Low Birth Weight and Adverse Health Outcomes during Adulthood in Twins: A Systematic Review

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Abstract

TITLE: Low Birth Weight and Adverse Health Outcomes during Adulthood in Twins: A Systematic Review By Sapha Hassan, BSc

OBJECTIVE: Our study aims to analyze the association between low birth weight and adverse health outcomes during adulthood in twin populations.

METHODS: Searches were conducted using databases inclusive of MEDLINE, CINAHL, Web of Science, and EBSCO. Two reviewers independently screened the papers, and a third reviewer resolved the conflicts between the two reviewers. Following abstract and title screening, full-texts were screened to obtain eligibility. Eligible full-text articles were then assessed for quality using a modified Downs and Black checklist.1 Studies with a score within one standard deviation of the mean were included in the analysis. A fixed effect model was used for analysis.
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CONCLUSION: There are not enough studies of similar nature (study types, similar body systems) to ensure a meaningful meta-analysis. We recommend that future research considers following up on twins to obtain data about adverse health outcomes during their adult lives.

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Low birth weight and adverse health outcomes during adulthood in twins: A systematic review

By Sapha Hassan, B.S.

Committee Chair: Shayesteh Jahanfar, PhD, MSc, BSc
Faculty Member: Andrea Bombak, PhD, MA, BSc
Academic Advisor: Joseph Inungu, MD, DrPH
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Abstract

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Methods: Searches were conducted using databases inclusive of MEDLINE, CINAHL, Web of Science, and EBSCO. Two reviewers independently screened the papers, and a third reviewer resolved the conflicts between the two reviewers. Following abstract and title screening, full-texts were screened to obtain eligibility. Eligible full-text articles were then assessed for quality using a modified Downs and Black checklist. Studies with a score within one standard deviation of the mean were included in the analysis. A fixed effect model was used for analysis.

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Conclusion: There are not enough studies of similar nature (study types, similar body systems) to ensure a meaningful meta-analysis. We recommend that future research considers following up on twins to obtain data about adverse health outcomes during their adult lives.
Introduction

According to the World Health Organization, it is estimated that 15-20% of all births worldwide are low birth weight, which equates to more than 20 million births per year.² Low birth weight, defined as being born less than or equal to 2500 grams, is known to be extensively related to poor child and adult health outcomes.³,⁴ Babies who are born with more severe low birth weights are more likely to develop chronic illness and difficulty with cognition.⁴,⁵ One study suggests that lower birth weight is associated with short telomere length and with lower cognitive ability;⁶ another demonstrates that low birth weight is associated with later development of non-insulin dependent diabetes mellitus,⁷ indicating that there is a positive relationship between being born low birth weight and adverse health outcomes.

Previous studies have confirmed that twin gestations are associated with higher perinatal morbidity and mortality when compared to gestations of singleton pregnancies,⁸,⁹ and multiple pregnancy is one of the major risk factors for preterm births.¹⁰ Babies born in a multiple pregnancy are more likely to be low birth weight when compared to their singleton counterparts.¹¹,¹² In 2015 in the United States, according to the Centers for Disease Control and Prevention (CDC), about 55% of twins were born low birth weight, and about 6% of singletons were reported as low birth weight.¹² Thus, twins are at a higher risk of being born low birth weight when compared to singletons, and by extension are more likely to develop adverse health outcomes that are associated with being born low birth weight.¹³

Twin studies give us information about the potential epigenetic etiologies of disease.¹⁴-¹⁶ One study examined the association between birth weight and rheumatoid arthritis (RA) in twins discordant for RA, concluding that birth weight was not associated with the development of RA in adult life when adjusted for appropriate confounders.¹⁷ Another study found that there was a positive association between low birth weight and development of type 2 diabetes when comparing within-pair differences in twins, suggesting that genetic factors contribute to outcomes later on in life.¹⁸

Our study aims to investigate the association between low birth weight among twins and long-term outcomes during adulthood. We compared longitudinal outcomes of twins of low birth weight compared with twins who were of normal birth weight. The methodology that our review follows is the Cochrane method of screening, analysis, and quality assessment. To our knowledge, there is no systematic review that uses this method and analyzes how low birth weight affects longitudinal outcomes in twins through the body systems we are investigating; thus, our study is unique in that sense. We studied this association across all body systems: circulatory, digestive, endocrine, lymphatic, muscular, nervous, reproductive, respiratory, skeletal, urinary, and integumentary systems.
Methods
The methodology follows the MOOSE Statement and is explained under six categories: search strategy, databases, study selection, data extraction, quality assessment, and statistical analysis.

