiovascular disease, metabolic and neurocognitive disorders or cancer37 38 40. Reports on specific pathophysiological processes leading to lung symptoms are rare, but may be explained by the reduced ability of alveolar macrophages to maintain homeostasis41.

We report on highly suggestive and suggestive levels of evidence concerning the association of HIV and pregnancy related mortality and sepsis, respectively. The pathological interactions between HIV infection and pregnancy related outcomes are poorly understood42 43, however, given the high number of women living with HIV, with the highest proportion in resource poor settings where there is a substantial risk of maternal mortality, there is an intersecting problem posing a major public health issue1. Systematic reviews have found no evidence to support that pregnancy somehow accelerates HIV progression. Our analysis did show highly suggestive evidence to support the associations of maternal HIV infection and pregnancy related mortality. This may be explained by generally poor health of women living with HIV, but also with HIV related thrombocytopenia leading to excessive bleeding44 45. Moreover, high levels of stigma and other social issues faced by women living with HIV might prevent or inhibit access to health care services46 47. Lower immune activation and suppression may be the underlying reason for high susceptibility to infections and sepsis in women living with HIV, the latter showing suggestive level of evidence in our analysis48 49.

The final two outcomes showing suggestive level of evidence in our analysis were risk of anemia in children and risk of bone fractures. For both outcomes, the mechanisms remain unclear. While anemia has been reported as one of the most common hematological complications to follow HIV infection, bone fractures have not been as commonly reported. Literature suggests effects of HIV on erythrocyte production in case of anemia50, while the effects on bone loss and fracture seem to be less clear, with most studies reporting various variables that may have a synergistic effects, such as tobacco smoking or drug use, low body weight and influence of low CD4+ cell counts and hepatitis C coinfections51.

Umbrella reviews provide top tier evidence and important insights, but there are a number of limitations that need to be considered. Meta-analyses contained studies that differed in their design, population and other characteristics. However, we applied an I2<50% as one of the criteria for class I evidence (convincing) in order to assign the best evidence grade only to robust associations. Second, many studies in our umbrella review reported HIV as self-reported information, but the agreement between self-reported and bio-humoral diagnosis is often poor52. Finally, meta-analyses have inherent limitations53 and their findings depend on which estimates are selected from each primary study and how they are applied in the meta-analysis.

**Conclusion**

Results show highly suggestive and suggestive evidence for HIV and presence of cough, prevalence of COPD, ischemic heart disease, pregnancy mortality and sepsis, and bone fractures. Public health policies should reflect and accommodate these changes, especially in light of the increases in life expectancy and incidence of comorbidities in this population. The elevated risk of the reported outcomes requires more research to improve both the prevention and early detection of these comorbidities in PLWHIV.

**Declarations of Interest**

All authors declare that they have no conflict of interest.

**Authors Contributors**

LS conceived the idea. IG, LY, LS, NV designed the protocol, carried out searches, screening, and analysed the data. IG, LY, LS, SS and SH extracted the data. IG, LS, LY and NV drafted the manuscript. All authors provided critical revisions and approved the final version of the manuscript.

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**Table 1. Credibility assessment criteria for meta-analyses of observational studies**

|  |  |
| --- | --- |
| **Evidence classification** | **Criteria** |
| **Convincing (class I)** | Associations with p < 0.000001; >1,000 cases (or >20 000 participants for continuous outcomes)having the event of interest; the largest component study reporting a nominal statisticallysignificant result (p < 0.05); a 95% PI that excluded the null; no large heterogeneity (I2 <50%);no evidence of small-study effect (p > 0.10); no excess significance bias (p > 0.10). |
| **Highly suggestive (class II)** | Associations with P < 0.000001; >1000 cases (or >20 000 participants for continuous outcomes)having the event of interest; the largest component study reporting a statisticallysignificant result (p < 0.05). |
| **Suggestive (class III)** | Associations with P < 0.001;>1000 cases (or >20 000 participants for continuous outcomes)having the event of interest |
| **Weak (class IV)** | Remaining statistically significant associations with P < 0.05. |

