

Lifestyle Risk Factors Associated with Adult Primary Brain Tumours: Quality
Assessment of Existing Systematic Reviews, Followed by Updated Analyses
and *De-Novo* Syntheses

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ABSTRACT

Background: A compilation of high quality systematic reviews (SRs) on lifestyle factors associated with adult glioma and meningioma was developed.

Methods and Materials: Phase 1 consisted of a systematic overview of existing SRs. For Phase 2, high quality SRs were incorporated in an update. Moderate or low quality SRs which had not been considered in a high quality review were eligible for a *de-novo* synthesis.

Results: Phase 1 resulted in seven moderate to low quality reviews. From this, in Phase 2, smoking, mobile phone and hair dye use were subjected to *de-novo* reviews. For smoking, it was suggestive that past smokers had an increased risk. For mobile phone use, there was no overall association, however it was suggestive that ipsilateral and high cumulative call time were associated with slight increased risk. No association was observed for personal hair dye use.

Conclusions: Despite these null associations, rigorous SR methods were used providing confidence in conveying these results.

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ABBREVIATIONS

AMSTAR- Assessment of Multiple Systematic Reviews

CADTH- Canadian Agency for Drugs and Technologies in Health

CNS- Central Nervous System

IARC- International Agency for Research on Cancer

ICD- International Classification of Disease

ICD-O- International Classification of Diseases for Oncology

MA- Meta-Analyses

MeSH- Medical Subject Headings

MOOSE- Meta-Analysis of Observational Studies in Epidemiology

NHCC- National Health Charities of Canada

NOC- N-Nitroso Compounds

NOS- New Castle Ottawa Scale

PBT- Primary Brain Tumour

PHAC- Public Health Agency of Canada

PRISMA- Preferred Reporting Items for Systematic Reviews and Meta-Analyses

REFMAN- Reference Manager

REVMAN - Review Manager

SES- Socioeconomic Status

SR- Systematic Review

SSI-Swedish Radiation Protection Authority

WHO- World Health Organization

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1.0. INTRODUCTION/LITERATURE REVIEW

1.1. Background on Primary Brain Tumours

Primary brain tumours (PBTs) are a heterogeneous family of benign and malignant tumors which arise from the cells surrounding the brain and within the brain itself(1-3). Not included in the definition of PBTs are spinal cord tumours, secondary/metastatic neoplasms, and central nervous system (CNS) lymphomas, which are classified as hematological tumours(4).

Benign brain tumours are generally regarded as “noncancerous” and are not considered a serious health hazard, as they are well differentiated, have not infiltrated other tissues and can be easily removed by excision(5). In contrast, malignant brain tumours are considered “cancerous” and should be observed with heightened attention since they are poorly differentiated, infiltrate other tissues and surgical therapy is considered difficult. Benign brain tumours have the potential to become malignant and due diligence should be applied (5).

It is also imperative to differentiate between primary and secondary, also known as metastatic, brain tumours. For PBTs, uncontrolled cell growth originates and is usually localized within the intracranial area. On the other hand, secondary brain tumours usually originate from elsewhere in the body eventually spreading and having an effect on the intracranial area(6).

Although PBTs are considered rare, since they make up only 2% of all adult cancers, attention must be focused on this disease due to its poor survival rate, severe morbidity and increasing healthcare costs(3, 4, 7). In the United States, it is estimated that treatment costs for primary malignant brain tumours are approximately twenty times greater compared to patients with other illnesses(8).

According to the National Health Charities of Canada (NHCC), the estimated incidence of PBTs amongst the Canadian population is 15 cases per 100,000 persons, with 5,000 incident cases each year (9). Symptoms of PBT include headaches, nausea, vomiting, seizures, hemiparesis and aphasia(1).

As will be discussed in further detail, PBTs are classified based on histology and are assigned a grade of severity (benign to malignant) from one to four (10). Based on classification standards, although there are approximately 50 different sub-types of PBTs, most study outcomes are based solely on two types(11). Gliomas and meningiomas are the most common intracranial tumours and make up approximately 70% of all adult PBTs(12).

1.2. Disease Classification Systems

The World Health Organization's (WHO's) International Classification of Diseases for Oncology (ICD-O) is used for classifying PBTs. The latest edition is ICD-O3, developed in the year 2000(13). ICD-O3 is derived from ICD-10 (The International Statistical Classification of Diseases, Injuries and Causes of Death, 10th edition), developed in the year 1992, which focuses on an array of illnesses and is not limited to only neoplasms(13).

ICD-O codes consist of values which indicate: (a) the tumour's histology (4 digits); (b) it's behavior code (1 digit)-whether it's benign (*0*), uncertain (*1*) and malignant (*c*); and it's grading (1 digit) - whether proliferation is minimal and resection is possible (*I*), whether proliferation is minimal but recurrence is possible (*II*); whether the cells are poorly differentiated (*III*); and whether the tumour is malignant with a poor prognosis (*IV*) (14, 15). The following is an example of an ICD-O code for glioblastoma, (ICD-O code 9440/3, WHO grade IV) (10).

While incorporating ICD-O codes, the most widely accepted reference for grouping PBTs by corresponding sub-types is the 2007 WHO Classification of Tumours of the Central Nervous System(10). As a reference document, it provides clear, categorical groupings for neoplasms of similar origins and is most commonly used by clinicians and cancer researchers. It should be re-iterated that the ICD-O codes, for the most part, are retained within the 2007 WHO Classification of Tumours of the Central Nervous System.

It should be noted that although not all publications may refer to the 2007 WHO Classification system when describing their PBTs of consideration, they still typically provide corresponding ICD-O coding.

1.3. Inconsistent Risk Factors

Research focusing on etiological risks for adult PBTs is considered a priority since it directly affects public health decisions for primary prevention. By focusing on primary prevention, considerable financial and societal burdens, on the healthcare system, patients, and their social networks, will eventually decline(4). Focusing on secondary and tertiary prevention will not address the root of the problem and will neither effectively reduce overall costs or incidence rates.

Research regarding the etiology or causes of PBTs, although plentiful in the world literature, has been inconsistent. Ionizing radiation and certain inheritable genetic syndromes have been the only known definitive causes(12, 16, 17).

Certain lifestyle and behavioural risk factors have been identified, with inconsistent results. As discussed in further detail (**Section 1.4. Issues and Basis of Study Development**), most of these lifestyle and behavioural risk factors have been identified and cited through narrative reviews(18, 19), not systematic reviews, which are considered the highest level of evidence(20). There are indeed some systematic reviews which focus on one particular risk factor at a time; however, they are not considered complex systematic reviews and often times these single systematic reviews are of poor methodological quality, which has the potential to heavily bias derived conclusions. As healthcare professionals and policy makers, having a complex systematic review available, which addresses multiple lifestyle and behavioural risk factors for adult PBTs systematically in a single document would prove to be a beneficial resource(21).

Lifestyle and behavioural risk factors are defined as modifiable actions at the level of the individual. Based on narrative reviews, and often times, poorly conducted systematic reviews, the following factors have been identified: the use of mobile phones, tobacco smoke, alcohol consumption, hair dyes, head trauma, dietary ingestion of N-nitroso compounds, artificial sweeteners and antioxidants(4, 12, 22).

1.4. Issues and Basis of Study Development

In 2008, the Canadian government publicly announced the importance of directing research efforts towards the study of fourteen pre-determined neurological conditions which affect a proportion of our population(23). As a joint effort, the Public Health Agency of

Canada (PHAC) and the Neurological Health Charities of Canada (NHCC) have partnered to fund a research program initiative called the National Population Health Study on Neurological Conditions, which includes multiple projects led by thirteen different research teams across the country(24). Each funded project generally falls into one of four streams: (a) Scope of neurological conditions; (b) Impact on individuals and families; (c) Risk factors; (d) Health services.

One such project, a complex SR of risk factors and prognostic factors associated with the fourteen neurological conditions was assigned to the University of Ottawa. My task was to identify the biological, genetic, lifestyle, socioeconomic, environmental, psycho-social and co-morbid risk factors associated with primary brain tumours. In addition, I was to also identify the factors influencing the natural progression of this disease.

In order to increase the timeline feasibility of the thesis, I will direct my efforts towards providing a smaller sub-set of the much larger project noted above, with a strict focus on identifying only lifestyle and behavioural risk factors associated with adult primary brain tumours, more specifically, glioma and meningioma. The work completed on the thesis will be included in the final deliverable to be received by PHAC and NHCC.

Although adult primary brain tumours are relatively rare, studying the lifestyle and behavioural risk factors for their development has great implications since it will influence primary prevention for a disease which has considerable direct and indirect costs(8). Since PHAC and NHCC have funded this initiative, they also see the impact and burden this neurological condition has on the Canadian population, and feel that now is the time to mitigate primary brain tumours as a whole by defining probable causes. In order to gather the evidence needed to inform important decisions, one must rely on evidence from SRs and MAs(25).

Presently, there is a dire need to conduct SRs and MAs for risk factors associated with adult primary brain tumours.

- Firstly, there is a need since currently, there are several literature reviews available which address multiple risk factors within their document, yet these methods are not systematic and should not be mistakenly considered at the

policy level(12, 22). Evidence from systematic reviews and meta-analyses should be used for knowledge translation since it is the most rigorous and transparent method for sharing information(20).

- Secondly, there is a need, since although there are a handful of existing SRs and MAs on risk factors for adult PBTs, most are outdated and are not of highest methodological quality, which may lead to biased information and misinformed decision-making(26). In addition, most of these SRs and MAs only focus on one specific risk factor which inhibits the ability to gather a larger picture of the disease and document retrieval is often times difficult.
- Therefore, ideally, the next step in this area is to complete a complex SR since there has yet to be a complex SR completed on lifestyle and behavioural risk factors for adult PBTs within the medical literature. Complex SRs are a compilation of SRs which include multiple research questions, as opposed to just one, and often times incorporates existing high quality SRs to reduce redundancy and to identify new evidence, when permitted(21, 27).

The goal of this thesis is to develop a single, comprehensive, complex SR with multiple-up-to date, high quality SRs and MAs on lifestyle and behavioural risks factors to be used as a beneficial resource for both policy makers (PHAC), community stakeholders (NHCC) and the larger academic community.

1.5. Rationale for Focusing on Adult Primary Brain Tumours (Glioma and Meningioma)

The focus of this thesis will be based on adult PBTs. Although childhood PBTs are equally important, the adult population warrants attention. A large proportion of the population who are experiencing PBTs are adults, as witnessed by the general trend of incident brain tumours. Incident cases substantially increase around the age of 30 and begin to decline at older age(4). In addition to the adult cohort having a larger number of incident cases, those who are over 45 years of age have increased incidence and prevalence of high-grade (malignant) PBTs, while rates for low-grade (benign) PBTs are more prevalent with decreasing age(12, 28). This is pertinent, since high-grade PBTs have poorer prognoses and are shown to increase health care utilization costs(8, 12).

Within the adult population, there are two specific sub-types of PBTs which are the most common. Gliomas, accounting for approximately 50% of all PBTs, are the most common malignant form of brain tumour affecting the adult population. Meningiomas, accounting for approximately 20% of all PBTs, are the most common benign tumour. Therefore, approximately 70% of all PBTs affecting the adult population are either classified as gliomas or meningiomas(28-32).

1.6. Description of Primary Brain Tumours Being Considered:

1.6.1. Glioma

Gliomas, which are most commonly found within the areas of the cerebral hemispheres, account for approximately 50% of all primary brain tumours(1, 29). Within the medical literature, glioma is generally used as an umbrella term to describe a handful of tumour entities which consist of glial cells(32, 33). Glial cells are seen as having a supportive function for their counterparts, the neurons, and make up approximately 90% of the nervous system(34, 35). The number of glial cells severely outweighs the number of neurons and as a result, one can conclude the dire consequences when tumours target these cells as origins for their proliferation(36). Glioma tends to affect a larger proportion of men compared to women(12).

Astrocytomas, oligodendrogliomas, ependymomas and mixed gliomas are all neoplastic entities which fall under the broader category of “glioma”(22, 32, 33, 37). It should be noted that often times in the literature, authors provide single effect estimates for glioma as a single disease entity. Although it has been done, it is rare for authors to focus on each sub-type separately.

1.6.1.a. *Astrocytoma*

The star-shaped astrocytomas make up the largest proportion, approximately half, of all glioma cases(29, 33, 38). Astrocytomas consist of different grades based on malignancy as outlined by the WHO'S ICD.

Pilocytic astrocytomas (ICD-O code 9421/1, WHO grade I) are classified as least invasive, followed by diffuse astrocytomas (ICD-O code 9400/3, WHO grade II), anaplastic astrocytoma (ICD-O code 9401/3, WHO grade III) and glioblastoma being the most

malignant (ICD-O code 9440/3, WHO grade IV)) (10, 39). Glioblastoma constitutes approximately 50% of all astrocytic tumours and is considered the most common malignant primary brain tumour with the lowest mean survival rate of 14 months after diagnosis(29, 37, 40).

1.6.1.b. *Oligodendroglioma*

Oligodendrogliomas which make up approximately 20% of all glial tumours originate from oligoastrocytes, a type of glial cell, which produces the myelin sheaths of neurons(33, 37). According to the WHO's ICD codes, there are mainly two forms of such tumour, oligodendroglioma (ICD-O code 9450/3, WHO grade II) and anaplastic oligodendroglioma (ICD-O code 9451/3, WHO grade III)(10, 39). Oligodendrogliomas are generally well-differentiated and are less malignant with a median survival of 10 years compared to anaplastic oligodendrogliomas which are more invasive with a median survival of 3 to 5 years (41, 42).

1.6.1.c. *Oligoastrocytoma, "Mixed Glioma"*

The most common form of "mixed glioma" is oligoastrocytomas which consists of cell types which appear similar to oligodendrogliomas and diffuse astrocytoma(43, 44). They make up approximately 2-10 % of all glial tumours(45). Based on the WHO's ICD codes, there are two forms, oligoastrocytoma (ICD-O code 9382/3, WHO grade II) and anaplastic oligoastrocytoma (ICD-O code 9451/3, WHO grade III)(10, 39). Similar to the case of oligodendrogliomas, oligoastrocytoma is considered less invasive with an approximate median survival of 8 years, compared to anaplastic oligoastrocytoma which is considered more malignant with a median survival of 3 to 5 years(41).

1.6.1.d. *Ependymoma*

Ependymomas make up approximately 5 to 6% of all glial tumours(46). Ependymomas originate from ependocytes which line the ventricles of the brain and spinal cord. These ventricles are cavities filled with cerebrospinal fluid(33). According to the WHO's ICD codes, based on increasing invasiveness, there are subependymomas (ICD-O code 9383/1, WHO grade I), myxopapillary ependymomas (ICD-O code 9394/1, WHO grade I), ependymoma (ICD-O code 9391/3, WHO grade II), anaplastic ependymoma (ICD-O code

9392/3, WHO grade III)(10). The 5 year survival rate for ependymoma upon diagnosis has been reported to be between 40-80%(47).

1.6.2. Meningioma

Meningiomas, which account for approximately 10-19% of all primary brain tumours, are most commonly identified as benign neoplasms which originate from the meninges covering the brain(33, 37) . More specifically, within the meninges, the tumours are derived from the arachnoid cap cells(48). As opposed to glial tumours which grow by infiltration of healthy tissues, meningiomas grow by expansion(38). Thus, a common symptom associated with this disease entity is increased intracranial pressure manifested through headaches(29). Meningiomas tend to affect a larger proportion of women compared to men(12).

In terms of grades of malignancy, there are meningiomas (ICD-O code 9530/0, WHO grade I), atypical meningiomas (ICD-O code 9539/1, WHO grade II) and anaplastic/malignant meningioma (ICD-O code 9530/3, WHO grade III) with a 5 year survival rate upon diagnosis of >90%, 50-90% and 40-60% respectively(10, 48).

Table 1. Adult PBTs being considered with corresponding WHO grades of severity(10)

Type of PBT	WHO Grade I	WHO Grade II	WHO Grade III	WHO Grade IV
GLIOMAS				
Astrocytoma	Pilocytic astrocytomas (ICD-O code 9421)	Diffuse astrocytomas (ICD-O code 9400)	Anaplastic astrocytoma (ICD-O code 9401)	Glioblastoma (ICD-O code 9440)
Oligodendrogloma		Oligodendrogloma (ICD-O code 9450)	Anaplastic oligodendrogloma (ICD-O code 9451)	
Oligoastrocytoma, “mixed glioma”		Oligoastrocytoma (ICD-O code 9382)	Anaplastic oligoastrocytoma (ICD-O code 9451)	
Ependymoma	Subependymomas (ICD-O code 9383) Myxopapillary ependymomas (ICD-O code 9394)	Ependymoma (ICD-O code 9391)	Anaplastic ependymoma (ICD-O code 9392)	
MENINGIOMAS	Meningiomas (ICD-O code 9530)	Atypical meningiomas (ICD-O code 9539)	Anaplastic/malignant meningioma (ICD-O code 9530)	

2.0. RESEARCH QUESTION AND OBJECTIVES

2.1. Overall Research Question

A broad research question can be formulated for the overall aim of the thesis:

Amongst adult males and females (≥ 18 years of age), what are the reported lifestyle and behavioural risk factors associated with adult glioma and/or meningioma?

It should be noted that questions based on etiology, are by nature, less structured compared to questions based on therapy or prognosis(49). Specific PICOS which make up each component of the thesis can be found in the methods section.

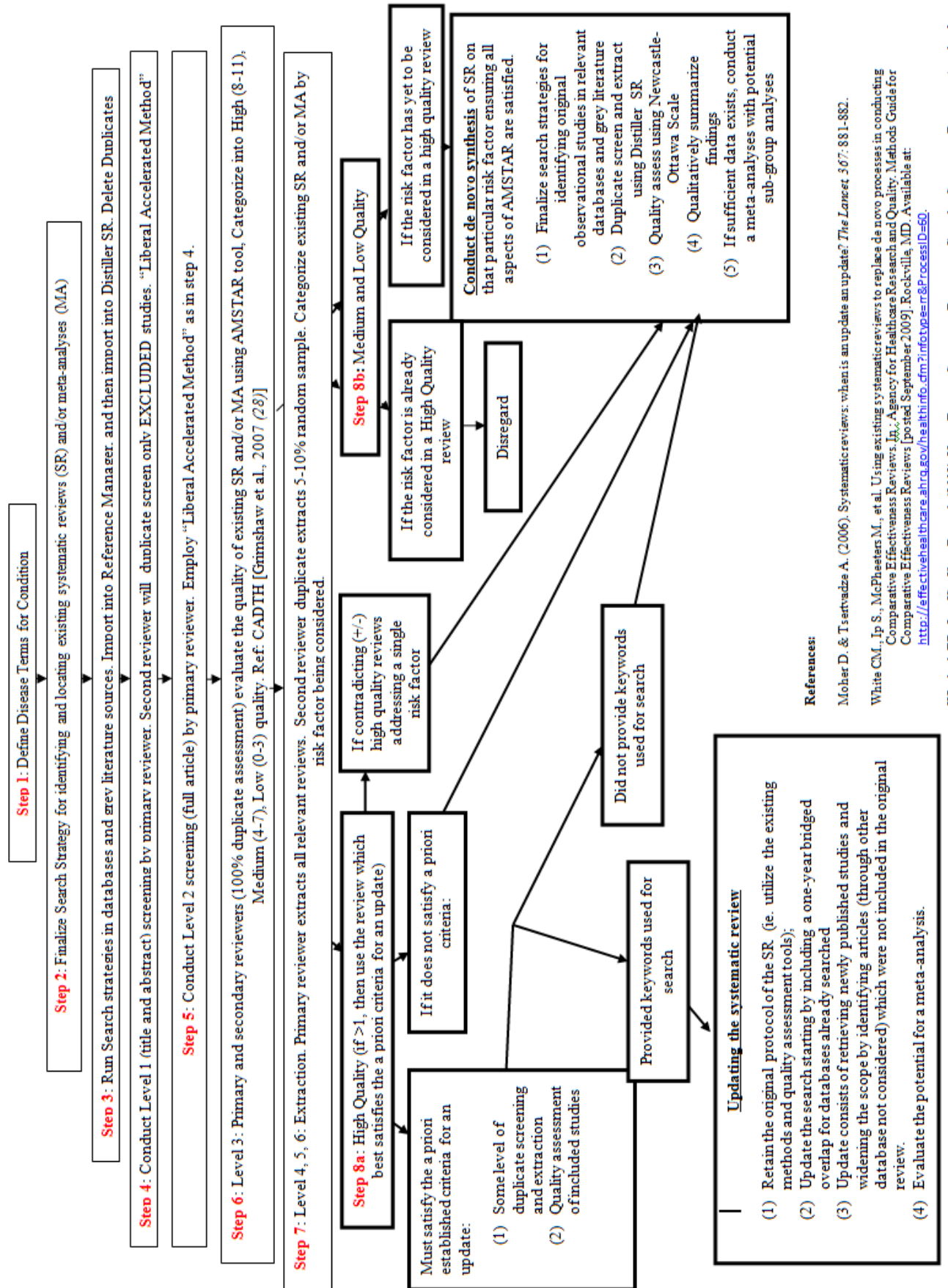
Due to the nature of the thesis, specific research questions and hypotheses for three candidate risk factors cannot be determined until the first two objectives (noted below) have been completed. This will allow for one to determine whether: (i) a new research question must be formulated for that risk factor, in the case of a *de-novo* synthesis; or (ii) the existing research question from the original authors must be used and applied, in the case of an update.