Search Strategy
A comprehensive list of Mesh terms was obtained by three means. Firstly, the definition of each concept was extracted from MEDLINE. Secondly, grey literature, conference proceedings, and reference lists of published articles were explored. Thirdly, specialists in the field were consulted to identify the Mesh terms. These included: “low birth weight,” “twin studies,” “longitudinal outcome(s),” adult outcome(s),” “multiple pregnancy,” “twin pregnancy,” and “observational studies.” Boolean logic was used to combine the concepts and eliminate irrelevant articles. Filters were employed to limit the search to observational studies only. The search was limited to English literature.

Databases
The following databases were searched, from the earliest available date (mentioned in brackets) to March 10, 2018: MEDLINE (1996), Cochrane Central Register of Controlled Trials (1991), CINAHL (1982), Database of abstracts of reviews of effects (1991), Web of Science (1990), and EBSCO (1946). The references of the retrieved articles were checked to find additional articles. Articles were stored in a reference manager, EndNote. References were then imported into a systematic review manager, Covidence, and duplicates were deleted.

Study Selection
The screening process was done on Covidence. Two reviewers were involved in the screening process. Screening was completed by two individuals; if consensus was not reached about whether or not to include a study in the subsequent screening or final analysis, a third reviewer determined if a study was to be included.

Data Extraction
The OR, 95% confidence interval (95%CI), test statistics for the interaction, and statistical significance of the analysis were extracted from selected studies. For papers not reporting OR and 95% CI, the raw data (i.e., number of events and total number of samples in the exposed and unexposed groups) were used to estimate OR and 95% CI.

Quality Assessment
Risk of bias and quality assessment of selected studies were assessed through a modified Downs and Black checklist for methodological quality assessment of health care interventions.\(^1\) Appendix I shows the full checklist that was used in quality assessment. Studies with a score within one standard deviation of the means score were included in the final meta-analyses.

Statistical Analysis
Meta-analyses were conducted using the generic inverse variance with a fixed- or random-effect model in Revman 5.2. The heterogeneity across individual studies were quantified by the \(I^2\) test. Low, moderate, or high degrees of heterogeneity were approximated by \(I^2\) values of 25%, 50% and 75%, respectively. If the \(I^2\) value was larger than 50% random-effect model was used. Reasons for heterogeneity were investigated by eyeballing extreme OR and sensitivity analysis.
**Subgroup Analysis**
We planned on conducting subgroup analyses using the following variables: zygosity (monozygotic or dizygotic), gestational age (yes or no), sex of twins (discordant or concordant), maternal age (yes or no), and twin data comparisons (if low birth weight was compared with singleton or twin standards of birth weight). However, we were unable to do this because of lack of studies.

**Sensitivity Analysis**
Sensitivity analysis was conducted by excluding data points with extreme OR or maximum weight to examine their impact on the overall OR. We were planning to investigate the public bias using inverted funnel plots. However, the plots can only be drawn if meta-analyses include more than 10 studies.
Results
Almost 4000 studies were identified through database searching. Duplicates were removed, and 2631 abstracts were screened. 114 full-text articles were assessed for eligibility, and 22 studies were assessed for quality using a modified Downs and Black checklist (see Appendix I for modified checklist). Studies were included in the quantitative analysis if their scores were within one standard deviation of the mean quality score. Figure 1 shows the PRISMA flow chart summarizing how articles were screened and how many were ultimately eligible for inclusion in this study.

Figure 1: PRISMA Flow Diagram
Table 1 shows the scores for quality assessment of the studies that passed the criteria for quantitative analysis. Studies were included if they were within one standard deviation of the mean score for each criterion.