|  |
| --- |
| **Table 2 Summarised physical health outcomes and evidence class reported in included meta-analyses of observational studies** |
|  | **Level of evidence** |
| **Outcome** | I | II | III | IV | NS |
| **CVD** | None | Cohort studies: risk of ischemic heart disease | None | Cohort studies: risk of AMI, CAD, any stroke, ischemic stroke | Case-control studies: risk of coronary stenosis; risk of calcified plaques; risk of any plaque |
| Case-control studies: risk of non-calcified plaques  |   |
| Case-control/cross-sectional studies: prevalence of IMT, flow-mediated vasodilatation, pulse wave velocity |   |
| **Gynecological outcomes** | None | Cohort studies: risk of pregnancy related mortality | None | Cohort studies: risk of stillbirth, perinatal mortality, infant mortality, pregnancy induced hypertension, caesarian-sepsis, caesarian-wound infection, caesarian-endometritis, low birthweight, preterm delivery | Cohort studies: risk of neonatal mortality, pregnancy related hypertension, pre-eclampsia, eclampsia, abnormal presentation, aesarian section; |
| Cohort/case-control studies: risk of uterine rupture, endometritis |   |
|
| **Metabolic and blood pressure outcomes** | None | None | None | Cohort studies: mean hemoglobin levels |   |
|  Cross-sectional/case-control studies: mean BMI, TGs, HDL, SBP, DBP levels | Cross-sectional/case-control studies: mean LDL, glucose, HbA1c levels |
| **Other outcomes** | None | Cross-sectional studies: prevalence of cough | Cohort studies: risk of fractures, sepsis, death | Cohort studies: risk of intracranial hemorrhage, renal disease, melanoma (pre- and post-HAART time period) |   |
|   | Case-control studies: risk of intracerebral hemorrhage |   |
| Cross-sectional studies: prevalence of breathlessness, anemia, CPPD | Cross-sectional studies: prevalence of ED. | Cross-sectional/case-control studies: prevalence of dental caries |
| Abbreviations: ES: effect size; CI: confidence interval; RR: relative risk; OR: odds ratio; MD: mean difference; SMD: standardized mean difference; SMD: weighted mean difference; HR: hazard ratio; NR: not reported; NP: not possible; NS: not significant; COPD: chronic obstructive pulmonary disease; ED: erectile dysfunction; BMI: body mass index; TGs: triglycerides; HDL: high density lipoprotein; SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL: low density lipoprotein; HbA1c: glycated hemoglobin |

Supplementary Table 1: AMSTAR 2 evaluation of included Meta-analyses

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Author of Meta-Analysis | Year of Meta-Analysis | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | AMSTAR 2 Rating |
| Calvert | 2013 | Yes | Yes | No | No | No | No | No | Yes | Yes | No | Yes | No | No | Yes | Yes | Yes | Critically low |
| D'Ascnezo | 2015 | Yes | No | No | No | Yes | Yes | No | No | No | No | No | No | No | Yes | No | No | Critically low |
| Dillon | 2013 | Yes | No | No | No | Yes | Yes | No | No | No | No | No | No | No | Yes | No | Yes | Critically low |
| Behrouz | 2016 | No | No | No | No | No | Yes | No | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | No | Critically low |
| Bigna | 2018 | Yes | Yes | No | Yes | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Low |
| Brocklehurst | 1998 | Yes | Yes | Yes | Yes | No | No | No | No | Yes | No | Yes | Yes | Yes | Yes | Yes | No | Low |
| Brown | 2017 | Yes | Yes | No | Yes | No | No | No | No | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Low |
| Browne | 2015 | Yes | Yes | No | Yes | No | No | No | No | Yes | No | Yes | Yes | Yes | Yes | Yes | No | Low |
| Calis | 2008 | Yes | No | No | Yes | No | No | No | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Critically low |
| Calvert | 2013 | Yes | No | No | Yes | No | No | No | No | Yes | No | Yes | Yes | Yes | Yes | Yes | No | Critically low |
| Luo | 2017 | Yes | No | Yes | Yes | No | Yes | No | Yes | Yes | No | No | Yes | No | No | Yes | Yes | Critically low |
| Oliveria | 2015 | Yes | No | Yes | Yes | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Yes | Yes | No | Yes | Critically low |
| Olsen | 2014 | Yes | No | Yes | Yes | No | Yes | No | Yes | Yes | No | Yes | No | No | Yes | Yes | Yes | Critically low |
| Gutierrez | 2017 | Yes | No | Yes | No | Yes | No | No | No | No | No | Yes | No | No | Yes | No | Yes | Critically low |
| Islam | 2012 | Yes | Yes | No | No | No | No | No | No | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Critically low |
| Islam a  | 2012 | Yes | Yes | No | Yes | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Low |
| Shiau | 2013 | Yes | Yes | Yes | Yes | Yes | Yes | No | No | No | No | Yes | No | No | Yes | Yes | Yes | Critically low |
| Sun | 2015 | Yes | No | No | Yes | No | Yes | No | No | No | No | Yes | No | No | Yes | Yes | Yes | Critically low |
| Xiao | 2015 | Yes | No | No | Yes | Yes | Yes | No | Yes | No | No | Yes | No | No | Yes | Yes | Yes | Critically low |