2.2. Objectives

The above stated research question identifies the following specific objectives for this study:

- (1) To systematically identify and assess the methodological quality of existing SRs and MAs which focus on lifestyle and behavioural risk factors associated with adult gliomas and/or meningiomas.
- (2) To apply a decision tool to the existing SRs and MAs (See Figure.1) which will be used to guide subsequent actions (either an update or a "from scratch" approach-also referred to as *de-novo* synthesis) based on their quality assessment score.
- (3) To systematically identify original observational studies pertaining to one additional risk factor (personal hair dye use) which has yet to be addressed in existing SRs and/or MAs.
- (4) To produce a complex systematic review with multiple up-to-date, high methodological quality SRs and MAs on three lifestyle and behavioural risk factors for adult gliomas and/or meningiomas, with the purpose of informing public policy.

Figure.1. Decision Tool for Subsequent Actions with Existing SRs and MAs (PHAC Project)



3.0. DESCRIPTION AND RATIONALE OF STUDY DESIGN

A visual representation of the overall study design/design tool can be found in Figure 1.

PHASE 1: A Systematic Search of Existing Systematic Reviews and Meta-Analyses

3.1. A Systematic Search of Existing Systematic Reviews and Meta-Analyses.

It has been estimated within the Medline database that the number of SRs available for access has increased from 500 in 1994 to 5000 in 2009(50). Although a relatively new area of consideration, using existing SRs and MAs to replace or complement *de novo* synthesis has become a viable option for topics with large breadth and when human resources and time are limited. It also helps reduce redundancy by avoiding replication of research on the same topic, which has become an issue within the medical literature(51).

In order to optimize the use of existing SRs and MAs, a comprehensive systematic search was conducted to identify all relevant existing SRs and MAs on lifestyle and behavioural risk factors associated with adult glioma and/or meningioma. Based on a preliminary search the reviews identified were often outdated and of varying quality. Ideally, all SRs and MAs should be current and of the highest methodological quality to ensure confidence in results(52). Reviews which are outdated and of lower methodological quality tend to produce biased results which have large implications for the accuracy of decisions made at the policy level(27, 53, 54). When replacing or complementing *de-novo* processes with existing SRs and MAs, it is best to incorporate high methodological quality reviews, not those of moderate or low quality(21, 27).

Available guidelines have recommended using systematic searches to identify existing reviews, screening based on relevancy, and quality assessment of such reviews(21, 27). Based on study quality, subsequent decisions were made regarding how best to proceed.

3.2. Decision Tool for Subsequent Course of Action Following Quality Assessment of Existing Systematic Reviews and Meta-Analyses

Each identified review was subjected to a decision tool developed a priori (**see Figure 1**) to guide subsequent actions based on its methodological quality (high, medium or low).

As part of the National Population Health Study of Neurological Conditions funded by

the federal government, this decision tool was developed in collaboration with the five research centers (Vancouver, Calgary, Ottawa, Toronto and Newfoundland). Feedback was provided, and the schematic tool was subsequently revised until the entire team felt that the tool was appropriate for use. This tool was designed for the much more encompassing complex SR focusing on all risk factors for onset and progression associated with fourteen neurological conditions. Percentage for random duplicate extraction and quality assessment differ between the PHAC project and the thesis.

Two options were presented in this tool: (a) If the existing SR + MA was of high quality and it satisfied certain a priori conditions, then an update was warranted; (b) Alternatively, if the existing SR+MA was of moderate or low quality and the risk factor had yet to be addressed in a high quality review, then it was eligible for a complete *de-novo* synthesis.

PHASE 2: Update or "From-Scratch" De-novo Synthesis

3.3. Conducting an Updated Analysis or Complete *De-novo* Synthesis of Existing Systematic Reviews and/or Meta-Analysis Based on Results from PHASE 1.

High quality reviews which satisfied certain conditions were eligible for an updated analysis. There have been conflicting views regarding the definition of an update. According to Moher & Tsertvadze(52), an update is defined as: "...a discrete event with the aim to search for and identify new evidence to incorporate into a previously completed systematic review." As defined by the same authors: "We use 'new evidence' broadly—evidence that has not been included in the previously completed review." Hence, the aim is to utilize existing resources (in the form of existing reviews) and to supplement it with the most currently relevant evidence.

Risk factors studied in medium and low quality reviews which had yet to be addressed in high quality reviews were automatically subjected to *de-novo* processes (outlined in section 5.2.2.). Since significant flaws in methodology were likely present, it was considered best to start from scratch (*de-novo*) rather than to propagate errors during an update. One may question why a complete *de-novo* process was warranted when one can correct the error and proceed from there. According to Moher & Tsertvadze(52): "Corrections of mistakes, errors...detected in previously completed systematic review would not constitute an

update...” Thus, a correction of an inappropriate method and/or implementation of an excluded crucial step would have been better subjected to *de-novo* synthesis in order to ensure best evidence.

3.4. *De-novo* Synthesis of Unaddressed Risk Factors (Personal Hair Dye Use)

Risk factors (personal hair dye use) which had yet to be addressed were subjected to *de-novo* synthesis (again, outlined in section 5.2.2.) *De-novo* reviews would be classified as current, and of high methodological quality.

The overall goal was to provide a complex SR, with up-to-date, multiple SRs and/or MAs on particular risk factors by identifying existing reviews, assessing their quality, and determining whether an update using existing reviews or complete *de-novo* process was warranted.

4.0 BRIEF OVERVIEW OF TOOLS AND INSTRUMENTS USED

4.1. Reference Manager

Reference Manager 12.0 (Thomson Reuters, Philadelphia, PA, USA) is a software program which allows for the organization of bibliographic references. An efficient feature of this software was that chosen articles from specific bibliographic databases, such as PubMed and Embase could be directly imported into Reference Manager. Although there were several bibliographic reference managing software programs available, Reference Manager was chosen as the best option as it was most compatible with the program discussed below, Distiller SR.

4.2. Distiller SR (Evidence Partners, Ottawa, Canada)

Distiller SR is a web-based systematic review software which allows one to efficiently conduct the phases of screening and extraction. All of the necessary published articles were stored in an online folder, which dismissed the need to physically print off these documents. Since these documents were stored online, two reviewers were able to simultaneously screen and extract articles effortlessly. They were able to track their progress daily; detect articles which were causing conflict, produce reports based on an article's ability to fulfill certain criteria, calculate kappa statistic for level of agreement and generate

evidence-based tables with extracted results. Another advantage of being stored online was that included or excluded articles based on screening relevancy could be easily tracked, removing the increased likelihood of misplacement caused by human error.

Distiller SR was composed of forms which were developed by the reviewers. Forms could be made for screening purposes, where the article must satisfy all questions before proceeding to the next phase of the systematic review process. The inability of an article to meet at least one question resulted in its exclusion. Forms could also be made for data extracting purposes, where questions were asked for retrieving certain information from the article.

An interesting feature of Distiller SR was that the interface displayed the title and abstract side by side with the form for screening. Thus, the time one took to screen an article for relevancy was expedited greatly.

4.3. PRISMA Flow Diagram

Preferred Reporting Items for Systematic Reviews and Meta-Analyses(55), also referred to as PRISMA is used by many academics as a checklist for determining the components which needed to be reported in a SR or SR+MA. A flow diagram was also provided which allowed one to visualize the number of articles included and excluded within a SR, with appropriate reasons for exclusions. The main objective of PRISMA was to guide and promote transparency when conducting SRs and MAs. Additional information can be found at www.prisma-statement.org.

4.4. AMSTAR

Assessment of Multiple Systematic Reviews, also referred to as AMSTAR is a checklist which was used to assess the methodological quality of SRs and MAs. There were 11 criteria which focused on questions ranging from the presence of an a priori protocol to comprehensive literature searches, to the evaluation of the presence for publication bias. The creators of this tool had established that it possessed great validity and reliability(56).

4.5. New-Castle Ottawa Scale

The New-Castle Ottawa Scale (NOS) is a tool which was used to assess the methodological quality of observational studies. Two separate scales were used for case-control and cohort studies with a total of 9 points possible for both. The questions posed focus on selection, comparability and exposure/outcome categories. Validation of the instrument has been underway, with content validity and reliability having already been established(57).

4.6. Review Manager (Thomson Reuters, Carlsbad, California)

Review Manger (v.12) is a program offered by the Cochrane Collaboration which is a web-based management tool for systematic reviews. Unlike Distiller SR (mentioned above), this program allowed one to aggregate data quantitatively, by means of a MA. Heterogeneity tests were conducted when one wished to pool the data through two types of statistical tests, Cochrane's Q and I^2 . One also had the option to pool data through either random or fixed effects using inverse variance, or other methods. Forests plots and inverted funnel plots (to assess publication bias) could also be generated.

4.7. MOOSE

Meta-analysis of Observational Studies in Epidemiology (MOOSE) are reporting guidelines used for presenting MAs which consist of observational studies. Its purpose was to ensure that reviews presented the sufficient data necessary to ensure transparency and to allow for duplication. Reporting items were suggested for background, search strategies, methods, results, discussion and conclusions(58).

5.0. METHODS (PHASE 1: A Systematic Search of Existing Systematic Reviews and Meta-Analyses)

5.1. A Systematic Search of Existing Systematic Reviews and Meta-Analyses

5.1.1. Literature Search Strategy

With the guidance of a health information specialist, Lindsey Sikora, at the University of Ottawa, search strategies were developed to identify existing SRs and MAs pertaining to lifestyle and behavioural risk factors for adult gliomas and/or meningiomas.

To effectively search for articles within bibliographic databases, there were a few terms

and concepts that one must be familiar with first. MeSH terms, also known as Medical Subject Headings, are controlled vocabulary headings used within MEDLINE/PubMED to index articles(59). When a newly published article is presented to the staff at the National Library of Medicine, it is assigned and indexed under a relevant MeSH term. Thus, when a user searches with that particular MeSH term, the article will be identified(59). Controlled vocabulary terms are not limited to MEDLINE/PubMED. Other bibliographic databases often have their own versions.

Keywords are also used to complement the search. Often times, for a particular term, there are no corresponding MeSH terms. As such, keywords must be used instead to search the abstract and title for the article related to the topic of interest. To ensure all relevant articles are captured, certain truncation characters are used, such as \$ and *(60). For example, the Canadian spelling of tumours includes the letter “u”, whereas the American spelling omits this letter. As such, by searching for tumo\$, the database will be instructed to retrieve all articles which focus on “tumours” and “tumors”. There are several other syntax applications used for keywords, and these can be found in the appendix (**Appendix A**). It is recommended that even though there may be an available MeSH term, it is best to complement with a corresponding keyword as well(61).

Boolean operators are important for executing search strategies as it explicitly tells the database how to search for your topic of interest. The Boolean operator “OR” widens the scope of the search by joining terms together where the database retrieves articles which have either or both (multiple) terms(62). The Boolean operator “AND” restricts the scope of the search by joining terms together where the database retrieves articles where both (multiple) terms must appear together(62).

In regards to the search for existing SRs and MAs, search strategies were developed and consisted of three concept groups: (a) Disease Terms; (b) Risk Terms; and (c) a filter for retrieving SRs and MAs only. As suggested by Sikora in order to limit the number of irrelevant articles retrieved, using filters would limit the search to identifying SRs and MAs only(61). Relevant MeSH terms and key words were identified for (a) Disease Terms; and (b) Risk Terms, and were grouped with the Boolean operator “OR”, within each concept group. The database specific filters were combined with the Disease Terms and Risk Terms with the Boolean operator “AND” to retrieve relevant articles. An initial draft search strategy

was developed for MEDLINE (In-Process & Other Non-Indexed Citations).

In order to be comprehensive, the search strategy developed for MEDLINE was adapted to several other bibliographic databases which were considered relevant: EMBASE, PubMed, CINAHL, AgeLine (AARP), TOXLINE, PsychINFO and The Cochrane Database of Systematic Reviews. Searches and alerts were in place to identify studies published up to December 31, 2011.

The definition of grey literature is greatly debated among academics. However, Conn *et al.* (63) have provided a comprehensive definition:

“Grey literature refers to studies with limited distribution (i.e. those not included in computerized bibliographic retrieval systems), unpublished reports, dissertations, articles in obscure journals, some online journals, conference abstracts, policy documents, reports to funding agencies, rejected or unsubmitted manuscripts, non-English language articles, and technical reports.”

Therefore, the ProQuest Database of Dissertations and Theses and the Google search engine were considered. By searching Google, documents such as conference proceedings and governmental reports may be identified.

Another useful explanation of grey literature was provided by Ms. Sikora, who described grey literature as a “round-about” method for searching articles. Essentially, she had described grey literature as not having to go directly to bibliographic database, which often times, must be commercially subscribed to, to search for literature(61).

In this regard, the Google Scholar search engine was considered, as many articles were freely available to the public and thus, a commercial focus was not necessarily implied.

To be comprehensive, “other sources” besides bibliographic databases and grey literature were considered. Bibliographies from relevant articles were hand searched to ensure that all applicable articles were identified. Hand searching of relevant journals such as Cancer Causes and Control, Cancer Epidemiology, Biomarkers & Prevention, and International Journal of Cancer were also conducted. The methods used for searching “other sources” were documented in the appendix to provide transparency (**Appendix A**).

5.1.2. A Priori Selection Criteria

Generalized over-arching inclusion criteria were determined by using the following PICOS framework:

- **Population:** Adults (≥ 18 years old, males and females)
- **Intervention/Exposure:** Lifestyle and behavioural risk factors
- **Comparator:** N/A
- **Outcomes:** Adult gliomas and/or meningiomas
- **Study Design:** SR or SR & MA

However, more specific, explicit inclusion/exclusion criteria were employed for identifying existing SRs and MAs:

To be included, the articles had to satisfy all of the following criteria:

- 1) Be related to primary brain tumours, more specifically, it had to include ONE or more of the following brain tumour sub-types: glioma, astrocytoma, oligodendroglioma, oligoastrocytoma, ependymoma, glioblastoma, meningioma.
- 2) Be related to lifestyle/behavioural risk factors (modifiable at the level of the individual) for developing (or protecting against) brain tumours. (Ex: mobile phone use, smoking, alcohol consumption, vitamin supplements, etc)
- 3) Published in English or French
- 4) Either a SR or a SR with a MA component.
 - a. To be considered a SR, at least one bibliographic database needed to be searched, and explicit inclusion/exclusion criteria had to be presented.
- 5) Full text had to be available.

To be excluded, the articles had to satisfy at least one of the following criteria:

- 1) Focused on other primary brain tumour sub-types which were NOT considered glioma, astrocytoma, oligodendroglioma, oligoastrocytoma, ependymoma, glioblastoma, meningioma
- 2) Secondary Tumours (also known as metastatic-defined as developed elsewhere and then spread to the brain)
- 3) Focused on mainly metastatic tumours (defined as spreading from the brain to other sites-with a focus on the other site)
- 4) Diagnostic Focus
- 5) Prognostic Focus
- 6) Risk factors which were NOT lifestyle/behavioural.
- 7) Focused on childhood brain tumours
- 8) Of the following methodological designs: observational study, randomized controlled study, literature review, commentaries, editorials, guidelines (without a SR portion)
- 9) Published in languages other than English or French
- 10) An MA without a systematic search component.

5.1.3. Study Selection Method

After the literature search, retrieved articles from all databases, grey literature and “other sources” were imported into a citation managing program, Reference Manager (RefMan)

v.10 (Thomson Reuters, Carlsbad, California) where duplicates were removed. Citations from RefMan were then exported into DistillerSR (Evidence Partners, Ottawa, Canada), a web-based software which allowed users to manage the screening and extraction phases of a SR. Distiller SR allowed for the creation of levels with multiple questions for the purpose of screening and extraction. The questions were presented beside the title and abstract of the study under scrutiny.

5.1.3.a. Level 1 Screening-Title and Abstract

Two levels were created for screening. The first level consisted of questions based on the explicit inclusion/exclusion criteria and only the title and abstract were subjected to these screening questions. These questions determined if articles moved to the next phase (**Appendix B**). Two specific questions, #1 and #7, had to be broadened to ensure that relevant article were not excluded at level 1 due to absence of identifying information in the title and abstract.

Question #1's scope was broadened to include any type of article which focused on brain tumours as a general term, regardless of whether it mentioned the analysis of specific brain tumour sub-types (glioma and meningioma). This was done as a precaution, since some studies conduct a sub-group analysis focusing on specific relevant sub-types, without mentioning it within their abstract. By allowing articles which focused on brain tumours as a general term through to level 2, the full text of the article could be examined to ensure whether risk estimates were provided for specific sub-types.

Question #7's inquiry of whether the review article is a SR or a SR + MA was relaxed with an option of "can't tell". This option is critically important, since it is common for author (s) to dismiss classifying their reviews as SRs or SRs + MAs in their titles and abstracts, whereas their methods section in the full text article clearly identifies them as such(64).

5.1.3.b. Level 2 Screening-Full Text

The second level consisted of more or less the same questions as Level 1 with some adjustments. Now, the full text article was examined to decide if the article was in fact relevant (**Appendix C**).

Question #1's scope in Level 2 was restricted in the sense that if the article did not provide a risk estimate for the sub-types under consideration (glioma or meningioma) then it was excluded.

Three additional questions were added in Level 2. Question # 6 and #7 were added to classify the type of risk factor being considered and the type of glioma or meningioma being considered, respectively. Question #10 was added to ensure the full text was available. Often times, only abstracts were available, and the full scope of the research could not be sought. Articles without full text were excluded.