**TABLE 1:** Quality assessment of the articles reviewed

<table>
<thead>
<tr>
<th>Study ID (Author, Year)</th>
<th>Clarity</th>
<th>External validity</th>
<th>Internal validity</th>
<th>Total Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bias</td>
<td>Confounding</td>
</tr>
<tr>
<td>Akerman 1992</td>
<td>4</td>
<td>2</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Bergvall 2007</td>
<td>5</td>
<td>2</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Cnattingius 2009</td>
<td>5</td>
<td>2</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>De Zeeuw 2012</td>
<td>4</td>
<td>2</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Groen-Blokhuis 2011</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Hestbaek 2003</td>
<td>4</td>
<td>2</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Hultman 2007</td>
<td>4</td>
<td>2</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Nelson 1995</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Ortingqvist 2009</td>
<td>5</td>
<td>2</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Rasanen 2000</td>
<td>5</td>
<td>2</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Suwanand 1997</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Villamor 2009</td>
<td>5</td>
<td>2</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Williams 1996</td>
<td>4</td>
<td>2</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Yokoyama 2007</td>
<td>5</td>
<td>2</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td><strong>Median (Range)</strong></td>
<td>4 (3-5)</td>
<td>2 (2-2)</td>
<td>5 (4-5)</td>
<td>3 (2-3)</td>
</tr>
</tbody>
</table>

Although 14 studies were eligible for inclusion in the final model, the outcomes that these studies looked into were distinct from each other; outcomes included attention-deficit disorders, colorectal cancer, and motor development. In order to be included in the meta-analyses, we needed at least two studies per body system to study the impact of low birth weight on longitudinal outcomes that are a part of each body system. Thus, two outcomes that are a part of two distinct body systems were included in the final meta-analysis: asthma (respiratory system) and cerebral palsy (nervous system). Tables 2 and 3 include descriptions of the final five articles that were included in the meta-analyses. The five articles included were all cross-sectional studies using data from four countries, consisting of data from over 35,000 twin participants.
TABLE 2: Description of the articles included in meta-analyses. All study designs are cross-sectional, and all studies used singleton standards to classify low birth weight.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Country</th>
<th>Number of Participants</th>
<th>Enrollment Period</th>
<th>Outcome</th>
<th>Maternal Age</th>
<th>Gestational Age</th>
<th>Zygosity (MZ/DZ)</th>
<th>Sex (MM/ MF/ FF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ortqvist 2009</td>
<td>Sweden</td>
<td>10918</td>
<td>2004-2007</td>
<td>Asthma</td>
<td>≤19: 18.4%</td>
<td>≤31: 24.8%</td>
<td>MZ: 13.4%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20-24: 16.1%</td>
<td>32-34: 18.1%</td>
<td>DZ: 28.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25-29: 13.9%</td>
<td>35-36: 18.1%</td>
<td>Unknown: 11.7%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30-34: 13.9%</td>
<td>37-38: 11.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥35: 11.8%</td>
<td>39-40: 10.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥41: 12.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rasanen 2000</td>
<td>Finland</td>
<td>4502</td>
<td>1975-1979</td>
<td>Asthma</td>
<td>&lt;25: 31.4%</td>
<td>&lt;33: 7.1%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25-30: 38.8%</td>
<td>33-36: 29.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;30: 29.8%</td>
<td>37-40: 60.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;40: 3.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Villamor 2009</td>
<td>Sweden</td>
<td>32580</td>
<td>1926-1958</td>
<td>Asthma</td>
<td>&lt;20: 2.7%</td>
<td>31-34: 12.9%</td>
<td>-</td>
<td>MM: 47.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20-24: 17.0%</td>
<td>35-36: 20.0%</td>
<td></td>
<td>FF: 52.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25-29: 29.9%</td>
<td>37-41: 58.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30-34: 27.4%</td>
<td>42-45: 3.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥35: 22.9%</td>
<td>Missing: 4.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelson 1995</td>
<td>USA</td>
<td>1079</td>
<td>1959-1966</td>
<td>Cerebral Palsy</td>
<td>-</td>
<td>-</td>
<td>MZ: 31.9%</td>
<td>Concordant: 63.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DZ: 58.6%</td>
<td>Discordant: 36.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unknown: 9.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suvanand 1997</td>
<td>India</td>
<td>250</td>
<td>1993-1994</td>
<td>Cerebral Palsy</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
TABLE 3: Impact of low birth weight on longitudinal outcomes by body system