A Measurement Tool to Assess systematic Reviews (AMSTAR) 2 questions; *1. Did the research questions and inclusion criteria for the review include the components of PICO?, 2.* Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?, 3. Did the review authors explain their selection of the study designs for inclusion in the review?, *4. Did the review authors use a comprehensive literature search strategy?, 5. Did the review authors perform study selection in duplicate?, 6. Did the review authors perform data extraction in duplicate?, 7. Did the review authors provide a list of excluded studies and justify the exclusions?, 8. Did the review authors describe the included studies in adequate detail?, 9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?, 10. Did the review authors report on the sources of funding for the studies included in the review?, 11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?, 12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?, 13. Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review?, 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?, 15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?, 16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?*

**Supplementary table 2. Health outcomes and evidence class reported in included meta-analyses of observational studies.**

| **Author,[reference]** |  **year** | **Outcome** | **Study design** | **N of studies** | **Cases** | **Sample size** | **ES** | **Mean ES (95%CI)** | **Pa** | **95% prediction intervalb** | **I2** | **p-value Egger** | **Observed/ expected significant studies** | **Excess significance test** | **Level of evidence** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Brown | 2016 | Presence of cough | Cross-sectional | 19 | 3547 | 30939 | OR | 2.138 (1.614-2.832) | 1.17E-07 | 0.64, 7.14 | 88.60% | 0 | 14.28/3 | <0.0001 | II |
| Calvert  | 2013 | pregnancy related mortality | Cohort | 23 | 3478 | 8982338 | RR | 7.774(5.399-11.194) | 2.88E-28 | 2.45, 24.64 | 53.80% | 0.396 | 13.75/0 | <0.0001 | II |
| Islam | 2012 | ischaemic heart disease | Cohort | 3 | 27503 | 1426249 | RR | 1.606(1.426-1.808) | 5.83E-15 | 0.61, 4.26 | 18.20% | 0.905 | 0.29/0 | 1 | II |
| Brown | 2016 | Presence of breathlessness | Cross-sectional | 12 | 1704 | 12242 | OR | 1.796(1.289-2.501) | 5.32E-04 | 0.61, 5.3 | 78.10% | 0.015 | 6.83/0 | <0.0001 | III |
| Calis | 2008 | Risk of anemia | Cross-sectional | 6 | 1636 | 2977 | OR | 4.507(2.447-8.302) | 1.35E-06 | 0.68, 29.95 | 73.30% | 0.718 | 4.84/1 | <0.0001 | III |
| Shiau  | 2013 | All fractures | Cohort | 4 | 10355 | 225,000,000 | RR | 1.579(1.246-2.001) | 0.00015426 | 0.63, 3.95 | 57.30% | 0.998 | 4/3 | 0.05 | III |
| Bigna et al | 2018 | COPD prevalence | Cross-sectional | 11 | 16196 | 327801 | OR | 1.16(1.066-1.263) | 0.00059631 | 0.94, 1.43 | 58.40% | 0.892 | 6.18/3 | 0.07 | III |
| Calvert | 2013 | Sepsis | Cohort | 4 | 79474 | 8801088 | OR | 3.429(2.047-5.745) | 2.87E-06 | 0.66, 17.7 | 8.60% | 0.633 | 2/0 | 0.04 | III |
| Gutierrez | 2017 | risk of death | Cohort | 6 | NP | 3522019 | HR | 3.641(2.123-6.245) | 2.67E-06 | 0.54, 24.36 | 97.60% | 0.941 | NP | NP | IV |
| Gutierrez | 2017 | risk of myocardial infarction | Cohort | 7 | NP | 1440789 | HR | 1.629(1.412-1.879) | 2.30E-11 | 1.09, 2.44 | 63.80% | 0.596 | NP | NP | IV |
| Gutierrez | 2017 | risk of coronary artery disease | Cohort | 9 | NP | 4885940 | HR | 1.517(1.207, 1.906) | 0.00035329 | 0.7, 3.29 | 93.30% | 0.017 | NP | NP | IV |
| Gutierrez | 2017 | any stroke | Cohort | 3 | NP | 53635 | HR | 1.819(1.528, 2.165) | 1.71E-11 | 0.59, 5.64 | 0.00% | 0.646 | NP | NP | IV |