What was Question #7 in Level 1 was now Question #9. It was modified, such that the "can't tell" option was no longer available. At this point, with the full text article, the reader was able to determine whether the review was a SR or SR+MA.

By analyzing the title and abstract followed by the full text article: (a) One was less likely to dismiss an article as irrelevant based only on their non-descript titles and abstracts; and (b) This ensured articles labeled as "can't tells" in Level 1 were further explored and decided upon. Studies which satisfy the screening questions in Level 2 then got promoted to the Level 3 and further, thus initiating the data extraction phase.

5.1.3.c. Liberal Accelerated Method for Duplicate Screening

In order to ensure feasibility while retaining the integrity of a SR, a method known as "liberal accelerated" was selected for the screening process. This method was opted for due to the sheer number of collected articles and the issue of limited resources. Based on this method, a unanimous decision by two reviewers (MH/RES and PQ) was needed for an article to be excluded. This ensured that articles excluded by the first reviewer (PQ) were re-assessed by a second reviewer. A safety net was essentially created when two opinions were needed to exclude an article. A kappa statistic, to determine inter-rater reliability was calculated to determine agreement for exclusion between the two reviewers. The second reviewer did not need to review the included articles since only one reviewer's decision was required to advance the article to the next level. The first reviewer then retrieved the full text and subjected the article to further scrutiny, and any non relevance would have been detected further on in the process(65). Any discordance between the two reviewers was resolved by

consensus.

5.1.4. Pilot Screening of Level 1 and Level 2.

Five (5) articles retrieved from the search strategies were selected and were subjected to the pilot screening forms for Distiller SR.

As noted before, a “liberally accelerated” method was used for screening whereby two reviewers were needed to exclude an article, and only one reviewer was needed to advance the article (65) (Distiller SR, Evidence Partners, Ottawa, Canada). Cohen’s kappa statistics for identifying the degree of agreement between two reviewers for exclusions were calculated.

The first attempt resulted in a Cohen’s kappa statistic of 0.59 for agreement on exclusions. This value fell within the interval of 0.41 to 0.60 which represented moderate agreement(66). Certain questions and prompts were identified as non-specific and resulted in some confusion. These were re-addressed.

Five new articles were selected for piloting. The second attempt resulted in a Cohen’s kappa statistic of 1.00, which fell within the interval of 0.81-1.00 representing almost perfect agreement(66). Because kappa was 1.00 at Level 1, a second reviewer was not needed in Level 2. Both reviewers had 100% unanimously agreed on deciding which articles were irrelevant at level 1. The level of agreement for exclusions was now identified as sufficient and the pilot forms for screening were now considered standardized.

5.1.5. Data Extraction Method

Levels 3 to 5 comprised of the data extraction phase and consisted of levels where information on the population, methods and results of the reviews were collected (**Appendix D**).The levels created were standardized between the two reviewers by piloting, at random, a few review articles which ensured that the questions and data extracted were valid and reliable. During the data extraction itself, both reviewers (PQ and WT) duplicate extracted 100% of relevant articles in phase 1.

5.1.6 Study Quality Assessment

The methodological quality of the SR or SR+ MA was assessed using the validated

AMSTAR instrument(56). Prompts for all 11 items of AMSTAR were developed in Level 6 of Distiller SR. With criteria developed by the Canadian Agency for Drugs and Technologies in Health (CADTH)'s Rx for Change Database, reviews with an AMSTAR score between 0-3, 4-7 and 8-11 were assigned quality assessment scores of low, medium or high, respectively(67). Articles extracted in Levels 3-5 were also subjected to duplicate quality assessment in Level 6 by a second reviewer (WT).

5.1.7. Presentation of Findings

Tables with extracted data from relevant existing SRs or SRs+ MAs were presented. Brief text summaries of the existing SRs and/or MAs and their quality assessment score were documented. A PRISMA flow diagram was used to document the process of identifying and excluding relevant existing SRs or SRs +MAs(55).

(PHASE 2 OVERVIEW: Update or De-novo Synthesis)

5.2. Conducting an Updated Analysis or Complete *De-novo* Synthesis of Existing Systematic Reviews and/or Meta-Analysis Based on Results from PHASE 1.

5.2.1. Updating an Existing Systematic Review and Meta-Analysis

5.2.1.a. Definition of an “update”

In order to reduce redundancy and to capitalize on available resources, existing SRs or SRs + MAs deemed of high methodological quality were used to replace complete "from scratch" *de-novo* processes(27). According to White *et al.* (27) and Whitlock *et al.* (21), there are several ways one can incorporate an existing SR into one's respective works. However, for the purposes of this thesis, I used the selected high quality review while updating it for new evidence(27).

Only high methodological quality reviews, with an AMSTAR score between 8 to11, were considered. High quality reviews are less prone to methodological biases compared to moderate to low quality reviews, which should be ineligible for an “update”(21, 27).

A common definition of what constitutes an “update” has been debated amongst academic circles. However, Moher *et al.*(68) have provided the most appropriate definition. He had classified an update as: “...a process aiming to identify new evidence to incorporate

into a previously completed systematic review.” He has provided two options for defining the term “new evidence”. One can search for new evidence immediately after a review has been completed, by using the same search strategy; however, the emphasis is on finding new evidence by expanding the number of databases searched. Another possibility, and the most commonly used, is to have a certain amount of time lapse, and to search the same databases for newly eligible studies since the date of the existing SR was published(52).

In order to be considered an “update”, the original methods (inclusion/exclusion criteria, search strategies, assessment tools, etc) employed by the author(s) of the review article had to be replicated and expanded. Correcting errors would not be considered an “update”(52).

5.2.1.b. Pre-Determined Conditions

Often times, although a review may score high on the AMSTAR scale, it does not necessarily imply that they have incorporated important components of a SR within their methods. To ensure that the updated SRs or SRs + MAs are of high methodological rigour, eligible high quality reviews had to satisfy two pre-determined conditions:

- (I) It must satisfy the a priori established criteria:
 - a. Displayed some level of duplicate screening and extraction
 - i. If the candidate reviews included some level of duplicate screening and extraction, it is more probable that selection bias and errors were minimized(69, 70).
 - b. Addressed quality assessment of included studies
 - i. Addressing quality assessment assures that low quality studies were not summarized with high quality studies, distorting the overall conclusions(71).
- (II) The manuscript had provided keywords used to search at least one database, to allow for some level of replication.

If there were multiple high quality SRs or SRs +MAs on a particular risk factor which provided similar conclusions, then the review which best satisfied the above two components were considered for an update. By ensuring the a priori established criteria were incorporated

in the existing SR, any subsequent updates would have minimal methodological errors propagated in their results.

5.2.1.c. Steps for Conducting an “Update”

Upon satisfying both pre-determined conditions, the review was updated to the present date, either quantitatively and/or qualitatively(27), adhering to the following processes:

- (I) Similar protocol of actions used by original authors was considered to address consistency (ie. research question, inclusion/exclusion criteria, screening, extraction and quality assessment methods)(52);
- (II) For databases already searched by original author(s), to identify current evidence, it has been suggested by White *et al.*(27), that a one year bridge be implemented, starting from one year before the search in the existing SR or SR+MA to the present date. However, to ensure feasibility of the thesis, this has been modified such that a one year bridge was implemented, starting from one prior to the last year searched in the existing SR or SR+MA to the present date.
 - a. Example: An existing SR conducted a search for the literature between the years 2005 to 2008. An update for the purposes of this thesis included a search for the literature from 2007 to the present date.
- (III) Utilizing and adapting the existing search strategy to identify new evidence (both current evidence and evidence not included previously in the review) in other relevant databases not explored by original author(s) was also done to ensure comprehensiveness(64).
- (IV) The potential for a meta-analysis was also evaluated.

5.2.1.d. Presentation of Results

The updated SR or SR +MA was presented as such: the original SR and/or MA was summarized broadly based on population, intervention, outcome, and results. Readers, if interested, were directed to the original article for further details of each included study. Following the text summaries of existing SRs or SRs + MAs, new evidence identified through the updating process was presented and discussed in depth. Based on the new and

original evidence, a final qualitative conclusion was included.

If a MA was attempted, data analyses steps outlined in section **5.2.2.g.** were followed. All numerical values from the original studies and new evidence were inputted into Review Manager (RevMan) version 5.0 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) to generate an updated pooled estimate.

If a MA was attempted, MOOSE guidelines were used to ensure that all components of the checklist were reported. If only a SR is done, then relevant components of MOOSE were adapted and reported(58).

5.2.2. Conducting a *De-novo* Synthesis

5.2.2.a. Conditions for Conducting a *De-novo* Synthesis

A SR or SR+MA for a specific risk factor were subjected to *de-novo* processes if it satisfied the following conditions:

- (1) If a high quality review on a specific risk factor did not satisfy any of the two pre-determined conditions listed in (**5.2.1.b. Pre-Determined conditions**) for an update.
- (2) If there were conflicting results between multiple high-quality reviews(21).
- (3) If a SR or SR+MA on a specific risk factor had been deemed moderate or low quality and had yet to be considered in a high quality review.
- (4) If a SR or SR+MA had yet to be attempted on a specific risk factor all-together, such as personal hair dye use.

5.2.2.b. Literature Search Strategy

Based on the risk factor which was inadequately addressed in the existing SR or SR+MA, a relevant PICO research question and hypothesis were developed. A search strategy was created and adapted to several relevant databases, and the grey literature was searched. The Disease Terms remained the same. The Risk Terms were interchanged with MeSH and keywords for the particular risk factor, and a filter developed by the Scottish Intercollegiate Guidelines Network (SIGN) was used to retrieve only observational studies(72).

5.2.2.c. A Priori Selection Criteria

A priori selection criteria were risk factor dependent. Eligibility was based on the PICO research question for that particular risk factor. Again, only English and French articles were considered.

5.2.2.d. Study Selection Method

Similar processes used for identifying existing SRs or SRs +MAs were applied here. Citations were imported into RefMan, duplicates removed, and the remaining citations were imported into DistillerSR for screening. The first two levels of screening, the use of liberal acceleration and the calculation of a kappa statistic, were also similar. The questions (inclusion/exclusion) within the screening levels, however, were adapted to the new PICO framework for that particular risk factor.

5.2.2.e. Data Extraction Method

Again, Levels 3 to 5 within Distiller SR consisted of questions collecting data from relevant articles. The information collected for these levels were easily generated into evidence tables. Questions within these levels included the population studied (age group, gender, setting), study characteristics (type of study, time frame, number of study participants, number in cases and controls), the intervention (type, dose, duration), the outcome, any adjusted covariates results, and limitations. During the data extraction itself, the first reviewer extracted the data from all relevant articles. Although it is always ideal to have complete duplicate data extraction, in order to ensure feasibility, a second reviewer extracted in duplicate a 25% random sample of the included articles. It was noted that this is common practice for authors with limited resources (64, 73).

5.2.2.f. Study Quality Assessment

As recommended by the Cochrane Collaboration, quality assessment of observational studies will be completed by using the NOS (57, 74). NOS was chosen since: it is widely used for quality assessing observational studies, quick to implement, and it has established face and content validity, along with inter-rater reliability (57, 74). Methodological issues between cohort and case control studies were evident, and the NOS accounted for such differences by subjecting both types of studies to different scales. The following components

were addressed for both scales: selection (4 stars), comparability (2 stars) and ascertainment of exposure/outcome of interest (3 stars). The maximum score on this scale was nine stars(57, 75).

Although standard scoring thresholds had yet to be determined, many studies have consistently used the threshold of ≥ 5 stars and <5 stars to represent studies of high and low quality(76-80) .

5.2.2.g. Data Analysis Methods

Based on the evidence tables generated through the data extraction process, a qualitative summary of results (the SR portion) were provided for the included studies.

A quantitative summary (the MA portion) was attempted if:

- (a) There were greater than three relevant study estimates;
- (b) Heterogeneity tests determined that the pooling of numerous point estimates was appropriate.

Relevant information from each study was inputted into RevMan which generated funnel plots and their associated heterogeneity statistics, I^2 and Cochrane's Q(81).

As outlined by the Cochrane Collaboration, I^2 percentages between 0%-40%, 30%-60%, 50%-90%, 75%-100% represents unimportant heterogeneity, moderate heterogeneity, substantial heterogeneity and considerable heterogeneity, respectively(82). Due to the low power of the Cochrane's Q test to detect true heterogeneity, the threshold for significance had been increased to $p=0.1$, meaning any p -value ≤ 0.1 was considered statistically significant for heterogeneity and any p -value >0.1 was considered homogeneous(82, 83).

After testing for heterogeneity, there were many options:

- (a) If the studies were homogeneous, then the studies may have been similar enough for their estimates to be pooled using a random effects model resulting in an overall pooled estimate;
- (b) (i) if the studies were heterogeneous, it may have been inappropriate to pool studies that were too dissimilar and a qualitative summary would have been suffice or;

(ii) one pooled, using a random effects model, however, as described below, a subgroup analysis to explain the sources of heterogeneity was attempted if there were sufficient number of articles available to do so (82).

Random effects models based on the DerSimonian and Laird method (DLM) was used to pool estimates together as opposed to using fixed effects models(82). Between study variances will always be present, and the random effects model accounts for this by including Tau squared (T^2) into the calculation(82, 84). Since variability is always present, random effects modeling generates more conservative estimates for determining significance by producing wider confidence intervals, allowing one to be more cautious in their conclusions. In regards to weights, a fixed effects model based on the inverse variance approach assigns heavier weights to studies with more precision (larger sample sizes and smaller standard errors) (82). Conversely, in a random effects model, the DLM method (variation of the inverse variance approach) assigns slightly more weight to smaller sized studies. This allows for smaller studies, with inherent variations, to have greater contribution to the model, since a common sized effect (fixed effects model) is disregarded(82).

Upon generating a forest plot, RevMan, was also able to produce an inverted funnel plot which addressed the influence of publication bias. An asymmetrical plot generally indicated the presence of publication bias, whereas a symmetrical plot generally indicated its absence(82).

5.2.2.h. Planned Sensitivity/Subgroup Analyses

It has been decided a priori from previous studies in the field, that if substantial heterogeneity existed and sufficient data was available, sub-group analysis would be attempted. These analyses were based on either patient characteristics (histological subtype, gender, race/ethnicity and exposure duration) and/or study-level characteristics (study design, adjustment for confounding variables, influence of funding, and quality assessment)(16, 85-90). By doing so, effect estimates which differed based on certain characteristics were identified and interpreted.

5.2.2. i. Presentation of Findings

Again, MOOSE guidelines were used for reporting SRs and MAs(58).The process of

identifying, including and excluding relevant articles were documented through the PRISMA flow diagram(55). Evidence tables derived from data extraction and subsequent qualitative summaries were presented. If a MA was attempted, a forest plot with the pooled estimate and corresponding 95% confidence intervals, along with statistical values for heterogeneity (Cochrane’s Q and I²) was be provided. An inverted funnel plot was also provided to address publication bias.

6.0. RESULTS (PHASE 1: A Systematic Search of Existing Systematic Reviews and Meta-Analyses)

6.1. Identification of Relevant Existing Systematic Reviews or Systematic Reviews and Meta-Analyses.

Bibliographic database searching resulted in the identification of 493 potentially relevant articles. 26 additional articles were identified through searching other sources, such as grey literature and disease specific journals. Thus, a total of 519 potentially relevant articles were imported into Distiller SR. After the removal of duplicates, a total of 355 records were subjected to Level 1 screening for relevancy based on title and abstract. 8 articles were in conflict and were resolved by consensus (eventually excluded) between the two reviewers The kappa statistic for level of agreement based on the 322 excluded articles for the two reviewers was 0.64, which represents substantial agreement(66). 33 records had satisfied Level 1 screening, and the full-text was retrieved for further scrutiny in Level 2 screening.

Articles in Level 1 screening may satisfy more than one exclusion criteria. As presented in **Table 2**, articles were classified into the exclusion categories based on the criteria which they had satisfied first (primary exclusions). Primary exclusions were determined by the order in which the questions were presented within the screening levels.

Table 2. Reasons for Exclusions at Level 1 Screening- Title and Abstract

Exclusion Criteria	Number of Excluded Articles
1. Is this article related to brain tumours? (answer: no)	86
2. Is this article related to lifestyle/behavioural etiological risk	214

factors for developing (or protecting against) brain tumours? (answer: no)	
3. Does this article consist of childhood primary brain tumours (answer: yes)	15
4. Article does not use general term “brain tumours” (answer: no)	1
5. Article focuses on irrelevant outcomes (answer: yes)	1
6. Focuses on mainly metastatic tumours (spreading from brain to other sites- focus on other sites) (answer: yes)	1
7. Article is an observational study (answer: yes)	1
8. Article is a literature review (answer: yes)	2
9. Article is neither a systematic review and/or meta-analysis (answer: yes)	1
Total	322

Thirty-three full text articles were subjected to Level 2 screening, among these, 4 articles were in conflict. These articles were resolved by consensus (and were eventually excluded) between the two reviewers. The kappa statistic for level of agreement based on the 26 excluded articles for the two reviewers was 0.66, which represents substantial agreement(66). Articles in Level 2 screening may satisfy more than one exclusion criteria; however, the primary exclusion criterion which was satisfied first will be presented in **Table 3**. A list of excluded studies at Level 2 can be found in the **Appendix E**.

Table 3. Reasons for Exclusions at Level 2 Screening- Full-Text Article

Exclusion Criteria	Number of Excluded Articles
1. Is this article related to brain tumours- must include sub-types of interest? (answer: no)	5
2. Is this article related to lifestyle/behavioural etiological risk factors for developing (or protecting against) brain tumours? (answer: no)	3
3. Does this article consist of childhood primary brain tumours (answer: yes)	1
4. Article focuses on etiological risk factors that are not lifestyle/behavioural (answer: yes)	1

5. Article is a literature review (answer: yes)	2
6. Article is a commentary or editorial (answer: yes)	1
7. Article does not focus on brain tumour sub-types of interest (answer: yes)	2
8. Article is neither a systematic review and/or meta-analysis (answer: yes)	6
9. Article is a meta-analysis only (answer: yes)	5
Total	26

The remaining 7 articles had met the a priori inclusion/exclusion criteria and were subjected to 100% duplicate data extraction and quality assessment by the second reviewer (WT). Slight differences were noted in both extraction and quality assessment responses, and were promptly resolved through consensus.

Figure 2. PRISMA Flow Diagram of Included/Excluded Studies

Source:

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. (2009). *Preferred Reporting Items for Systematic Review and Meta-Analyses: The PRISMA Statement*. PLoS Med 6(6): e1000097. Doi: 10.1371/journal.pmed1000097.