<table>
<thead>
<tr>
<th>Body System</th>
<th>Outcome</th>
<th>Number of Studies</th>
<th>Number of Participants</th>
<th>OR (95%CI)</th>
<th>Heterogeneity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous</td>
<td>Cerebral Palsy</td>
<td>2</td>
<td>1,318</td>
<td>4.88 (2.34-10.19)</td>
<td>79%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Asthma</td>
<td>3</td>
<td>37,008</td>
<td>1.33 (1.24-1.44)</td>
<td>77%</td>
</tr>
</tbody>
</table>

Asthma

Figure 2 shows the meta-analysis for the association between low birth weight and development of asthma later on in life. Three studies were included in this meta-analysis, with just over 37,000 twins being studied. A fixed-effect model was used, and the meta-analysis showed $I^2=77\%$ and OR (95%CI) = 1.33 (1.24-1.44). Due to high heterogeneity, a random-effect model was tested; however, the heterogeneity was unchanged with this model, hence the fixed effect is reported. Although the results were significant ($p<0.00001$), this outcome shows high heterogeneity and ultimately favored low birth weight.

Cerebral Palsy

Figure 3 shows the meta-analysis for the association between low birth weight in twins and development of cerebral palsy. This meta-analysis included two studies that looked at about 1,300 twin participants. A fixed-effect model was used and yielded $I^2=79\%$ and OR (95%CI) = 2.44 (2.34-10.19). Due to high heterogeneity, a random-effect model was tested. Similarly with the previous outcome, heterogeneity remained to be 79%, thus a fixed-effect model was kept and is shown in Figure 3.
Sensitivity Analysis
We were able to perform sensitivity analysis on the asthma outcome due to having more than two studies in our meta-analysis. Sensitivity analysis was impossible for the cerebral palsy outcome due to not being able to eliminate a study, as there were only two studies eligible for the meta-analysis. However, we were able to perform sensitivity analysis for the asthma outcome. Figure 4 shows the meta-analysis without Ortqvist 2009 included. This study provided 46.5% of the weight of the comparison; when eliminating the study, heterogeneity decreased from 77% to 54%, and new OR (95% CI) is 1.21 (1.09-1.35), previously was OR (95%CI) was 1.33 (1.24-1.44).

Figure 4: Sensitivity analysis investigating the association between low birth weight and development of asthma. Ortqvist 2009 was not included in this analysis.
Discussion
Our review investigated published articles that explored the association between low birth weight and adverse health outcomes during adulthood. This study is unique in that it uses the Cochrane method of reviewing articles and classifies outcomes by body system. To our knowledge, there is no systematic review that investigated this particular exposure and subsequent outcomes in twins.

Our review indirectly explored the concept of the fetal origins of adult disease (FOAD), initially popularized by Dr. David Barker in the 20th century, and how it applies to twin studies. Dr. Barker initially observed that events during early development and intrauterine environmental exposures have an impact on risk of development of disease in adulthood. The first evidence of the validity of this hypothesis was a study published in 1989 that showed that low birth weight was associated with increased risk of coronary artery disease. This hypothesis has been applied to a number of studies to understand if there is a correlation between early developmental factors and adult health outcomes, particularly the development of chronic disease. Twin studies in particular are valuable to understanding the FOAD hypothesis as they control for genetic and environmental confounding factors, thus being helpful in understanding how epigenetic factors apply to health outcomes.

Asthma
Because our methodology did not yield many studies, we were only able to perform two meta-analyses for two outcomes. The first meta-analysis was performed on three twin studies to assess development of asthma in normal vs. low birth weight twin participants. This meta-analysis (shown in Figure 2) showed that there was high heterogeneity ($I^2 = 77\%$) among the three studies that were included. Thus, there was high variation among these three studies. It is already known that children born with low gestational age or low birth weight are at an increased risk of asthma; furthermore, it is known that twins are more likely to be born at a lower gestational age and lower birth weight than their singleton counterparts. Although this fact was found true in several past studies, interestingly our results show high heterogeneity across the three studies that were assessed in our review.

Asthma is a chronic disease that is typically developed during childhood. The Copenhagen Studies on Asthma in Childhood concluded that 40% of lower lung function cases had asthma present at birth; in other words, children who developed asthma later in life (in this study, at the age of 7) demonstrated lung function deficits in the neonatal period, suggesting support for the hypothesis that later chronic disease can be predicted by early developmental factors. However, other studies have suggested the opposite; these studies essentially attribute asthma development more to environmental exposures rather than on lung function at birth and subsequent lung functioning later on in life.