| Gutierrez | 2017 | Ischemic stroke | Cohort | 4 | NP | 522867 | HR | 1.278 (1.138, 1.434) | 3.1594E-05 | 0.88, 1.85 | 28.50% | 0.201 | NP | NP | IV |
| Gutierrez | 2017 | Intracranial hemorrhage | Cohort | 3 | NP | 1132506 | HR | 2.22 (1.593, 1.434) | 2.49E-06 | 0.2, 24.74 | 7.70% | 0.332 | NP | NP | IV |
| Brocklehurst | 1998 | Stillbirth | Cohort | 8 | 889 | 29746 | OR | 2.02 (0.79, 5.1666) | 1.42E-01 | 0.1, 39.66 | 77.10% | 0.068 | 1.36/1 | 1 | IV |
| Brocklehurst | 1998 | Perinatal mortality | Cohort | 9 | 202 | 27766 | OR | 1.546 (0.999, 2.395) | 3.01E-02 | 0.59, 4.05 | 27.50% | 0.022 | 2.8/0 | 0.07 | IV |
| Brocklehurst | 1998 | Infant mortality | Cohort | 9 | 853 | 6836 | OR | 3.933 (2.856, 2.053) | 4.81E-17 | 1.81, 8.54 | 41.80% | 0.354 | 7.7/1 | <0.0001 | IV |
| Calvert | 2013 | Pregnancy induced hypertension | Cohort | 11 | 627199 | 8836983 | OR | 1.455 (1.031, 2.053) | 3.30E-02 | 0.52, 4.06 | 79.30% | 0.726 | 5.22/2 | 0.06 | IV |
| Calvert | 2013 | Uterine rupture | Cohort/case-control | 2 | 71 | 23386 | OR | 3.135 (1.512, 6.5) | 2.13E-03 | NP | 0.00% | NP | 1/0 | <0,0001 | IV |
| Calvert | 2013 | Endometritis | Cohort/case-control | 8 | 81 | 2268 | OR | 2.519 (1.509, 4.205) | 0.00040821 | 0.93, 6.85 | 18.80% | 0.748 | 3.72/0 | <0.0001 | IV |
| Calvert | 2013 | Caesarian- sepsis | Cohort | 4 | 7 | 743 | OR | 5.817 (2.42, 13.986) | 8.3374E-05 | 0.85, 39.9 | 0.00% | 0.484 | 1.02/0 | 0.58 | IV |
| Calvert | 2013 | Caesarian - wound infection | Cohort | 10 | 906 | 57392 | OR | 1.746 (1.194, 2.551) | 0.00401302 | 0.74, 4.14 | 30.00% | 0.087 | 4.57/0 | <0.0001 | IV |
| Calvert | 2013 | Caesarian- endometritis | Cohort | 12 | 3478 | 58229 | OR | 1.866 (1.284, 2.713) | 0.00107965 | 0.7, 4.95 | 47.00% | 0.414 | 5.39/0 | <0.0001 | IV |
| D'Ascenzo | 2015 | Risk of non-calcified plaques more than 0  | Case-control | 4 | 600 | 1172 | OR | 3.262 (1.302, 8.173) | 0.01162414 | 0.05, 204.15 | 83.60% | 0.091 | 3.15/0 | <0.0001 | IV |
| Xiao | 2015 | Low birthweight | Cohort | 43 | NR | 21465 | OR | 1.98 (1.757, 2.23) | 2.82E-29 | 1.08, 3.64 | 71.80% | 0 | NP | NP | IV |
| Xiao | 2015 | Preterm delivery  | Cohort | 40 | NR | 27281 | OR | 1.623 (1.488, 1.77) | 1.11E-27 | 1.15, 2.29 | 51.90% | 0.156 | NP | NP | IV |
| Behrouz et al  | 2016 | Risk of intracerebral hemorrhage | Case-control | 6 | 841 | 177719 | RR | 3.896 (2.037, 7.449) | 3.9262E-05 | 0.47, 32.32 | 85.20% | 0.181 | 5.55/1 | <0.0001 | IV |
| Islam\_a | 2012 | renal disease  | Cohort | 3 | NR | 3227 | RR | 3.867 (2.183, 6.848) | 3.53E-06 | 0.01, 1053.69 | 43.80% | 0.489 | NP | NP | IV |
| Olsen | 2014 | Melanoma, in the post-HAART time period | Cohort | 6 | 284 | 702897 | RR | 1.501 (1.123, 2.006) | 0.00611078 | 0.68, 3.31 | 54.50% | 0.292 | 1.93/1 | 0.67 | IV |
| Olsen | 2014 | Melanoma, in the pre-HAART time period | Cohort | 3 | 235 | 1054700 | RR | 1.282 (1.104, 1.489) | 0.0011601 | 0.5, 3.22 | 0.00% | 0.295 | NP | 0.5 | IV |
| Luo | 2017 | Prevalence of ED | Cross-sectional | 5 | 690 | 4252 | RR | 2.438 (1.588, 3.745) | 4.659E-05 | 0.56, 10.63 | 87.30% | 0.779 | 2.39/2 | 0.49 | IV |
| Dillon | 2013 | BMI | Cross-sectional/case-control | 36 | NR  | 24725 | SMD |  -0.319 (-0.452, -0.186) | 2.66E-06 | -1.06, 0.44 | 93.40% | 0.684 | NP | NP | IV |
| Dillon | 2013 | TGs | Cross-sectional/case-control | 15 | NR | 13198 | SMD | 0.261 (0.085, 0.437) | 0.00372672 | -0.16, 0.98 | 91.30% | 0.128 | NP | NP | IV |
| Dillon | 2013 | HDL | Cross-sectional/case-control | 14 | NR | 12710 | SMD |  -0.586 (-0.86, -0.312) | 2.7353E-05 | -1.72, 0.55 | 96.20% | 0.072 | NP | NP | IV |