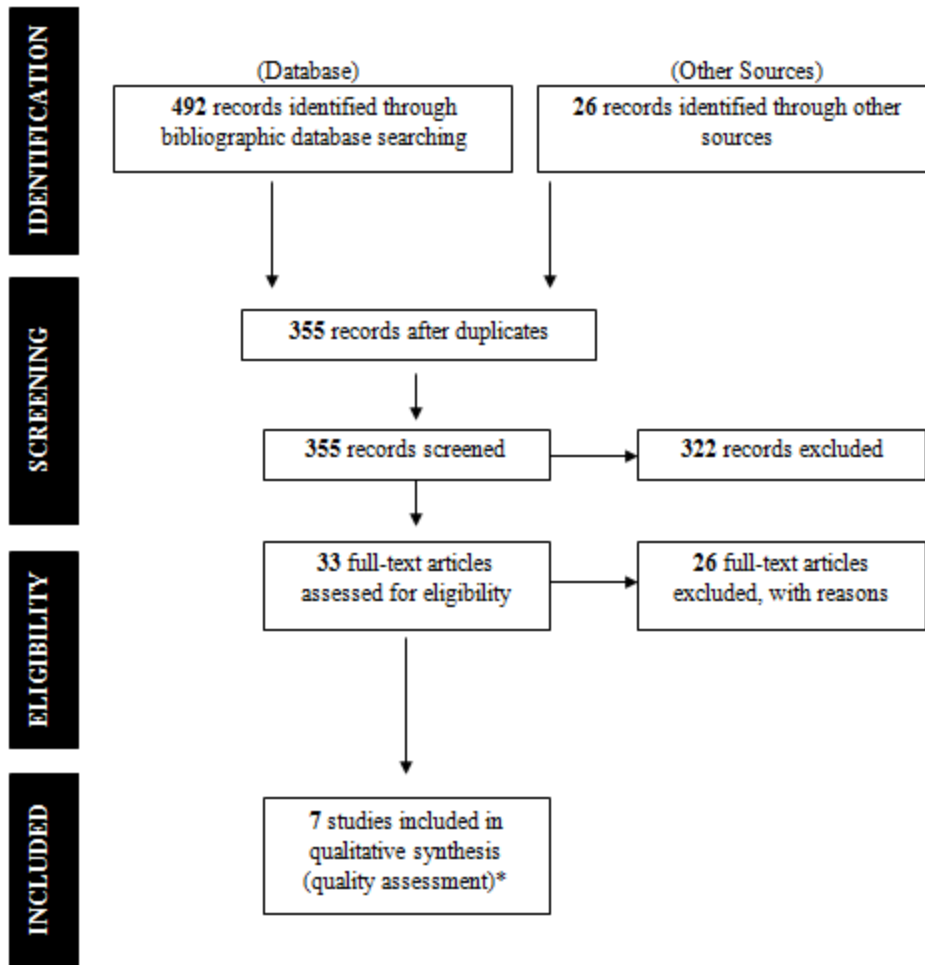


Table 4. Risk factors of Systematic Reviews and Meta-Analyses Identified (formatting from Clarke(91))

Lifestyle/Behavioural Risk Factor	Number of Reviews Identified	References
Mobile Phone Use	5	(Lahkola <i>et al.</i> , 2006; Kan <i>et al.</i> , 2008; Khurana <i>et al.</i> , 2009; Myung <i>et al.</i> , 2009; Repacholi <i>et al.</i> , 2012)
Smoking	1	(Mandelzweig <i>et al.</i> , 2009)
Diet	1	(Huncharek <i>et al.</i> , 2003)

Table 5. Included Existing Systematic Reviews and Meta-Analyses

(1)Review Article; (2) AMSTAR Score	Exposure(s) being considered:	(1)Disease Status/Entities being considered; (2) Classification System Used	Types of Included Studies	Years included in search strategy	Databases Searched	Results (never or non-regular user as referent group)	Overall Conclusion:
Mobile Phones							
(Lahkola <i>et al.</i> , 2006): “Meta-Analysis of Mobile Phone Use and Intracranial Tumors” (5- <i>Moderate</i>)	The association between mobile phone use up to five years.	(1) Glioma and Meningioma; (2) Not Mentioned.	Case-Control Studies, Prospective Cohort Studies	Inception to December 1, 2005	Pubmed & Browsed reference list of retrieved articles.	#1: Glioma, mobile phone users, OR 0.96 (0.78-1.18). #2: Meningioma, mobile phone users, OR 0.87 (0.72-1.05).	The use of mobile phones up to five years does not increase the risk of glioma and/or meningioma.
(Kan <i>et al.</i> , 2008): “Cellular Phone Use and Brain Tumor: A Meta-Analysis” (4- <i>Moderate</i>)	Cellular phone use.	(1) High Grade Glioma, Low Grade Glioma and Meningioma; (2) Not Mentioned.	Case-Control Studies	1966-April 2006	Medline & bibliographies were searched for additional articles	#1: High grade glioma, cellular phone use, OR 0.86 (0.70-1.05). #2 : Low grade glioma, cellular phone use, OR 1.14 (0.91-1.43)- #3 : Meningioma, cellular phone use, OR 0.64 (0.56-0.74)	No overall increased risk of glioma and/or meningioma among cellular phone users.
(Khurana <i>et al.</i> , 2009): “Cell Phones and	The association between long term use of	(1) Glioma and Meningioma; (2) Not Mentioned.	Case-Control Studies	Inception to December 1, 2008	Pubmed	#1: Glioma, long-term users (>=10 years) of cell phones, OR 1.3 (1.1-1.6). #2: Glioma, long-term	There is a statistically significant increase in developing glioma and not meningioma among

Brain Tumors: A Review Including the Long-Term Epidemiologic Data.” (3-Low)	cell phones (>=10 years). In addition, also analyzed ipsilateral vs contralateral.					ipsilateral cell phone users (>=10 years), OR 1.90 (1.4-2.4) #3: Glioma, long-term contralateral cell phone users (>=10 years), OR 1.20 (0.90-1.27). #4: Meningioma, long-term users (>=10 years) of cell phones, OR 1.1 (0.8-1.4). #5: Meningioma, long-term ipsilateral cell phone users (>=10 years), OR 1.3 (0.9-1.8) #6: Meningioma, long-term contralateral cell phone users (>=10 years) OR 0.80 (0.5-1.3).	long term users of cell phones (>=10 years) ipsilaterally.
(Myung <i>et al.</i> , 2009): “Mobile Phone use and Risk of Tumors: A Meta-Analysis” (7-Moderate)	The association between the use of mobile phones (use vs. never or rarely use).	(1) Glioma and Meningioma; (2) No Classification System mentioned	Case-Control Studies	Medline (1968 to August 2008); EMBASE (1977 to August 2008); Cochrane (1953 to August 2008)	Medline, Embase, Cochrane & bibliographies of relevant articles.	#1: Glioma, ever users vs. never/rare users, OR 1.09 (0.89-1.34). #2: Glioma, the Hardell studies, ever vs. never/rare users, OR 1.37 (0.88-2.12). #3: Glioma, the INTERPHONE studies, ever vs. never users, OR 0.84 (0.75-0.96). #4: Glioma, other groups conducting studies, ever vs. never/rare users. OR 1.06 (0.76-1.48). #5: Meningioam, ever vs. never users, OR 0.83 (0.75-0.92). #6: Meningioma, the INTERPHONE studies, ever vs. never users. OR 0.77 (0.68-0.88) #7: Meningioma, other groups conducting studies, ever vs. never users. OR 0.95 (0.80-1.13)	A protective effect was observed for meningiomas, which was mainly influenced by INTERPHON-E'S decreased risk estimate. A slight increase in risk was observed for gliomas; however, these results are non significant.
(Repacholi <i>et al.</i> , 2011)	Regular users compared to	(1)Glioma and Meningioma;	Case-Control,	Inception to	Medline, Embase,	#1: Glioma, short term users, OR 1.03 (0.86-1.24). Long term	There is no association between wireless phone

“Systematic Review of Wireless Phone Use and Brain Cancer and Other Head Tumors.” (5-Moderate)	non users and non-regular users. Additional analysis by short term and long term users (≥ 10 years)	(2) No Classification system mentioned.	Cohort, Case-only, Ecological	November 13, 2010	WHO-Institute of Electrical and Electronics Engineers EMF Studies database, EMF Portal.	users, 1.40 (0.84-2.31). #2: Glioma, ever users (ever having been a regular user), OR 1.07 (0.89-1.29). #3: Meningioma, short term users, OR 0.82 (0.72-0.94). Long term users, OR 1.25 (0.51-3.10) #4: Meningioma, ever users (ever having been a regular user), OR 0.93 (0.77-1.12).	use and glioma and meningioma.
Smoking							
(Mandelzweig <i>et al.</i> , 2009): “Smoking and Risk of Glioma: a Meta-Analysis” (5-Moderate)	#1: Primary exposure of interest: (1) Smoking (Ever vs. Never) #2: Secondary exposures considered: (2) Smoking (Current Vs. Never) (3) Dose Response (a-smoking duration-each additional 10 years of smoking; b-smoking intensity-additional 10 cigarettes per day; c-age at smoking initiation for men and	(1) Glioma; (2) Not mentioned. However, included studies with a medical confirmation of diagnosis of glioma	Case-Control Studies, Prospective Cohort Studies	Inception to 2008	Medline & reviewed bibliographies of included studies and review articles	#1: Glioma, cohort studies, ever smokers compared to never smokers, RR 1.10 (1.01-1.20). #2: Glioma, case-control studies, ever smokers compared to never smokers, RR 1.00 (0.88-1.15). #3: Glioma, both types of study designs combined, ever smokers compared to never smokers, RR 1.06 (0.97-1.15). #4: Glioma, cohort, past smoker, RR 1.16 (1.05-1.29). case-control, past smoker, RR 0.90 (0.73-1.11). #5: Glioma, for both types of study designs combined, past smokers compared to never smokers, RR 1.10 (0.99-1.22) #6: Glioma, increase in risk for for each additional 10 years of smoking, RR 1.10 (0.94-1.08). #7: Glioma, increase in risk for each additional 10 cigarettes smoked per day, RR 1.02 (0.96-1.08) #8: Glioma, increase for additional 10 pack years, RR	There is no association between smoking and glioma. However, when combining cohort studies, there is a small increase in risk for EVER smoker and PAST smoker.

	women)					1.00 (0.96-1.04)	
Diet							
(Huncharek <i>et al.</i> , 2003): “Dietary Cured Meat and the risk of Adult Glioma: A Meta-Analysis of Nine Observational Studies.” (4- <i>Moderate</i>)	Dietary intake of N-nitroso compounds from cured meats.	(1) Glioma; (2) Not Mentioned.	Case-Control Studies	January 1866-April 2002	Embase, MEDLARS, CancerLit, CD version of Current Contents & Manual search of bibliographies and review articles.	#1: Glioma, high cured meat consumers vs. low, RR 1.48 (1.20-1.83) #2: Glioma, high intake of hot dogs vs. low, RR 0.90 (0.63-1.25). #3: Glioma, high intake of bacon vs. low, RR 1.31 (1.00-1.71). #4: Glioma, high intake of ham vs. low, RR (1.27-2.14).	Among high cured meat intakers, there is a statistically significant risk for glioma, albeit; there are several limitations which question its accuracy.

Table 6. Methodological Quality Assessment of Existing Systematic Reviews and Meta-Analyses using AMSTAR

	<i>Mobile Phone Use</i>					<i>Smoking</i>	<i>Diet</i>
	(Lahkola <i>et al.</i> , 2006)	(Kan <i>et al.</i> , 2008)	(Khurana <i>et al.</i> , 2009)	(Myung <i>et al.</i> , 2009)	(Repacholi <i>et al.</i> , 2011)	(Mandelzweig <i>et al.</i> , 2009)	(Huncharek <i>et al.</i> , 2003)
AMSTAR Criteria							
Was an ‘a priori’ design provided? ^a	X	X	X	X	√	X	X
Was there duplicate study selection and data extraction? ^b	X	X	X	X	X	X	X
Was a comprehensive literature search performed? ^c	X	X	X	√	X	X	√
Was the status of publication used as an inclusion criterion? ^d	√	X	X	X	X	X	X
Was a list of studies (included & excluded) provided? ^e	X	X	X	X	X	√	√
Were the characteristics of the included studies provided? ^f	√	√	√	√	X	√	√
Was the scientific quality of the included studies assessed and documented? ^g	X	X	X	√	√	X	X
Was the scientific quality of the included studies used appropriately in formulating conclusions? ^h	√	√	√	√	√	√	√
Appropriate methods used to combine findings? ⁱ	√	√	X	√	√	√	X
Was publication bias assessed? ^j	√	√	X	√	X	√	X
Was the conflict of interest included? ^k	X	X	√	√	√	X	X
Overall AMSTAR score & Classification of Quality^l	5 (Moderate)	4 (Moderate)	3 (Low)	7 (Moderate)	5 (Moderate)	5 (Moderate)	4 (Moderate)

AMSTAR criteria below can also be found in its original publication (Shea, 2009)

a Authors should mention the existence of an a priori protocol

b There should be two independent reviewers for selection and extraction. A consensus procedure must have also been in place.

c (1) At least two databases had to be searched with (2) years included; (3) keywords and MeSH terms had to be provided; (4) if feasible, a search strategy had to be included; and (5) the search had to be supplemented with additional material.

d (1) Authors should have searched for studies regardless of publication status and; (2) noted any exclusions based on publication and language.

e Authors should have a list of included and excluded studies.

f Included studies should be displayed in an aggregated table.

g Assessing the scientific quality of included studies should be done.

h Results from assessing the scientific quality of included studies should be used in conclusions and recommendations.

i If results were pooled, then specific statistical tests (Cochrane’s Q, I², etc) should have been done to ensure the appropriate statistical model (fixed effects, random effects, etc) was used for combining data.

j Assessing the presence of publication bias should have been done either through graphical aids (funnel plot) or statistical tests (Egger’s, Begg’s).

k Conflicts of interest should be provided. l AMSTAR classification system used by Canadian Agency for Drugs and Technologies in Health (CADTH): 0-3 (Low), 4-7 (Moderate); 8-11 (High) (Grimshaw *et al.*, 2011)

6.2. Qualitative Summaries and Results from AMSTAR Quality Assessment

A total of 7 existing SRs and MAs were identified as relevant and were included for analysis. All reviews were of medium and low quality and had failed to satisfy at least eight out of eleven AMSTAR criteria **See Table 6**. Five reviews on mobile phone use had AMSTAR quality scores ranging from 3-7 (26, 87, 92-94). One smoking review had a score of 5(95) and another diet review had a score of 4 (96).

6.2.1. Mobile Phone Use

Excluding the review conducted by Myung *et al.*, (93) (since the authors did not identify the studies and their estimates within the text, and had simply provided the total number of studies which were used to pool), the total number of individual observational studies included in the remaining four mobile phone use reviews was twenty-nine, and after removing duplicate studies, the total was nineteen.

Lahkola et al., (2006):

Qualitative Summary: The earliest review identified through the systematic search was conducted by Lahkola *et al.*,(92) in 2006. The authors had conducted a SR and MA to determine whether there was an association between mobile phone use (up to five years) and glioma/meningioma. At the review level, mobile phone use was defined as use up to five years; however, there was no indication of frequency. At the review level, a classification system for defining glioma and meningioma, was also not addressed. A comprehensive search strategy with Boolean operators (AND/OR) was not provided; however, they did provide keywords used to search the PubMed database. Bibliographies of included studies were searched, and explicit inclusion criteria were applied.

A total of nine odds estimates were pooled using the random effects model for glioma, and a total of eight odds estimates were pooled using the fixed effects model for meningioma. Among mobile phone users, there was a 4% decrease in odds, OR 0.96 (0.78-1.18) and a 13% decrease in odds, OR 0.87 (0.72-1.05) for glioma and meningioma, respectively. Based on the funnel plot provided, the review was free from publication bias.

Overall, the review had concluded that mobile phone use up to five years did not increase the risk for glioma or meningioma.

Limitations noted at the individual study level included recall bias regarding exposure ascertainment and the inability to assess long term use greater than ten years. Limitations at the review level included the introduction of bias from pooling heterogeneous observational studies which differ in exposure definitions, populations and methods. Another limitation was the pooling of studies which did not uniformly control for the same confounding variables and the lack of quality assessment of included studies.

Quality Assessment: This review was considered moderate quality as it had satisfied five out of eleven AMSTAR criteria. The grey literature was searched. The characteristics of included studies were presented in a transparent table. The Cochrane's Q test of homogeneity was conducted to ensure appropriate statistical models (fixed or random effects) were used to pool the data. The presence of publication bias was assessed using graphical inverted funnel plots, and although a tool was not used to assess the scientific quality of each included study, the authors did discuss broad methodological limitations upon formulating conclusions and recommendations.

There were, however, plenty of unfulfilled AMSTAR criteria. There was no mention of an a priori protocol. There were two independent reviewers for data extraction but not for screening and there was no mention of a consensus procedure for disagreements. A comprehensive literature search was not performed as only one bibliographic database was searched. A list of excluded studies was neither provided nor mentioned within the manuscript or an external appendix. The scientific quality of included studies was not assessed, and any potential conflicts of interests were not disclosed.

Kan et al., (2008):

Qualitative Summary: The authors had conducted a SR and MA in an attempt to quantify the association between cellular phone use and certain sub-types of brain tumours. It was assumed based on further scrutiny at the review level that "cellular phone use" was considered "regular use". There was a failure at the review level to define what "regular use" was being compared to. It could have been no use, light use or heavy use. At the individual

study level, it was ensured that each study had defined what “regular use” meant. As a result, some studies had similar exposure definitions for “regular use”, and others had quite different definitions. At the review level, a classification system for defining high grade glioma, low grade glioma and meningioma was also not addressed. A comprehensive search strategy with Boolean operators (AND/OR) was not provided; however, they did provide keywords used to search the Medline database. Bibliographies of included studies were searched, and explicit inclusion/exclusion criteria were applied to all identified studies. The authors had conducted Cochrane’s Q test for homogeneity, and although some sub-types were homogeneous, a random effects model was used for all pooled analyses since variability is taken into account, which is inevitably present within the data.

Although the authors had provided separate pooled estimates for glioma and meningioma within their MA, they had presented odds estimates of aggregated brain tumour sub-types. Three case-control studies focused on both glioma and meningioma together and had sample sizes ranging from 1,249 to 2,241. All three had reported a negative association, with two estimates being statistically significant, and one being not statistically significant.

Regarding “regular” cellular phone users, a total of five odds estimates were pooled for high-grade glioma resulting in a 14% decrease in odds, OR 0.86 (0.70-1.05), and a total of five odds estimates were pooled for low-grade glioma resulting in a 14% increase in odds, OR 1.14 (0.91-1.43), respectively.

Regarding “regular” cellular phone users, a total of five odds estimates were pooled for meningioma resulting in a 36% decrease in odds, OR 0.64 (0.56-0.74). According to the Egger’s and Begg’s statistical tests, the review was free from publication bias. Overall, the review had concluded that there was no overall increase in risk for glioma and meningioma amongst cellular phone users.

Limitations noted at the study level included information/recall bias from obtaining exposures from individual participants. Limitations noted at the review level by the authors include the reviews inability to control for all confounding variables uniformly. As noted above, however, there were many other limitations which the authors had failed to address, such as the variation in definitions of “regular cell phone use” among the studies and what “regular cell phone use” was being compared to.

Quality Assessment: This review was considered moderate quality as it had satisfied four out of eleven AMSTAR criteria. Characteristics of included studies were provided in a transparent table. Appropriate methods were used to pool data as tests for heterogeneity were considered and proper models were used. Publication bias was addressed, and although a tool was not used to assess the scientific quality of each included study, the authors did discuss broad methodological limitations upon formulating conclusions and recommendations.

The following criteria, however, were unfulfilled. There was no mention of an a priori protocol. Duplicate screening and extraction were not addressed. A comprehensive literature search was not done as only one bibliographic database was searched. Grey literature was not searched, and a list of excluded studies was not provided. A tool was not used to assess the scientific quality of included studies and conflicts of interests were not disclosed.