Although this is not an exhaustive review on all studies investigating asthma development, these examples of conflicting results can explain the high heterogeneity that was observed in the present review. After following the previously described methodology, we only included three studies in our review, which can also be attributed to high variation in results. Thus, in order to concretely conclude that there is a positive or negative association between low birth weight and development of asthma, more studies need to be done to assess this relationship.

Cerebral Palsy
Cerebral palsy is a lifelong physical disability that is associated by movement and posture disorders, as well as impairments in communication, intellectual ability, and neurological functioning. Worldwide, cerebral palsy is estimated to affect 17 million people, affecting about 1 in 500 neonates. The onset of cerebral palsy is during childhood, and there is currently no cure to the disorder. After following
the methodology for our present review, we were able to perform a meta-analysis on two articles that investigated the impact of low birth weight on cerebral palsy development in twin study participants.

Although studies have been conducted for several years regarding the etiology and pathways of cerebral palsy, there is still little known about the risk factors of developing the disorder. However, it is known that multiple pregnancy increases the risk of cerebral palsy 2-fold in each twin, and twins conceived via in vitro fertilization each have a 4-fold risk in developing cerebral palsy, particularly because of the predisposition to cerebral damage that twins have when compared to singletons. In twins, zygosity and sex pairing have both been previously studied in cerebral palsy development and survival. This study showed that the prevalence of cerebral palsy was higher in the low birth weight and same sex twin groups, suggesting evidence for the role of low birth weight in the etiology of the disorder.

The high heterogeneity observed in the meta-analysis (shown in Figure 3) for the association between low birth weight and development of cerebral palsy can be attributed to a number of factors, primarily due to the lack of studies that assessed the association between low birth weight and cerebral palsy. Past studies have indicated that there is a correlation between the two, but after going through our review’s methodology, we were only able to perform a meta-analysis for two studies for this particular outcome. Thus, this likely affected the variation of results across the two studies. In order to have more valid and reliable results for this meta-analysis, more studies are necessary.
Conclusion
In conclusion, the present systematic review screened almost 4,000 articles to study the association between low birth weight and long-term health outcomes in both children and adults. After following the previously described methodology, 14 articles were eligible for inclusion following quality assessment; however, based on our study objectives, we were only able to include five articles in the meta-analyses due to outcomes not overlapping with one another. The two outcomes we assessed were asthma and cerebral palsy, and the overall odds favored development of these two conditions in low birth weight twins. Both meta-analyses demonstrated high heterogeneity (over 70% for each outcome) with both a fixed- and random-effect model, suggesting high variation among the study data for each outcome. This is likely due to the lack of studies that were included in this review. Thus, we recommend that future twin studies collect data regarding low birth weight as a potential risk factor for developing longitudinal outcomes in order to draw more viable conclusions.
References


15. Brix TH, Hagedus L. - Twins as a tool for evaluating the influence of genetic susceptibility in thyroid autoimmunity. 2011;- 72(- 2).


Appendix I
Modified Downs and Black Quality Assessment Tool

Study Clarity:
1) Is the objective clearly described?
2) Are the main outcomes to be measured clearly described?
3) Is the exposure clearly described?
4) Are the principal confounders in each group of subjects to be compared clearly described?
5) Are the main findings of the study clearly described?

External Validity:
6) Were the subjects asked to participate in the study representative of the entire population from which they were recruited?
7) Was there an overall participation rate of at least 70%?

Internal Validity – Bias:
8) If any of the results of the study were based on data dredging, was this made clear?
9) In case-control studies, is the time period between the exposure and outcome the same for cases and controls? In cohort studies, do the analyses adjust for different lengths of follow-up for subjects?
10) In case-control studies, was the exposure misclassification likely to bias the reported association towards the null? In cohort studies, did the exposure status change during the follow-up?
11) Were the statistical tests used to assess the main outcomes appropriate?
12) Were the main outcome measurements clearly described, and valid and reliable?

Internal Validity – Confounding (selection bias):
13) In case-control studies, were the cases and controls recruited from the same population? In cohort studies, were study subjects in different exposure groups recruited from the same population?
14) Were study subjects recruited over the same period of time?
15) Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?