| Dillon | 2013 | SBP | Cross-sectional/case-control | 15 | NR | 11909 | SMD |  -0.4 (-0.554, -0.247) | 3.21E-07 | -0.97, 0.17 | 84.10% | 0.279 | NP | NP | IV |
| Dillon | 2013 | DBP | Cross-sectional/case-control | 15 | NR | 11909 | SMD |  -0.339 (-0.509, -0.168) | 9.7975E-05 | -0.99, 0.31 | 87.80% | 0.044 | NP | NP | IV |
| Calis | 2008 | Mean hemoglobin levels | Cohort | 5 | NR | 2228 | SMD  |  -0.783 (-1.097, -0.47) | 9.44E-07 | -1.89, 0.33 | 81.40% | 0.489 | NP | NP | IV |
| Sun  | 2015 | Intima-media thickness  | Cross-sectional/case-control | 28 | 5360 | 16021 | WMD  | 0.049 (0.03, 0.067) | 2.23E-07 | -0.04, 0.14 | 96.90% | 0.083 | NP | 1 | IV |
| Sun  | 2015 | Pulse wave velocity  | Cross-sectional/case-control | 13 | 1547 | 2838 | WMD | 0.537 (0.283, 0.792) | 3.3837E-05 | -0.38, 1.45 | 83.90% | 0.188 | NP | 1 | IV |
| Sun  | 2015 | Flow mediated vasodilation  | Cross-sectional/case-control | 12 | 553 | 1099 | WMD |  -1.858 (-2.623, -1.092) | 2.01E-06 | -4.34, 0.63 | 88.90% | 0.622 | NP | 1 | IV |
| Brocklehurst | 1998 | Neonatal mortality | Cohort | 3 | 51 | 1517 | OR | 1.153 (0.596, 2.228) | 2.63E-01 | 0, 340.39 | 25.10% | 0.003 | 0.56/0 | 1 | NS |
| Browne | 2015 | Risk of developing pregnancy related hypertension | Cohort  | 14 | 2790 | 24335 | RR | 1.263 (0.872, 1.828) | 2.17E-01 | 0.36, 4.47 | 78.60% | 0.201 | 7.32/5 | 0.29 | NS |
| Browne | 2015 | Risk of developing pre-eclampsia  | Cohort | 17 | NR | NR | RR | 1.013 (0.868, 1.182) | 8.73E-01 | 0.66, 1.55 | 63.90% | 0.252 | 6.16/4 | 0.3 | NS |
| Browne | 2015 | Risk of developing eclampsia  | Cohort | 5 | 280 | 5503 | RR | 1.609 (0.139, 18.679) | 7.04E-01 | 0, 21754 | 97.00% | 0.194 | 2.72/2 | 0.67 | NS |
| Calvert | 2013 | Pre-eclampsia | Cohort | 9 | 713 | 14971 | OR | 1.036 (0.602, 1.783) | 9.00E-01 | 0.19, 5.55 | 70.70% | 0.015 | 3.32/2 | 0.5 | NS |
| Calvert | 2013 | Eclampsia | Cohort | 4 | 262 | 26550 | OR | 2.567 (0.15, 43.86) | 5.15E-01 | 0, 2045733.38 | 96.60% | 0.274 | 2.22/1 | 0.33 | NS |
| Calvert | 2013 | Abnormal presentation | Cohort | 2 | 56 | 918 | OR | 1.17 (0.676, 2.025) | 5.74E-01 | NP | 0.00% | NP | 0.21/0 | 1 | NS |
| Calvert | 2013 | Caesarian section | Cohort | 19 | 8363 | 43323 | OR | 1.202 (0.814, 1.775) | 0.354283 | 0.22, 6.56 | 88.40% | 0.002 | 7.28/4 | 0.15 | NS |
| D'Ascenzo | 2015 | Risk of coronary stenosis  | Case-control | 9 | 1061 | 1672 | OR | 1.378 (0.862, 2.203) | 0.180694 | 0.31, 6.2 | 71.80% | 0.012 | 5.21/1 | 0.01 | NS |
| D'Ascenzo | 2015 | Risk of calcified plaques more than 0  | Case-control | 3 | 332 | 1045 | OR | 1.17 (0.53, 2.171) | 0.619728 | 0, 749.13 | 51.70% | 0.146 | 1.03/0 | 0.56 | NS |
| D'Ascenzo | 2015 | Risk of plaques more than 0  | Case-control | 6 | 567 | 1533 | OR | 0.874 (0.427, 1.788) | 0.711934 | 0, 9.8 | 83.10% | 0.244 | 4.44/3 | 0.19 | NS |
| Dillon | 2013 | LDL | Cross-sectional/case-control | 14 | NR | 12710 | SMD | -0.154 (-0.337, 0.029) | 0.09886 | -0.88, 0.57 | 91.20% | 0.684 | NP | NP | NS |
| Dillon | 2013 | glucose | Cross-sectional/case-control | 6 | NR | 4036 | SMD | 0.354 (-0.341, 1.05) | 0.317876 | -2.23, 2.94 | 98.50% | 0.31 | NP | NP | NS |
| Dillon | 2013 | HbA1c | Cross-sectional | 3 | NR | 6099 | SMD | -0.068 (-0.392, 0.255) | 0.678643 | -3.85, 3.71 | 82.10% | 0.803 | NP | NP | NS |
| Oliveira | 2015 | dental caries prevalence | Cross-sectional/case-control | 5 | 233 | 405 | OR | 1.58 (0.764, 3.269) | 0.217033 | 0.14, 17.57 | 64.40% | 0.011 | 2.27/1 | 0.39 | NS |
| **Summary Statistics** |  |  | **Median = 8 (range: 2-43)** | **Median = 8 (range: 2-43)** | **Median = 847 (range: 7- 627,199)** | **Median = 18,743 (range: 405 to 2.25E+08)** |  |  |  |  |  |  |  |  |  |