Khurana et al., (2009):

Qualitative Summary: The authors had conducted a SR and MA to determine whether there was an association between laterality (ipsilateral compared to contralateral) of long-term cell phone use and glioma/meningioma. At the review level, long-term use was defined as ≥ 10 years; however, its frequency was not discussed. At the review level, the use of a classification system for defining the glioma and meningioma, was also not addressed. A comprehensive search strategy with Boolean operators (AND/OR) was not provided; however, they did provide the keywords used to search the PubMed database. Additional supplementary materials were not considered. The review had explicit inclusion criteria and ensured that all studies had a ≥ 10 year latency period and also had information on laterality. The eleven relevant studies fell into two main categories. They were either part of the Swedish Hardell Studies or the European INTERPHONE studies. The authors did however ensure that there was no overlap amongst patients for each of the eleven studies. A fixed effects model was used to pool the data, although a heterogeneity test was not done to determine whether this model was appropriate.

There were a total of six case-control studies which focused on glioma. Two studies had produced positive odds estimates, although they were both not statistically significant. One study had produced a null odds estimate. Three studies had produced protective odds

estimates which were all not statistically significant. There were a total of five case-control studies which focused on meningioma. Two studies had produced positive odds estimates. Both again, lacked statistical significance. One study had produced a null odds estimate. Two studies had produced statistically non-significant protective odds estimates.

A total of six odds estimates were pooled for the overall effect of long-term use on glioma, resulting in a 30% increase in odds, OR 1.3 (1.1-1.6). A total of four odds estimates were pooled for the effects of both long-term ipsilateral and contralateral use on glioma, resulting in a 90% and 20% increase in odds, respectively, OR 1.90 (1.4-2.4) and OR 1.20 (0.90-1.27). A total of five odds estimates were pooled for overall effect of long-term use on meningioma, resulting in a 10% increase in odds, OR 1.1 (0.8-1.4). A total of three odds estimates were pooled for the effects of both long-term ipsilateral and contralateral use on meningioma, resulting in a 30% and 20% decrease in odds, respectively, OR 1.3(0.9-1.8), OR 0.80 (0.5-1.3).

The presence of publication bias was unknown as the authors had failed to address it. Overall, the review had concluded that there was a statistically significant increase in risk for glioma, and not meningioma, among ipsilateral long-term users of cell phones (≥ 10 years).

Limitations noted at the study level were mostly directed at the INTERPHONE studies. Recall bias as a result of obtaining information through questionnaires and surveys was a major issue. Underestimation of true risk was likely as the study populations (cases and controls) were very small. Exposure comparisons were misrepresentative as: (1) Never users and non-regular users referred to as reference could still have been exposed, since cordless phone use was not adjusted for; (2) In laterality analysis, when ipsilateral use was considered, users with contralateral tumour prevalence were considered non-exposed and vice-versa. The definition of “regular” phone user (at least 1/week for more than 6 months) was insufficient and should have been defined as “light” user. Limitations noted at the review level include the authors’ inability to assess homogeneity of data across all participating INTERPHONE countries due to missing information. A major strength at the review as stated by the authors was its inclusion of two Hardell studies, in which Kan *et al.*,(87) had excluded.

Quality Assessment: This review was considered low quality as it had satisfied three out of eleven AMSTAR criteria. Characteristics of included studies were presented in a transparent

table, sources of conflict of interests were disclosed, and although a tool was not used to assess the scientific quality of each included study, the authors did discuss broad methodological limitations upon formulating conclusions and recommendations.

The following criteria, however, were unfulfilled. There was no mention of an a priori protocol. Duplicate screening and extraction were not addressed. A comprehensive literature search was not done as only one bibliographic database was searched and supplementary materials were not considered. Grey literature was not searched, and a list of excluded studies was not provided. A tool was not used to assess the scientific quality of included studies and methods used to pool data were not previously supported since tests of heterogeneity were not conducted.

Myung et al., (2009):

Qualitative Summary: The authors had conducted a SR and MA to determine whether there was an association between mobile phone use and generalized tumours. The sub-group analysis for glioma/meningioma will be the focus of this summary. Mobile phone use at the review level was defined as “use” compared to “never use” or “rare use”. However, the definitions for the exposure categories were not further defined. At the review level, the use of a classification system for defining the outcomes of interest, glioma and meningioma, was also not addressed. A comprehensive search strategy with Boolean operators (AND/OR) linking was not provided; however the keywords used to search the three databases were provided. Additional supplementary sources were considered, and explicit inclusion criteria were presented. Based on I^2 tests for heterogeneity, either fixed effects or random effects models were used to pool the data.

It is difficult to provide the proportion of studies which have indicated a positive or negative association as the authors had not provided individual study sample sizes and odds estimates. The authors simply provided the pooled estimates.

Overall, for glioma, ten odds estimates were pooled using a random effects model, resulting in a 9% increase in odds due to exposure, OR 1.09 (0.89-1.34). When stratifying within this category: three odds estimates using a random effects model were pooled for the Hardell studies, four odds estimates using a fixed effects model were pooled for the INTERPHONE studies, and three additional odds estimates using a random effects model

were pooled for the “Other Studies”. As a result, there was a 37% increase, OR 1.37 (0.88-2.12), 16% decrease, OR 0.84 (0.75-0.96), and 6% increase, OR 1.06(0.76-1.48) in odds due to exposure, respectively.

Overall, for meningioma, nine odds estimates were pooled using a fixed effects model, resulting in a 17% decrease in odds due to exposure, OR 0.83 (0.75-0.92). When stratifying within this category: four odds estimates using a fixed effects model were pooled for the INTERPHONE studies, and five additional odds estimates using a fixed effects model were pooled for the “Other Studies”. As a result, there was a 23 % decrease, OR 0.77 (0.68-0.88), and 5% decrease, OR 0.95 (0.80-1.13) in odds due to exposure, respectively.

The presence of publication bias for studies included in the analysis of overall generalized tumour risk was assessed using funnel plots and Egger’s test and its absence was noted. Overall, the review had concluded that there was a protective effect observed for meningioma, which was mainly due to INTERPHONE’s decreased risk estimate, and that there was slight increase in risk for glioma, although statistical insignificance has inhibited any concrete conclusions.

Limitations noted at the study level, include recall bias, selection bias, and random errors within INTERPHONE, which prevented the detection of a positive risk estimate. Limitations noted at the review level, include the pooling of case-control studies which are not considered the highest level of evidence, and the study’s inability to control for confounding variables in the Hardell studies.

Quality Assessment: This review was considered moderate quality as it had satisfied seven out of eleven AMSTAR criteria. A comprehensive search strategy was performed since three databases were searched, with years considered, keywords provided, and supplementary materials were sought. Characteristics of included studies were presented in a transparent table, the Newcastle-Ottawa Scale was used to quality assess the methodological quality of included studies, and appropriate recommendations and conclusions were provided from this analysis. I^2 was calculated to determine the appropriate statistical model which would be used to pool data. The likelihood of publication bias was assessed for overall generalized tumour risk through funnel plots and statistical tests, and sources of conflicts were disclosed.

The following criteria, however, were unfulfilled. An a priori protocol was not provided and the grey literature was not searched. Lists of excluded studies were omitted and duplicate screening, but not extraction, were in place.

Repacholi et al., (2011):

Qualitative Summary:

The authors had conducted a SR and MA to determine whether there was an association between wireless phone use and glioma/meningioma. Wireless phone use at the review level was divided into three exposure categories: (a) an “ever user” was defined as ever having used a cell phone for at least 1 call/week for >6 months; (b) a “short term user” was defined as ever having used a cell phone for at least 1 call/week for >6 months for 1-6 years; (c) a “long term user” was defined as initiation of cell phone use ≥ 10 years ago. At the review level, the use of a classification system for defining the outcomes of interest, glioma and meningioma, was not addressed. A comprehensive search strategy with Boolean operators (AND/OR) was not provided; however keyword used to search the four databases were presented. Additional supplementary sources were not considered, and the inclusion criteria which was presented in the external appendix, was not relatively explicit. Although the authors had completed I^2 tests for heterogeneity, they still used random effects model to pool all data as often times they were heterogeneous.

For glioma, in regards to the analysis looking at “ever users” a total of eight studies were considered. Four studies had noted a positive association, with two resulting in non-significance, one being marginally significant, and the other being statistically significant. Three studies had noted a negative association, which had failed to reach statistical significance. One study had concluded null results. For the analysis looking at “long term use”, a total of five studies were considered. Three studies resulted in a positive association with two being statistically significant. Two studies reported a negative association, with one being statistically significant. For the analysis looking at “short term use”, a total of eight studies were considered. Four studies reported a positive association with three failing to reach statistical significance. Three studies reported a negative association with two failing to reach statistical significance. One study had reported null findings. For meningioma, in regards to the analysis looking at “ever users” a total of six studies were considered. Three

studies reported a positive association with two being non-statistically significant, and one being marginally significant. Three studies reported a negative association with one being statistically significant. For the analysis looking at “long term use”, a total of two studies were considered. One study reported a statistically significant positive association, and the other reported a negative association which lacked significance. For the analysis looking at the “short term use”, a total of four studies were considered. Two studies reported a positive association with both being statistically significant. The remaining two studies had reported a negative association, with one being significant and the other being non-significant.

A total of eight odds estimates were pooled for “ever use” and glioma, resulting in a 7% increase in odds due to exposure, OR 1.07 (0.89-1.29). A total of eight odds estimates were pooled for “short term use” and glioma, resulting in a 3% increase in odds due to exposure, OR 1.03 (0.86-1.24). A total of five odds estimates were pooled for “long term use” and glioma, resulting in a 40% increase in odds due to exposure, OR 1.40 (0.84-2.31).

A total of six odds estimates were pooled for “ever use” and meningioma, resulting in a 7% decrease in odds due to exposure, OR 0.93 (0.77-1.12). A total of four odds estimates were pooled for “short term use” and meningioma, resulting in an 18% decrease in odds due to exposure, OR 0.82 (0.72-0.94). A total of two odds estimates were pooled for “long term use” and meningioma, resulting in a 25% increase in odds due to exposure, OR 1.25 (0.51-3.10). The authors did not test for publication bias, and thus, its presence is unknown. Overall, the review had concluded that the association between wireless phone use and glioma/meningioma were inconclusive, which is likely due to the confidence intervals crossing the point of unity.

Limitations noted at the individual study level included recall bias, selection bias, lack of data on long term use and the possibility of information bias through misclassification of exposure. For the INTERPHONE study, specifically, the preventative risk estimates were most likely due to a lower participatory rate of non users amongst controls compared to cases. At the review level, pooling multiple risk estimates does not eliminate the inherent biases present within each study. As noted at the critical review stage, a major strength of the SR and MA was its ability to define at the review level, the exposure categories and their definitions followed by their subsequent comparisons.

Quality Assessment: This review was considered moderate quality as it had satisfied five out of eleven AMSTAR criteria. An a priori protocol was provided in an external appendix. Within this systematic overview, this has been the only SR and MA on mobile phone use which has addressed the presence of an a priori protocol, and has noted its importance in providing unbiased transparency for research objectives and methodologies. The authors had used their own quality assessment tool whereby weights were assigned. These results were used to discuss broad methodological limitations when formulating conclusions and recommendations. Appropriate models were used to pool data based on tests for heterogeneity and sources of conflict of interests were disclosed.

The following criteria, however, were unfulfilled. It was not explicitly stated whether there was duplicate screening and extraction. A comprehensive search was not performed as extra supplementary sources were not considered and the grey literature was not searched. A list of excluded studies was not presented and neither was a table of characteristics of included studies. Publication bias was also not addressed.

6.2.2. Smoking

Since there was only one relevant smoking review, a total of seventeen individual observational studies were assessed.

Mandelzweig *et al.* (2009):

Qualitative Summary: The authors had conducted a SR and MA to determine whether there was an association between smoking and glioma. At the review level, the primary exposure was defined as “ever” versus “never” smoking. Secondary exposures were defined as “current” versus “never” smoking and “past” versus “never” smoking. Nevertheless, further definitions to explain these exposure categories were not further elaborated on. At the review level, the use of a classification system for defining glioma within the review was also not addressed; however, they did include studies which had a medical confirmation.

A comprehensive search strategy with Boolean operators (AND/OR) was not provided; however, they did provide keywords used to search the Medline databases and bibliographies of included studies were searched. Explicit inclusion criteria were presented. Cochrane’s Q test for homogeneity was conducted, and both fixed and random effects models were used. However, the authors had only presented results from the random effects

methods, since variability is taken into account, which is inevitably present within these types of studies.

Out of the eleven included case-control studies, six studies with sample sizes ranging from 145 to 864 had derived positive odds estimates; however none were statistically significant as their 95% confidence intervals had all crossed the null value of 0. Four studies with sample sizes ranging from 404 to 2,809 had derived negative odds estimates; however, they as well, were not statistically significant. One study with a sample size of 818 had calculated separate odds estimates for each sex, with a positive association for men and a negative association for females, although both were not significant.

Out of the six included cohort studies, five studies with sample sizes ranging from 89,826 to 1,177,705 had concluded that there was a positive association. Even though a large proportion of cohort studies had conclude that there was increased risk associated with smoking, they all lacked statistical significance as they all crossed the point of unity. The single cohort study which had derived a protective risk estimate had a sample size of 34,018; however, its estimate was also non-significant.

Seventeen estimates were pooled for “ever” use compared to “never” use for glioma, resulting in a 10% increase in risk within cohort studies, RR 1.10 (1.01-1.20), and a null effect within case-control studies RR 1.00 (0.88-1.15). When both study designs were pooled together, there was a 6% increase in risk for glioma, RR 1.06 (0.97-1.15). Ten estimates were pooled for “current” use compared to “never” use for glioma, resulting in a 7% increase in risk within cohort studies, RR 1.07 (0.92-1.24), and a 12% decrease in risk within case-control studies RR 0.88 (0.73-1.07). Nine estimates were pooled for “past” use compared to “never” use for glioma, resulting in a 16% increase in risk within cohort studies, RR 1.16 (1.05-1.29), and a 10% decrease in risk within case-control studies, RR 0.90 (0.73-1.11). When both study designs were pooled together, there was a 10% increase in risk for glioma, RR 1.10 (0.99-1.22).

Dose-response analyses had concluded that there was a 1% increase in risk for glioma for each additional 10 years of smoking, RR 1.10 (0.94-1.08). There was a 2% increase in risk for glioma for each additional 10 cigarettes smoked per day, RR 1.02 (0.96-1.08) and a null effect for glioma for each additional 10 pack years, RR 1.00 (0.96-1.04). According to the Egger’s and Begg’s statistical tests, the review was free from publication bias. Overall the

authors had concluded that there was no association between smoking and glioma; however they wanted to direct attention to the statistically significant association between “ever” smoker and “past” smoker compared to “never” smoker within cohort studies.

Limitations noted at the study level include the issue of reverse causation. It is quite possible, that those who were diagnosed with glioma began to smoke instead of smoking preceding glioma. Although one can ask if the exposure came first during the interview, one cannot be entirely confident. Survival bias could have been present, since smoking is generally initiated in early adulthood and for two main cohort studies, the mean age at the start of recruitment was 56 years. Thus, those who started smoking early, and developed glioma within a 10-20 year span, would have been missed from being included in possible studies. Proxies were used for some studies, and as such recall bias could have been present. Further exploration of type of cigarettes on glioma risk, such as filtered compared to non-filtered was not addressed.

Limitations noted at the review level include the pooling of studies which have heterogeneous exposures, definitions and procedures. Among the pooled studies, different confounding variables were controlled. Two included studies used death certificate data instead of incident cases, and the use of “ever” use versus “never” use is an uninformative variable; however, it seems like the mostly commonly used dichotomous option used within studies.

Quality Assessment: This review was considered moderate quality as it had satisfied five out of eleven AMSTAR criteria. A list of included studies was provided in a table, and a list of excluded articles was referred to in-text. The characteristics of included studies were presented in a transparent table. The Cochrane’s Q test of homogeneity was conducted; however a random effects model was used since it provided more conservative estimates. The presence of publication bias was assessed using statistical tests, and although a tool was not used to assess the scientific quality of each included study, the authors did discuss broad methodological limitations upon formulating conclusions and recommendations.

There were, however, plenty of unfulfilled AMSTAR criteria. There was no mention of an a priori protocol. Duplicate screening and extraction was not discussed. A comprehensive literature search was not performed as only one bibliographic database was

searched. The grey literature was not searched. The scientific quality of included studies was not assessed, and any potential conflicts of interests were not discussed.

6.2.3. Diet

With only one relevant diet review, a total of nine individual observational studies were assessed.

Huncharek *et al.* (2003):

Qualitative Summary: The authors had conducted a SR and MA to determine whether there was an association between dietary intake of *N*-Nitroso compounds (NOC) and glioma. A previous review had concluded that maternal intake of NOCs was associated with childhood brain tumours, and the authors wanted to determine whether this association was true for the adult population through individual ingestion. At the review level, dietary intake of NOCs use was not explicitly defined. The authors had simply divided intake into “high” compared to “low” intake. The authors had noted this limitation and had discussed that it was not possible to quantify the exposure categories since the studies themselves often did not do so. The use of a classification system for defining the outcome of interest, glioma, within the review was also not addressed.

A comprehensive search strategy with Boolean operators (AND/OR) was not provided; however, they did provide keywords used to search four databases and bibliographies of included studies were considered. The authors also provided explicit inclusion/exclusion criteria. A Cochrane’s Q test for homogeneity was calculated to determine whether the estimates were similar enough to pool, and subsequent aggregation of data was done through a variance based method using 95% confidence intervals.

Out of the nine case-control studies, four studies had derived positive odds estimates. Boeing *et al.*, (97) had achieved statistical significance with their estimate and Lee *et al.*, (98) had achieved statistical significance with the estimate for their male sample. The remaining odds estimates lacked statistical significance. One study had concluded no association with a null estimate. Another study had concluded a negative association with NOC, and a positive association with any type of cured meat intake. Both estimates lacked statistical significance. Two other studies had provided separate odds estimates for different types of NOC containing meats.

A total of six odds estimates were pooled for “high” compared to “low” overall NOC intake for glioma, resulting in a 48% increase in risk due to exposure, RR 1.48 (1.20-1.93). A total of five odds estimates were pooled for “high” compared to “low” hot dog intake for glioma, resulting in a 10% decrease in risk due to exposure, RR 0.90 (0.63-1.25). A total of six odds estimates were pooled for “high” compared to “low” bacon intake for glioma, resulting in a 31% increase in risk due to exposure, RR 1.31 (1.00-1.71). A total of four odds estimates were pooled for “high” compared to “low” ham intake for glioma, resulting in a 64% increase in risk due to exposure, RR 1.64 (1.27-2.14). The authors did not test for publication bias, and thus, its presence is unknown. Overall, the review had concluded that there is a statistically significant increase in glioma risk among individuals who ingest high levels of NOCs; however, several limitations question its accuracy.

Limitations noted at the study level include decreased statistical power to detect an effect due to small number of patients who are enrolled in each study, the failure of multiple studies which did not quantitatively define their exposure categories and recall bias due to case-control designs which inevitably leads to misclassification bias. Another limitation was the failure of studies to control for total energy intake as an important confounder. The authors had recalculated the pooled estimates by withdrawing the only study (Kaplan *et al.*, (99)) which controlled for this variable, and the pooled estimates increased significantly. This signified total energy intake as an important confounding variable, and without controlling for it, spurious high estimates are derived.

Limitations noted at the review level, and also applicable to other reviews in this area, include the vague exposure classification of “high” versus “low” intake as a direct result of the uninformative exposures within individual studies. There was also limited information available to conduct a dose-response analysis. As well, glioma, itself, is quite heterogeneous, and it would have been more informative if the authors were able to stratify into sub-types such as oligodendroglioma and glioblastoma.

Quality Assessment: This review was considered moderate quality as it had satisfied four out of eleven AMSTAR criteria. A comprehensive search strategy was conducted since four databases were searched, years of search considered and keywords were provided. Additional supplementary materials were also searched. A list of included and excluded studies was

presented, and the characteristics of included studies were presented in a transparent table. Although a tool was not used to assess the scientific quality of each included study, the authors did discuss broad methodological limitations upon formulating conclusions and recommendations.

The following criteria, however, were unfulfilled. The presence of an a priori protocol was mentioned; however, upon follow up to the reference provided, it was simply a book describing methods for SRs and MAs which were not specific to the authors' study. Although there was mention of two reviewers for duplicate extraction, there was only one reviewer for the screening process. The grey literature was not searched, a quality assessment tool was not considered and publication bias was not assessed. It is not clear whether appropriate methods were used to pool the data, since although they did assess heterogeneity, a variance-based method was used, which is uncommon since either a fixed or random effects is routinely used. Sources of conflict of interest were also not disclosed.

6.3. Subsequent Actions Based on Results from Phase 1

As discussed in the methods portion of the thesis (**Section 5**), only reviews deemed of high quality (8-11) by the AMSTAR quality assessment scoring tool would be subjected to an update. An update consists of identifying new evidence available since the last literature search of the high quality review. For mobile phone use, four reviews were considered moderate quality, and one review was considered low quality. Since there were considerable methodological flaws in all four reviews, a *de-novo* synthesis was needed to provide the most current, best-evidence regarding the association between mobile phone use and glioma/meningioma.

The smoking and diet reviews were both also considered moderate quality, and needed to be subjected to *de-novo* processes; however, only a *de-novo* review was conducted for smoking for this thesis due to lack of resources.

7.0 SMOKING (PHASE 2: Update or De-novo Synthesis)

7.1. Brief Background/ Issues and Basis for Study Development

The association between smoking and glioma and/or meningioma may be plausible as result of NOC exposure. NOCs are found within cigarettes and these compounds are generally considered carcinogenic (100). Using animal models within controlled laboratory settings, researchers who have injected NOCs intravenously into rats and have observed brain tumour formation(100, 101). As such, researchers were unsure as to whether cigarette exposure to NOCs would have the same effect on brain tumour formation in humans. Since smoking is known to cause neoplasms elsewhere in the body, such as the lungs, it is hypothesized that cigarette smoking will have similar effects on the brain(102).

As indicated in Phase 1, the only available SR and MA on smoking and onset of brain tumours published before December 31, 2011 was conducted by Mandelzweig *et al.*, (95). With an AMSTAR score of 5 (moderate methodological quality) it was considered eligible to be subjected to *de-novo* processes. The purpose of this current review is to address certain aspects within AMSTAR which Mandelzweig and colleagues had failed to address. As a result, certain conclusions from the review in question may differ. Mandelzweig *et al.*,(95) had also looked at glioma specifically; our aim is to also include meningioma as a primary outcome and to assess the effects of passive smoking as well. An a priori protocol was already developed and can be found in **Appendix F**.

7.2. Research Question and Objectives

Components of the intended research question were constructed within a PICO framework.

- **Population:** Adults (≥ 18 years old, males and females)
- **Intervention/Exposure:** Tobacco smoking as risk factor (Active, Passive)
- **Comparator:** N/A
- **Outcomes:** Glioma sub-types (astrocytoma, glioblastoma, oligoastrocytoma, oligodendroglioma, ependymoma) and meningioma
- **Study Designs:** Case-control and cohort studies.

Research Question: Based on available case-control and cohort studies, is tobacco smoking (active/passive) associated with adult onset of glioma sub-types (astrocytoma, glioblastoma, oligoastrocytoma, oligodendroglioma, ependymoma) and/or meningioma?

Objectives:

- To identify relevant observational studies (case-control and cohort) focusing on the effects of tobacco smoking and the onset of glioma and/or meningioma in an attempt to provide an overall conclusion regarding this association.
- If permissible (at least three study estimates), to conduct a MA on relevant studies (with data pertaining to Never vs. Ever Smoker, Never vs. Current Smoker and Never vs. Past Smoker).
- To provide a current-up to date, high methodological quality SR and MA on the association between smoking and glioma/meningioma, as dictated by AMSTAR criteria, to be used by health policy makers and relevant stakeholders.

7.3. Literature Search Strategy

With the guidance of a health information specialist at the University of Ottawa, search strategies were developed and tailored for the following bibliographic databases: PubMed, Medline, Embase, CINAHL and PsycINFO (**Appendix G**). AARP Ageline and TOXLINE were excluded as they were deemed irrelevant based on the searches conducted in Phase 1. Grey Literature sources, such as ProQuest Dissertation and Thesis Database, as well as Google and Google Scholar were searched. “Other sources” of literature were also considered. Bibliographies of included studies were searched, studies included in previous reviews were considered and hand-searching of disease-specific journals, such as Cancer Causes and Control and the International Journal of Cancer was completed as well.

All search strategies generally followed the same template. The following concept groups: Disease terms, risk terms, smoking terms, and a filter for identifying observational studies were all combined with the Boolean operator AND. Search terms within each concept group were combined the Boolean operator OR. Searches were conducted to include all published relevant articles up to December 31, 2011.

7.4. A Priori Selection Criteria

Studies were included if they had satisfied all of the following inclusion criteria:

- Studies focused on the onset on at least one of the following brain tumours: glioma, astrocytoma, oligodendroglioma, oligoastrocytoma, ependymoma, glioblastoma, meningioma
- Studies focused on smoking (tobacco-either active or passive) as exposure and provided risk estimates with 95% confidence intervals.
- Smoking was the main exposure variable, and was not combined with another exposure variable as part of an interaction term.
- Studies had to be of either case-control or cohort study design.
- Studies had to be published in English or French.
- Full-text of studies had to be retrievable.
- Studies had to be published before December 31, 2011.

Studies were excluded if they had satisfied at least one of the following exclusion criteria:

- Studies focused on childhood primary brain tumours.

7.5. Study Selection Method

After the removal of duplicates, identified studies were subjected to two levels of screening (title/abstract and full text) using the same screening questions for each level within Distiller SR (Evidence Partners, Ottawa, Canada) (**Appendix H**). A method known as “liberal accelerated” screening was used whereby only one reviewer’s input was needed to advance an article to the next level; however decisions from two reviewers were needed to exclude an article. The first reviewer (PQ) screened 100% of the articles, and the second reviewer (RES) duplicate screened the excluded articles identified by the first reviewer. Conflicts were resolved by consensus and a kappa statistic was determined for the strength of agreement for excluded studies between the two reviewers.

7.6. Data Extraction Method

Studies which satisfied the a priori selection criteria were subjected to the data extraction process. Information on study characteristics, participants, exposures, outcomes and results were recorded (**Appendix I**). The first reviewer extracted data from all relevant studies, and the second reviewer (MA) duplicate extracted a random 25%.

7.7. Study Quality Assessment

As recommended by the Cochrane Collaboration, quality assessment of observational studies were completed by using the NOS(57, 74). NOS was chosen since: it was widely

used for quality assessing observational studies, was quick to implement, and it had established face and content validity, along with inter-rater reliability(57, 74). Methodological issues between cohort and case control studies were evident, and the NOS accounted for such differences by subjecting both types of studies to different scales. The following components were addressed for both scales: selection (4 stars), comparability (2 stars) and ascertainment of exposure/outcome of interest (3 stars). The maximum score on this scale was nine stars(57, 75).

Although standard scoring thresholds had yet to be determined, many studies had consistently used the threshold of ≥ 5 stars and <5 stars to represent studies of high and low quality(76-80).

7.8. Statistical Analysis

Quantitative summaries were considered for the following analyses: (a) never vs. ever smoker; (b) never, vs. current smoker; and (c) never vs. past smoker.

Ever, current and past categories were chosen since they had relatively broad definitions and were used by most of the included studies. A MA was attempted if there were greater than three relevant studies per analysis and if heterogeneity tests determined that the pooling of numerous risk estimates was appropriate. Analysis was analyzed by cohort and case-control estimates separately.

Degree of heterogeneity was determined by conducting the following statistical tests, Cochrane's Q and I^2 (81). As outlined in the Cochrane Collaboration, I^2 percentages between 0%-40%, 30%-60%, 50%-90%, 75%-100% represents unimportant, moderate, substantial, and considerable heterogeneity, respectively(82). Due to the low power of the Cochrane's Q test to detect true heterogeneity, the threshold for significance was increased to $p=0.1$, meaning any p -value ≤ 0.1 was considered statistically significant for heterogeneity and any p -value >0.1 was considered homogeneous(82, 83).

Random effects models based on the DerSimonian and Laird Method (DLM), a variation of the inverse variance method was used to pool estimates together as opposed to using the fixed effects models(82, 84). Since variability is always present, random effects modeling generates more conservative estimates for determining significance by producing

wider confidence intervals, allowing one to be more cautious in their conclusions. The standard errors and the log risk or odds ratios of eligible point estimates were inputted into REVMAN, resulting in pooled adjusted point estimates(84). If sufficient data existed, subgroup analyses based sex and histological sub-type were attempted. Publication bias was assessed for symmetry through inverted funnel plots generated by REVMAN.

7.9. Results

Bibliographic database searching resulted in the identification of 378 potentially relevant articles. 31 additional articles were identified through searching other sources, such as grey literature, disease specific journals and studies included in existing reviews. Thus, a total of 409 potentially relevant articles were imported into Distiller SR (Evidence Partners, Ottawa, Canada). After the removal of duplicates, a total of 286 were subjected to Level 1 screening for relevancy based on title and abstract. No articles were in conflict. The kappa statistic for level of agreement based on the 242 excluded was 0.40, which represented moderate agreement(66). 44 studies had satisfied Level 1 screening, and the full-text was retrieved for further scrutiny in Level 2 screening.

Forty-four full text articles were subjected to level 2 screening. The kappa statistic for level of agreement based on the 31 excluded articles for the two reviewers was 0.61, which represented substantial agreement(66). For the excluded articles with reasons at Level 2, see **Appendix J**.

The remaining 13 articles had satisfied the a priori inclusion/exclusion criteria and were subjected to 25% duplicate data extraction and quality assessment by the second reviewer (MA). Slight differences were noted in both extraction and quality assessment responses, and were promptly resolved by consensus.

Figure 3. PRISMA flow diagram of included/excluded studies

Source:

Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group. (2009). *Preferred Reporting Items for Systematic Review and Meta-Analyses: The PRISMA Statement*. PLoS Med 6(6): e1000097. Doi: 10.1371/journal.pmed1000097.

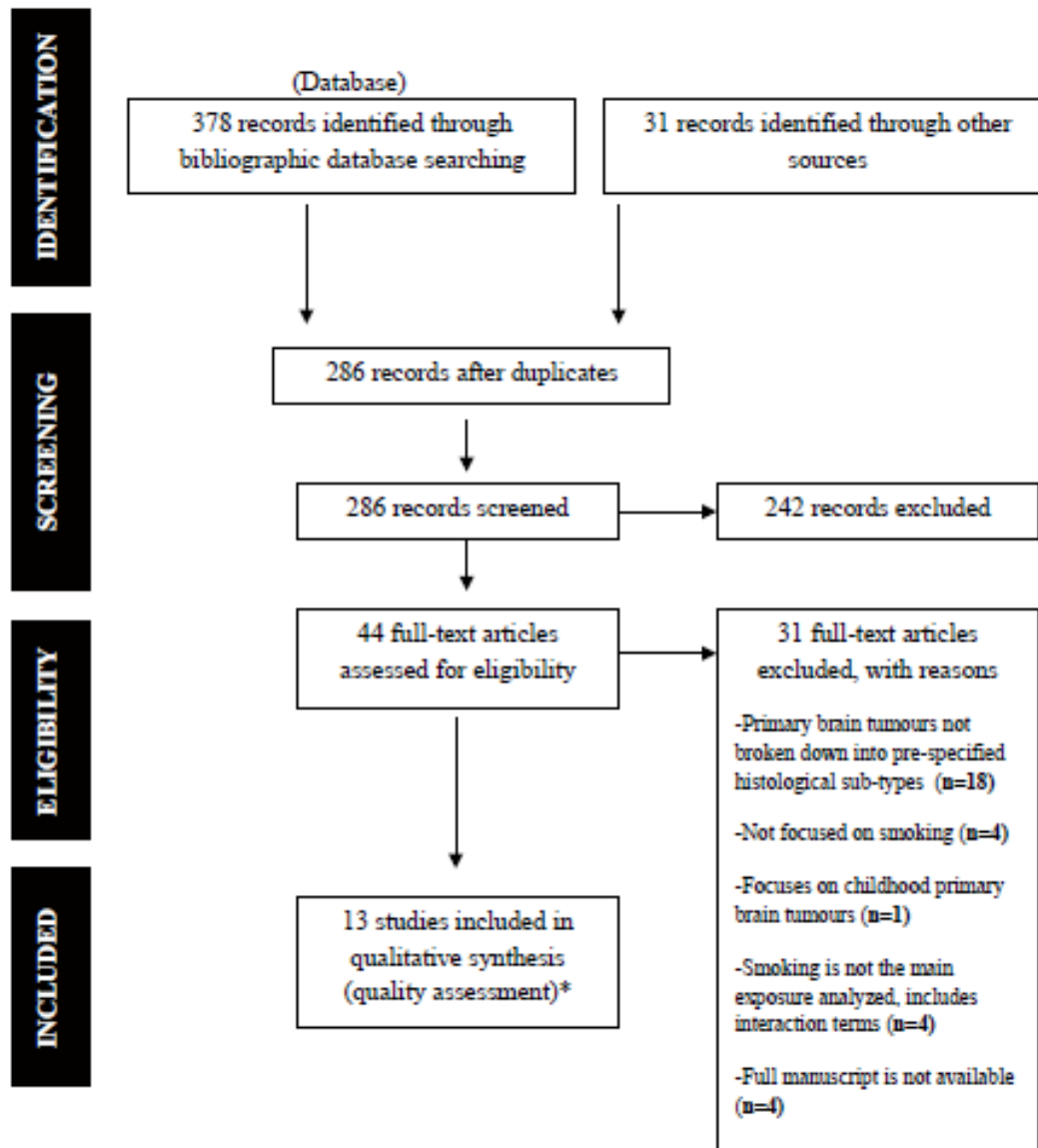


Table 7. Included Studies Identified for the Association between Smoking (Active/Passive) and Glioma and Meningioma

COHORT STUDIES								
Article , Location & NOS score	(1)Outcome; (2) Case ascertainment	Cohort Information	Sample Size	(1) Follow-up Period	(1) Age; (2) Sex	Confounding Variables	Risk Estimates (never smokers as reference)- Ever, Past, Current	Overall Conclusions
(Holick <i>et al.</i> , 2007); (USA) NOS: 8	(1) Glioma; (2) Confirmation through medical records. Did not provide ICD-O codes for glioma specifically, but did provide ICD-O codes for sub-type analysis. Even then, did not provide full results for sub-type analysis.	NHS -registered female nurses HPFS -male health professionals NHSII -registered female nurses	NHS (230/115,087), HPFS (110/46,327), NHSII (25/96,504)	(1) NHS-26 years, NHSII-14 years; total of 4,388,515 person years follow up for women. HPFS-16 years, total of 667,673 person years follow up for men.	(1) NHS-30 to 55 years. HPFS- 40 to 75 years. NHSII-20 to 42 years. (2) NHS & NHS II-female. HPFS-male	Age, total meat intake, alcohol, coffee consumption	#1: Males, Past, RR 1.57 (0.80-3.09) #2: Males, Current, RR 0.75 (0.29-1.93) #3: Women, Past, RR 1.30 (0.87-1.96) #4: Women, Current, RR 1.11 (0.78-1.58) #5: Both, Past, RR 1.37 (0.97-1.95) #6: Both, Current, RR 1.06 (0.76-1.47)	No association between smoking and glioma risk.
(Efird <i>et al.</i> , 2004) (USA) NOS: 6	(1)Malignant glioma; (2) ICD-O 938X/3-948X/3	Kaiser Permanente Medical Care Program of Northern California (KPMCP-NC)	(130/133,811)	(1) mean of 13.2 years \pm 6.7 SD	(1) \geq 25 years; (2) Male and Female	Age, sex, race, education, alcohol, coffee consumption , cigar and pipe smoking	#1: Both, Ever, RR 1.4 (1.0-2.1) #2:Both, Past, RR 1.3 (0.9-2.0) #3: Both, Current, RR 1.6 (1.0-2.5)	Women, not men who smoke have an increased risk for glioma.
(Silvera <i>et al.</i> , 2006) (Canada)	(1)Glioma; (2) ICD-M codes 9380/3-9473/3 and 9490/0-9506/0.	Canadian National Breast Screening Study	(117/89,709)	(1) mean of 16.4 years	(1) 40-59 years; (2) Females	Age, education, BMI, parity, Age at first live birth, age at menarche,	#1: Females, Ever, HR 1.30 (0.88-1.93) #2: Females, Past, HR 1.51 (0.97-2.34) #3: Females, Current, HR 1.05 (0.62-1.78)	Compared to never smokers, former smokers and not current smokers are

<i>NOS: 7</i>						menopausal status, study center and allocation group.		at an increased risk.
(Johnson <i>et al.</i> , 2011) (USA) <i>NOS: 6</i>	(1)Meningioma; (2) ICD-9th 192.1, 192.3, 225.2, 225.4, 237.6	Iowa Women's Health Study	(125/27,791)	(1)mean of 10.5 years, 291,021 person years follow-up	(1)55-69 years; (2) females	Age	#1: Females, Ever, RR 0.90 (0.60-1.33)	There is no association between smoking and meningioma
(Benson <i>et al.</i> , 2008) (UK) <i>NOS: 7</i>	(1)Glioma & Meningioma; (1) Glioma (ICD-O 9380-9481) & Meningioma (ICD-O 9530-9539)	Million Women Study	Glioma(646/1563), Meningioma(390/1563)	(1)Mean of 6.2 years	(1)50-65 years; (2) Females	Height, BMI, SES, alcohol intake, strenuous exercise, age at first birth, parity, OC use	#1: Females, Glioma, Past, RR 1.09 (0.91-1.31) #2: Females, Glioma, Current, RR 0.91 (0.73-1.15) #3: Females, Meningioma, Past, RR 0.86 (0.67-1.10) #4: Females, Meningioma, Current, RR 0.88 (0.66-1.16)	There is a lack of association between smoking and glioma/meningioma risk.
CASE-CONTROL STUDIES								
Article & Location	(1)Outcome; (2) Case ascertainment	Control Population	Sample Size	Response Rate	(1) Age; (2) Sex	Confounding Variables	Risk Estimates (compared to never smokers)	Overall Conclusions
(Zheng <i>et al.</i> , 2001) (USA)	(1)Glioma; (2) Histological confirmation	Population (driver's license)	(375/2434)	Cases (91%), Controls (82% <65 yr and 80% ≥64 yr)	(1)40-85 years; (2) Males and Females	Age, BMI, level of education, strenuous/moderate exercise, duration of living in a residence served by chlorinated surface	#1: Male, Ever, OR 0.9 (0.6-1.2) #2: Male, Past, OR 0.8 (0.5-1.1) #3: Male, Current, OR 1.0 (0.7-1.6) #4: Female, Ever, OR 0.8 (0.6-1.2) #5: Female, Past, OR 1.0 (0.6-1.6) #6: Female, Current, OR 0.7 (0.4-1.1)	Smoking is not associated with glioma.