Abbreviations: ES: effect size; CI: confidence interval; RR: relative risk; OR: odds ratio; MD: mean difference; SMD: standardized mean difference; SMD: weighted mean difference; HR: hazard ratio; NR: not reported; NP: not possible; NS: not significant; COPD: chronic obstructive pulmonary disease; ED: erectile dysfunction; BMI: body mass index; TGs: triglycerides; HDL: high density lipoprotein; SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL: low density lipoprotein; HbA1c: glycated hemoglobin

a P value of summary random effects estimate.

b Prediction intervals are reported only for meta-analyses including at least 3 studies.

1Evidence class criteria: class I (convincing): statistical significance with P<10−6, more than 1,000 cases (or >20,000 participants for continuous outcomes), the largest component study reported statistically significant effect (P<0.05); 95% prediction interval excluded the null; no large heterogeneity (I2 <50%), no evidence of small study effects (P>0.10) and excess significance bias (P>0.10); class II (highly suggestive): statistical significance with P<10−6, more than 1,000 cases (or >20,000 participants for continuous outcomes), the largest component study reported statistically significant effect (P<0.05); class III (suggestive): statistical significance with P<10−3, more than 1,000 cases (or >20,000 participants for continuous outcomes); class IV (weak): the remaining statistically significant associations with P<0.05.