NOS: 5						water, having a first degree relative with disease.		
(Hurley <i>et al.</i> , 1996) (Australia) NOS: 7	(1)Glioma; (2)ICD-O (938-946)	Population (electoral roll)	(416/422)	Cases (66% of eligible); Controls (43.5% of eligible)	(1)20-70yrs; (2) Males and Females	Age, gender, reference date	#1: Male, Ever, RR 1.64 (1.10-2.45) #2: Female, Ever, RR 0.99 (0.62-1.62) #3: Both, Ever, RR 1.29 (0.95-1.75)	There is no association between tobacco smoking and glioma risk
(Lee <i>et al.</i> , 1997) (USA) NOS: 6	(1)Glioma; (2) ICD-O codes 9380-9481	Population (random digit dialing)	(434/430)	Cases (82%), Controls (63%)	(1)≥20 yrs; (2) Males and Females	Age, education and income	#1: Men, Ever, OR 0.9 (0.5-1.5) #2: Women, Ever, OR 1.3 (0.6-2.6)	Smoking is not associated with glioma risk.
(Blowers <i>et al.</i> , 1997) (USA) NOS: 6	(1)Glioma; (2) ICD-O 191-191.9	Population (neighbourhood)	(94/94)	Cases (67%), Controls (93%)	(1)25-74yrs; (2) Females	n/a	n/a ^a	No association between smoking and glioma
(Lee <i>et al.</i> , 2006) (USA) NOS: 5	(1)Meningioma; (2) Histological confirmation	Hospital (spouses of the females who were back pain patients-hospital based)	(219/260)	Cases (86.2%), Controls (75.4%)	(1)all ages; (2) Females	Age, hospital, race, menarche age, pregnancy, menopause, OC use, thyroid disorders, radiation treatment	#1: Female, Past, OR 0.7 (0.4-1.1) #2: Female, Current, OR 0.5 (0.3-0.9)	Based on this study, there is a protective effect of current smoking status
(Phillips <i>et al.</i> , 2005) (USA)	(1)Meningioma; (2) Histological confirmation	Population (random digit dialing and Medicare eligibility lists)	(200/400)	n/a	(1)average age: 56.4 yrs (15.6 SD); (2) Males and Females	Matched: age and sex. Controlled for educational status	#1: Male, Ever, OR 2.1 (1.1-4.2) #2: Female, Ever, OR 0.7 (0.5-1.1)	Active smoking is associated with meningioma risk among men but not

NOS: 5								women. Passive smoking was associated with meningioma risk within spouses (men and women).
(Hu <i>et al.</i> , 1999) (CHINA)	(1)Meningioma; (2) Histological confirmation	Hospital (controls with non neurological diseases)	(183/366)	100% for cases and controls approached	(1)all ages; (2) Males and Females	Income, education, occupational exposure to chemicals, consumption of fruits and vegetables	n/a ^a	Cigarette smoking is associated with glioma risk in women, but not in men.
NOS: 6								
(Ryan <i>et al.</i> , 2006) (AUSTRALIA)	(1)Glioma & Meningioma; (2) ICD (191-192)	Population (electoral roll)	Glioma: (110/417) Meningioma: (60/417)	Cases (90.5%); Controls (63.3%)	(1)25-74yrs; (2) Males and Females	Age, sex	#1: Both, Glioma, Ever, RR 1.19 (0.73-1.95) #2: Both, Meningioma, Ever, RR 1.77 (0.80-3.92)	There is no association between smoking and risk for glioma or meningioma
NOS: 6								

^aRisk estimates given for this study are not applicable for the Never , Ever, Past, Current comparison. However, results are applicable to the overall systematic review, and are discussed in text.

7.9.1. Description of Identified Studies

Thirteen observational studies were identified overall. A total of five cohort studies were identified: three studies focused on glioma(100, 101, 103); one study focused on meningioma (102) and one study focused on both (104). A total of eight case-control studies were identified: four studies focused on glioma (98, 105-107), three studies focused on meningioma(108-110), and one study focused on both (111). All thirteen studies had used either a disease classification guide or histological confirmation to identify the disease outcome of interest. The eleven studies included within the MA have controlled for a number of variables such as age, sex, education, alcohol and coffee consumption, body mass index and income, among many others. As a caveat, not all studies had controlled for the same confounding variables.

7.9.2. Quality Assessment

Quality assessment scores using the NOS ranged from 5 to 8 for all thirteen studies out of a possible 9 points. In general, the cohort studies (scores ranging from 6 to 8) were of higher methodological quality compared to the case-control studies (scores ranging from 5 to 7). Sub-group analyses based on quality scores could not be attempted, as there were not enough studies to stratify by similar quality score, histological sub-types and exposure categories. As noted earlier, a cut-off score of 5 would be used to determine high compared to low quality; however, this may not be a good indicator, as all of the studies had scored above 5. If a sub-group analysis was plausible, then using the median score as a cut-off would have been more appropriate.

7.9.3. Age at Initiation

Two studies had addressed age at initiation (years) of active smoking and glioma risk. Hu *et al.*, (110) had looked at the following categories of initiation (≤ 20 , 21-25, and ≥ 26). Overall, there was no association with all point estimates below the null value of 1, with insignificant 95% confidence intervals. Silvera *et al.*,(101) had looked at the categories of <20 , 20-21 and >21 , with hazard ratios of 1.67 (1.03-2.72), 0.85 (1.03-2.72) and 1.37 (0.71-2.65), respectively.

Hurley *et al.*, (106) had looked at the effects of <20 and ≥20 for meningioma. Interestingly enough, men had a greater risk for meningioma compared to women for both age categories. The most significant and increased risk was for men who began smoking at ≥20 years, RR 2.72 (1.48-5.02).

7.9.4. Duration of Smoking (years)

Four studies had addressed duration of active smoking (years) and glioma risk. Holick *et al.*, (100) had looked at 1-14, 15-24, 25-34 and ≥35 years for both males and females. A majority of the estimates were elevated; however they were not statistically significant and did not follow a dose response trend by duration. For males, the highest risk estimate was for ≥35 years of duration, although it was insignificant, RR 1.29 (0.76-1.17). Zheng *et al.*, (105) had looked at <30, 30-40 and >40 years for both males and female, with no association for all estimates. Hurley *et al.*, (106) had looked at <10, 10-19 and ≥20 years for both males and females, and there was a non significant increasing trend for females, but not males. Males actually had the highest risk when smoking for <10 years at RR 2.49 (1.25-4.92). Silvera *et al.*, (101) had looked at <10, 11-20 and >20 years for females and had noted a non significant increasing dose-response trend.

Only one study conducted by Phillips *et al.*, (109) had assessed the association between <16, 16-25 and >25 years of duration and meningioma risk. All estimates were not significant, and did not follow a dose-response trend; however males tended to have higher risk estimates compared to females.

7.9.5. Quantity of Cigarettes per day

Two studies had addressed number of cigarettes smoked per day and glioma risk. Zheng *et al.*, (105) had looked at <11, 11-20 and >20 cigarettes/day and had concluded no association for both males and females. Silvera *et al.*, (101) had looked at <10, 11-19, >20 cigarettes per day for females and had noted an increased risk for the latter two categories; albeit they were not significant.

One study conducted by Phillips *et al.*, (109) had assessed the association between ≤20 and >20 cigarettes per day on meningioma risk for both males and females. There was

no association for women; however there was a non-significant dose response increase for men.

7.9.6. Pack Years

Five studies have assessed the association between pack-years of active smoking and glioma risk. Each study had a different method of calculating pack-years. Holick *et al.*, (100) had looked at 1-9, 10-24, 24-44 and ≥ 45 pack-years, with each pack-year representing the number of pack of cigarettes smoked a day multiplied by number of years smoked. There was no dose-response trend present for both males and females, and results were insignificant. Hurley *et al.*, (106) had looked at 0- <9 , 9- <24 and ≥ 24 pack-years for both males and females, with each pack-year representing a year of smoking 20 cigarettes a day. There was no clear dose-response trend and results were insignificant.

The rest of the following studies had not further explained what had constituted a pack-year within their analyses. Silvera *et al.*, (101) had looked at <5 , 6-15 and >15 pack-years. For females, a dose-response trend was lacking, and results were insignificant. Zheng *et al.*, (105) had looked at <25 , 25-49, >49 pack-years. No association was present for males and females. Hu *et al.*, (110) had looked at ≤ 111 , 112-383 and ≥ 384 pack-years for males with no association. The authors' had also looked at ≤ 169 and ≥ 170 pack-years for females with the latter having a 6 fold increase in odds, OR 6.12 (2.01-18.63).

One study had assessed the association between pack-years of active smoking and meningioma risk. Phillips *et al.*, (109) had looked at <12 , 12-32, >32 pack-years for both males and females with no clear explanation of what had constituted a pack-year. Males tended to have an elevated risk compared to women; however there was no dose-response trend.

7.9.7. Passive Smoking

Two studies have assessed the association between passive smoking and glioma risk. Blowers *et al.*, (107) concluded that there was no association for females co-habiting with a smoking spouse. They did, however, find an elevated risk for women who were raised by smoking parents in the household, although its 95% CIs crossed the null value of 1. Ryan *et al.*, (111) had also assessed the association between ever being exposed to passive smoke and

glioma. There was an elevated insignificant risk. The same authors had also assessed 1-12, 13-27 and 28+ years of exposure with elevated estimates; albeit none had followed a dose-response trend and all were non statistically significant.

Ryan *et al.*, (111) had also assessed the association between ever being exposed and meningioma. There was an increased risk which was marginally significant, RR 1.91 (1.01-3.63). Again, the three categories with respect to years of exposure were assessed for meningioma as well. All estimates were elevated; however dose response trend was not present and results were insignificant.

7.9.8. EVER vs. NEVER SMOKERS

7.9.8.a. Cohort Studies

For glioma, only two cohort studies had analyzed the association between ever compared to never smoker. One study had noted a 40% increase risk among ever smokers compared to never smoker; however it bordered significance, RR 1.4 (1.0-2.1) (103). The remaining study had noted a 30% increase risk in females; however, it was non-significant, HR 1.30 (0.88-1.93) (101).

For meningioma, there was no association, RR 0.90 (0.60-1.33) (102).

7.9.8.b. Case-Control Studies

For glioma, four case-control studies had analyzed the association between ever compared to never smoker; however two studies had provided separate estimates for males and females, and thus have two entries each into the analysis. It was ensured that the male and female population had separate control groups. Heterogeneity tests had shown the presence of unimportant heterogeneity based on I^2 test ($I^2=8\%$), and the Cochrane's Q test did not reach significance for heterogeneity ($p=0.36$). Based on pooled adjusted odds estimates, there is a 2% increase in odds for ever smokers compared to never smokers; however this association is not statistically significant, as the 95% confidence intervals encompass the null value of 1. Based on **Figure 5**, the presence of publication bias was absent for this analysis, based on the symmetry of the inverted funnel plot.

For meningioma, two studies had assessed this association. One author had noted a 77% increase in risk; however its 95% confidence intervals did not demonstrate significance, RR 1.77 (0.80-3.92)(111). The remaining author had provided separate estimates for males and females. For males, there was a two fold increase in odds for ever compared to never smokers, and this association was considered statistically significant, OR 2.1 (1.1-4.2). For females, there was no association, OR 0.7 (0.5-1.1) (109).

Figure 4. Forest Plot for Glioma: Ever Vs. Never Smoker, Adjusted, Case-Control Studies

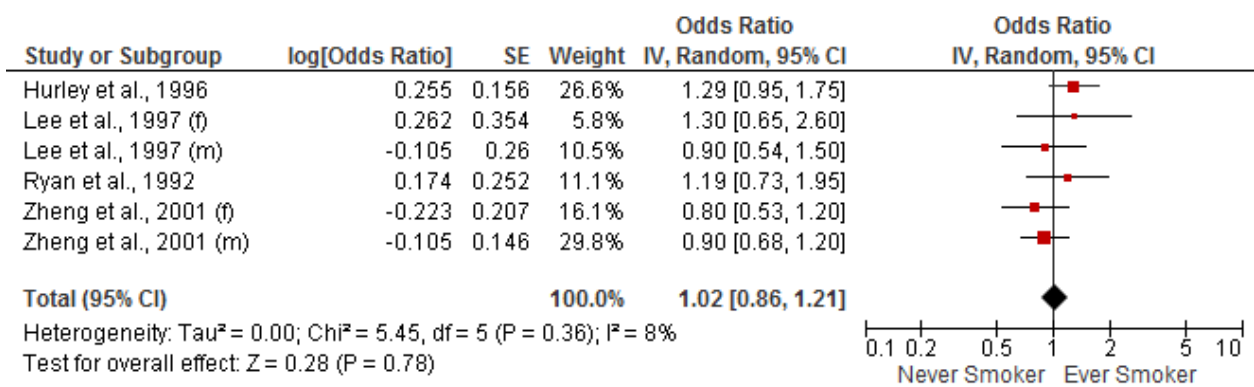
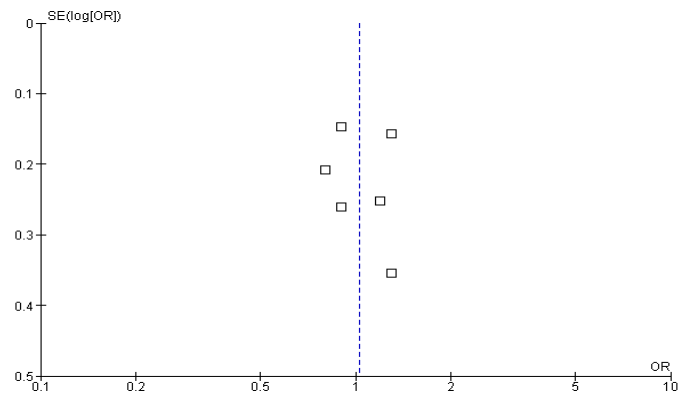


Figure 5. Inverted Funnel Plot for Glioma: Ever Vs. Never Smoker, Adjusted, Case-Control Studies



7.9.9. CURRENT vs. NEVER SMOKERS

7.9.9.a. Cohort Studies

Four cohort studies had analyzed the association between current compared to never smoker for the risk of glioma. Based on pooled adjusted risk estimates, there was a 7% increase in risk for glioma amongst current smokers compared to never smokers; although this association lacks statistical significance, RR 1.07 (0.86-1.33), ($I^2=31\%$, $p=0.21$).

There was sufficient data to conduct a sub-group analysis for females only. Based on pooled adjusted risk estimates, there is no association between current smoking and glioma risk amongst females, RR 0.98 (0.81-1.17), ($I^2=0\%$ and $p=0.63$). There may be the slight presence of publication bias based on the inverted funnel plot in Figure 7. For meningioma, the only study identified had concluded no association for females, RR 0.88 (0.66-1.16) (104).

Figure 6. Forest Plot for Glioma: Current Vs. Never Smoker, Adjusted, Cohort Studies

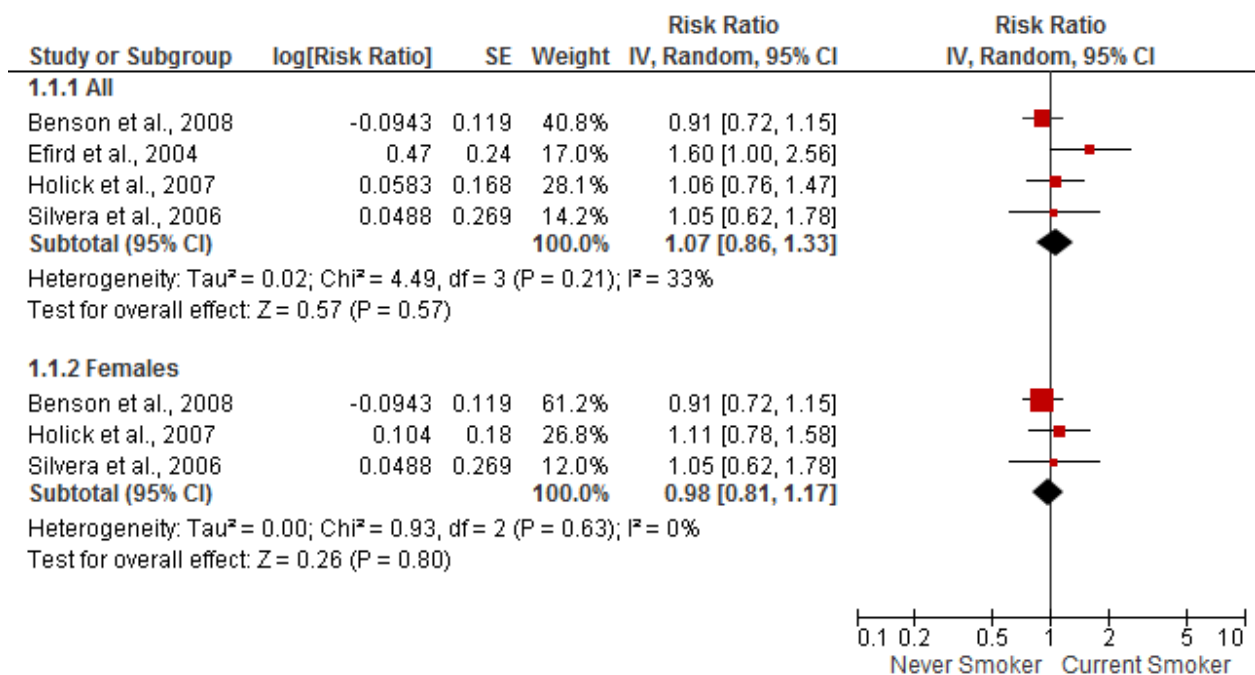
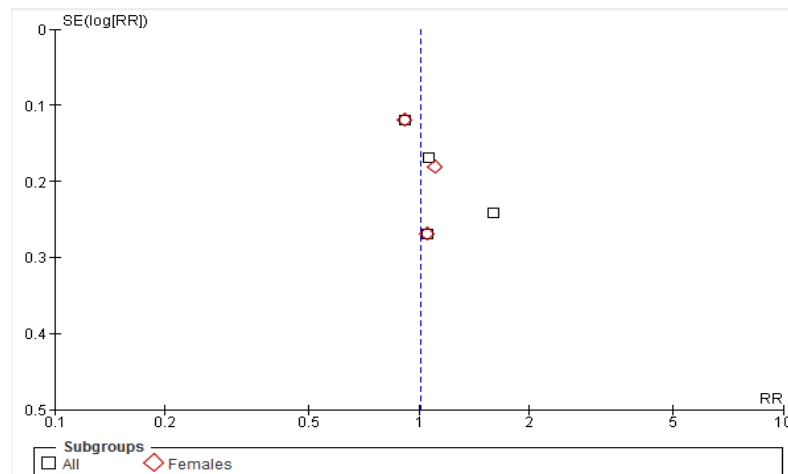


Figure 7. Inverted Funnel Plot for Glioma: Current Vs. Never Smoker, Adjusted, Cohort Studies



7.9.9.b. Case-Control Studies

For glioma, only one case-control study had assessed that association between current versus never smoker. The authors had provided separate odds estimates for males and females. For both sexes, there was no association, OR 1.0 (0.7-1.6) and OR 0.7 (0.4-1.1) respectively(105). For meningioma, the only study identified had concluded a marginally statistically significant inverse association amongst females, OR 0.50 (0.3-0.9) (108).

7.9.10. PAST vs. NEVER SMOKERS

7.9.10.a. Cohort Studies

Four cohort studies had assessed the association between past versus never smoker. Based on pooled adjusted risk estimates, there was a 20% increase in risk for glioma amongst past smokers compared to never smokers; and this association was statistically significant as the 95% confidence intervals do not encompass the null value of 1, RR 1.20 (1.04-1.38) ($I^2=0\%$, $p=0.43$).

There was sufficient data to conduct a sub-group analysis for females only. Based on pooled adjusted risk estimates, there is a 17% increase in risk amongst past smokers for glioma; albeit this association borders significance, RR 1.17 (0.99-1.39) ($I^2=5\%$ and $p=0.35$). There may be the slight presence of publication bias based on the inverted funnel plot in **Figure 9**. For meningioma, the only study identified had concluded no association for females, RR 0.86 (0.67-1.10)(104).

Figure 8. Forest Plot for Glioma: Past Vs. Never Smoker, Adjusted, Cohort Studies

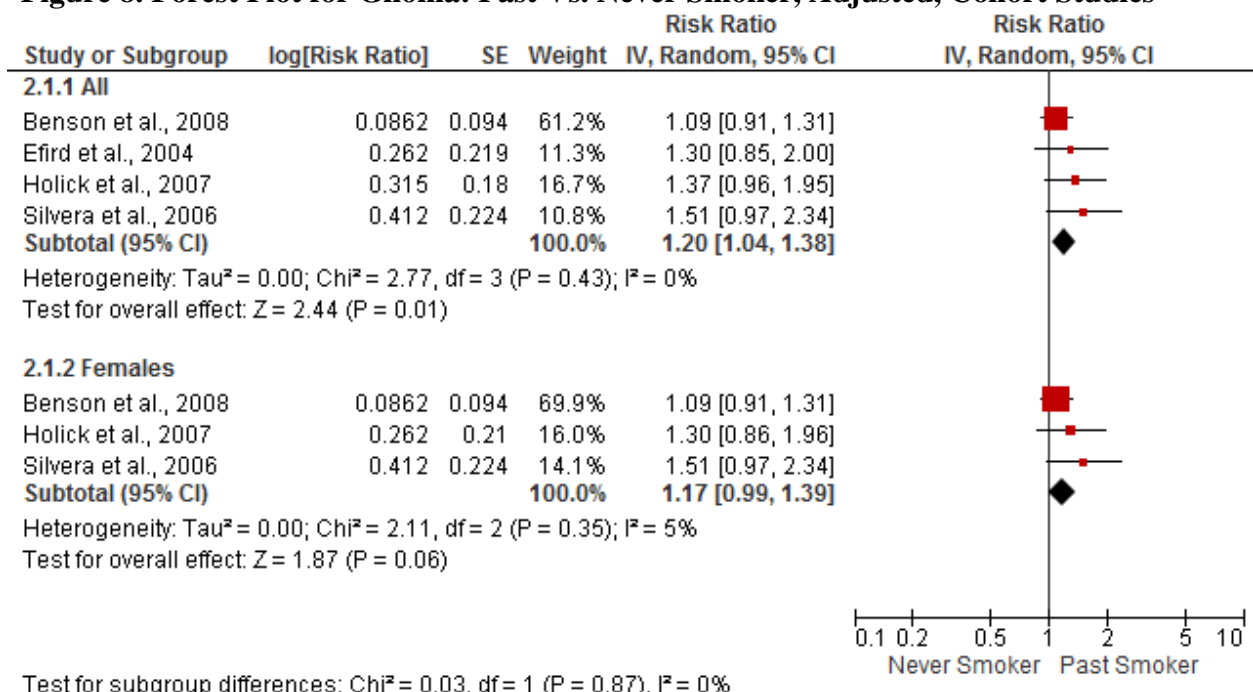
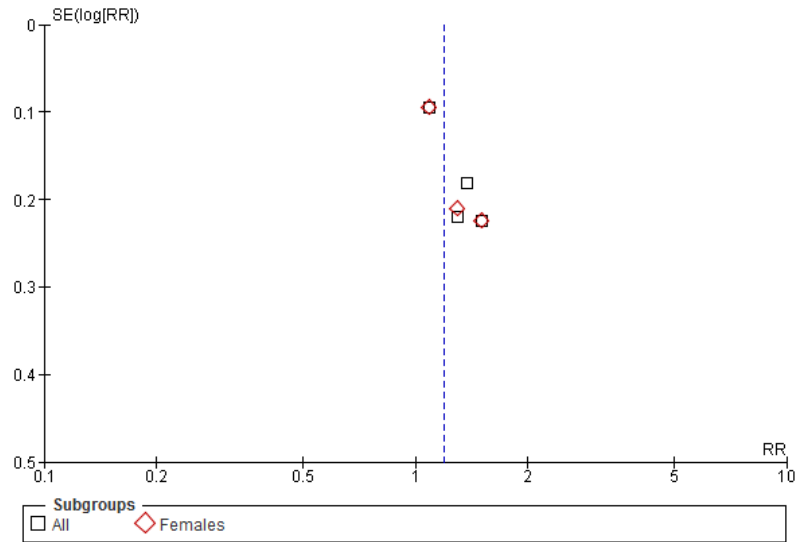


Figure 9. Funnel Plot of Comparison: Past Vs. Never Smoker, Adjusted, Cohort Studies



7.9.10.b. Case-Control Studies

For glioma, only one case-control study had assessed that association between past versus never smoker. The authors had provided separate odds estimates for males and females. For both sexes, there was no association, OR 0.8 (0.5-1.1) and OR 1.0 (0.6-1.6) respectively(105). For meningioma, the only study identified had concluded no association amongst females, OR 0.7 (0.4-1.1)(108).

8.0. MOBILE PHONE USE (PHASE 2: Update or De-Novo Synthesis)

8.1. Brief Background/ Issues and Basis for Study Development

Several reviews have analyzed the association between mobile phone use (non-ionizing radiofrequency fields) and PBTs with inconsistent findings. It has been hypothesized that the head's increased exposure to radiofrequencies due to the proximity of mobile phone

devices may have an effect on tumour formation(112). This concern has become increasingly prevalent as the level of Megahertz (MHz) exposure has increased over the years due to technological advances. The 1980s were dominated by analogue phones which emitted 450 and 900 MHz, then came digital phones in the 1990s which emitted 900 and 1,800 MHz, then followed 3G mobile phones in 2003, which emit 1,900 MHz (113). The pattern of increasing MHz is concerning as MHz exposure had almost doubled within a 10 year span, and it has only been increasing with the introduction of the 3G network. This topic is an area which needs to be of great focus, as the use of mobile phones has become a norm within society. As well, despite the conflicting results, the International Agency for Research on Cancer (IARC) has agreed to classify radiofrequency electromagnetic fields (those associated with mobile phone use) as a category 2B, possibly carcinogenic to humans(114). It would be of great interest to determine whether conducting a SR and MA on the world literature concerning mobile phones using proper systematic review methods would support this decision made by IARC.

As indicated in Phase 1, there were five low to moderate quality SRs and MAs on mobile phone use and onset of brain tumours published before December 31, 2011. With AMSTAR scores ranging from 3 to 7 (low to moderate), reviews on this specific topic were considered eligible to be subjected to *de-novo* processes. The purpose of this current review is to address certain aspects within AMSTAR which these authors have failed to address. As a result, certain conclusions from the reviews in question may differ. An a priori protocol was already developed and can be found in **Appendix K**.

8.2. Research Question and Objectives

Components of the intended research question were constructed within a PICO framework.

- **Population:** Adults (≥ 18 years old, males and females)
- **Intervention/Exposure:** Mobile phone use and/or cordless phone use
- **Comparator:** Non-regular users
- **Outcomes:** Glioma sub-types (astrocytoma, glioblastoma, oligoastrocytoma, oligodendroglioma, ependymoma) and meningioma
- **Study Designs:** Case-control and cohort studies.

Research Question: Based on available case-control and cohort studies, are mobile phone use and/or cordless phone use associated with adult onset of glioma sub-types (astrocytoma, glioblastoma, oligoastrocytoma, oligodendroglioma, ependymoma) and/or meningioma?

Objectives:

- To identify relevant observational studies (case-control and cohort) focusing on the affects of mobile phone use and the onset of glioma and/or meningioma in an attempt to provide an overall conclusion regarding this association.
- If permissible (at least three study estimates), to conduct a MA on relevant studies (with data pertaining to latency (Non-User vs. Short-term and Long-term). Sub-group analysis based on laterality, type of phone used (analog versus digital) and cumulative call time will be considered if data is sufficient.
- Short term: “ Ever having been a user for 1-9 years”
- Long term: “ Ever having been a user for ≥ 10 years”
- To provide a current-up to date, high methodological quality SR and possible MA on the association between mobile phone use and glioma/meningioma, as dictated by AMSTAR criteria, to be used by health policy makers and relevant stakeholders.

8.3. Literature Search Strategy

With the guidance of a health information specialist at the University of Ottawa, search strategies were developed and tailored for the following bibliographic databases: PubMed, Medline, Embase, CINAHL and PsycINFO (see **Appendix L**). AARP Ageline and TOXLINE were excluded as they were deemed irrelevant based on the searches conducted in Phase 1. Grey Literature sources, such as ProQuest Dissertation and Thesis Database, as well as Google and Google Scholar were searched. “Other sources” of literature were also considered. Bibliographies of included studies were searched, studies included in previous reviews were considered and hand-searching of disease-specific journals, such as Cancer Causes and Control and the International Journal of Cancer was completed as well.

All search strategies generally followed the same template. The following concept groups: Disease terms, risk terms, mobile phone terms, and a filter for identifying

observational studies were all combined with the Boolean operator AND. Search terms within each concept group were combined the Boolean operator OR. Searches were conducted to include all published relevant articles up to December 31, 2011.

8.4. A Priori Selection Criteria

Studies were included if they had satisfied all of the following inclusion criteria:

- Studies focused on the onset on at least one of the following brain tumours: glioma, astrocytoma, oligodendroglioma, oligoastrocytoma, ependymoma, glioblastoma, meningioma
- Studies focused on mobile phone use (cellular-handheld) as exposure and must provide risk estimates with 95% confidence intervals.
- Mobile phone use (or cordless) had to be the main exposure variable, and could not be combined with another exposure variable as part of an interaction term.
- Studies had to be of either case-control or cohort study design.
- Studies had to be published in English or French.
- Full-text of studies had to be retrievable.
- Studies had to be published before December 31, 2011.

Studies were excluded if they satisfied at least one of the following exclusion criteria:

- Studies focused on childhood primary brain tumours.

8.5. Study Selection Method

After the removal of duplicates, identified studies were subjected to two levels of screening (title/abstract and full text) using the same screening questions for each level within Distiller SR (Evidence Partners, Ottawa, Canada) (**Appendix M**). A method known as “liberal accelerated” screening was used whereby only one reviewer’s input is needed to advance an article to the next level; however decisions from two reviewers are needed to exclude an article. The first reviewer (PQ) screens 100% of the articles, and the second reviewer (RES) duplicate screens the excluded articles identified by the first reviewer. Any

conflicts were resolved by consensus and a kappa statistic was determined for the strength of agreement for excluded studies between the two reviewers.

8.6. Data Extraction Method

Studies which had satisfied the a priori selection criteria were subjected to the data extraction process. Information on study characteristics, participants, exposures, outcomes and results were recorded (**Appendix I**). The first reviewer extracted data from all relevant studies, and the second reviewer (MA) duplicate extracted a random 25% sample.

8.7. Study Quality Assessment

As recommended by the Cochrane Collaboration, quality assessment of observational studies were completed by using the NOS (57, 74). NOS was chosen since: it was widely used for quality assessing observational studies, was quick to implement, and it had established face and content validity, along with inter-rater reliability(57, 74). Methodological issues between cohort and case control studies were evident, and the NOS accounted for such differences by subjecting both types of studies to different scales. The following components were addressed for both scales: selection (4 stars), comparability (2 stars) and ascertainment of exposure/outcome of interest (3 stars). The maximum score on this scale was nine stars(57, 75).

Although standard scoring thresholds had yet to be determined, many studies had consistently used the threshold of ≥ 5 stars and <5 stars to represent studies of high and low quality(76-80).

8.8. Statistical Analysis

Quantitative summaries were considered for the following analyses based on latency: (a) non- user vs. short-term user (c) non- user vs. long-term user. An MA was attempted if there were greater than three relevant studies per analysis (in this case, the larger INTERPHONE studies and the pooled Hardell studies were considered multiple studies) and if heterogeneity tests determined that the pooling of numerous risk estimates was appropriate. If pooling was deemed inappropriate, then a qualitatively summary would be considered

sufficient. Secondary analyses based on laterality and type of phone (analog, digital or cordless) were provided if the data were available.

Degree of heterogeneity was determined by conducting the following statistical tests, Cochrane's Q and I^2 (81). As outlined in the Cochrane Collaboration, I^2 percentages between 0%-40%, 30%-60%, 50%-90%, 75%-100% represents unimportant, moderate, substantial, and considerable heterogeneity, respectively(82). Due to the low power of the Cochrane's Q test to detect true heterogeneity, the threshold for significance was increased to $p=0.1$, meaning any p -value ≤ 0.1 was considered statistically significant for heterogeneity and any p -value >0.1 was considered homogeneous(82, 83).

Random effects models based on the DerSimonian and Laird Method (DLM), a variation of the inverse variance method was used to pool estimates together as opposed to using the fixed effects models(82, 84). Since variability is always present, random effects modeling generates more conservative estimates for determining significance by producing wider confidence intervals, allowing one to be more cautious in their conclusions. The standard errors and the log risk or odds ratios of eligible point estimates were inputted into Review Manager v.5, resulting in pooled adjusted point estimates (84). If sufficient data existed, sub-group analyses based sex, differing patterns of cellular phone usage and histological sub-type was attempted. Publication bias was assessed for symmetry through inverted funnel plots generated by Review Manager.

8.9. Results

Bibliographic database searching resulted in the identification of 328 potentially relevant articles. 39 additional articles were identified through searching other sources, such as grey literature, disease specific journals and studies included in existing reviews. Thus, a total of 367 potentially relevant articles were imported into Distiller SR (Evidence Partners, Ottawa, Canada). After the removal of duplicates, a total of 188 were subjected to Level 1 screening for relevancy based on title and abstract. 38 articles were in conflict and were resolved by consensus (eventually excluded) between the two reviewers. The kappa statistic for level of agreement based on the 134 excluded was 0.61, which represents substantial

agreement(66). 54 studies had satisfied Level 1 screening, and the full-text was retrieved for further scrutiny in Level 2 screening.

Fifty-four full text articles were subjected to Level 2 screening, among these, 8 articles were in conflict. These articles were resolved by consensus (and were eventually excluded) between the two reviewers (PQ and RS). The kappa statistic for level of agreement based on the 31 excluded articles for the two reviewers was 0.45, which represents moderate agreement(66). For a list of excluded articles and their reasons at Level 2 screening, see **Appendix N**.

The remaining 23 articles had met the a priori inclusion/exclusion criteria and were subjected to 25% duplicate data extraction and quality assessment by the second reviewer (MA). Slight differences were noted in both extraction and quality assessment responses, and were promptly resolved through consensus.

Figure 10. PRISMA Flow Diagram of Included/Excluded Studies

Source:

Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group. (2009). *Preferred Reporting Items for Systematic Review and Meta-Analyses: The PRISMA Statement*. PLoS Med 6(6): e1000097. Doi: 10.1371/journal.pmed1000097.

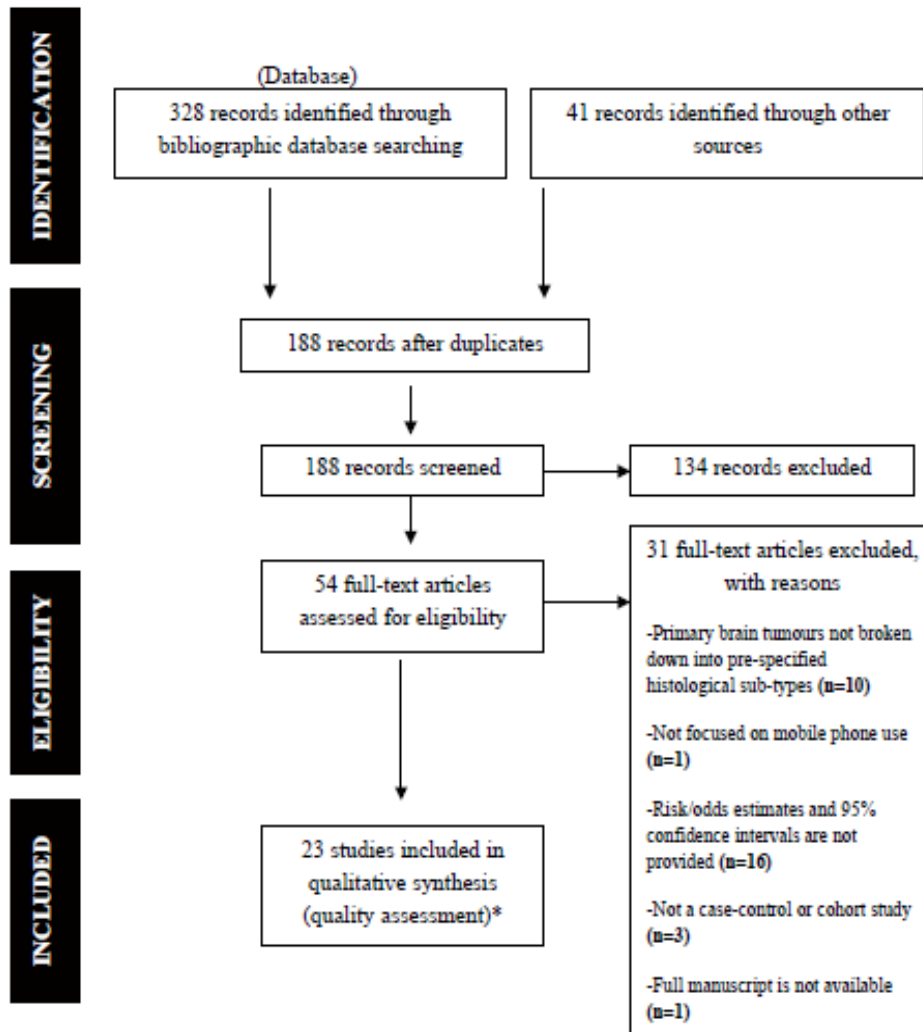


Table 8. Included Studies Identified for the Association between Mobile Phone Use and Glioma and Meningioma

Article & Location; NOS Score	(1)Outcome; (2) Case ascertainment	Control Population OR Cohort Information	Sample Size (cases/contr ols)-	Response Rate OR Follow-up Period	(1) Age; (2) Sex	Confounding Variables	Exposure Variables Assessed
INTERPHONE STUDIES							
(INTERPHONE Study Group, 2010) (Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden and UK) NOS: 6	(1) Glioma & Meningioma; (2) Histological confirmation	Population (sampling frame)	Glioma (2708/2972) Meningioma (2409/2662)	Glioma cases=64% ; Meningioma cases=78% ; Controls=53%	(1)30-59; (2) both	Age, sex, study centre, education (as surrogate for socioeconomic status), and ethnicity (only in Israel)	-Regular use, Time since first use (1-1.9 yrs, 2-4 yrs, 5-9 yrs, ≥ 10 yrs), Cumulative call time (with no hands free device). Further stratified by laterality.
(Cardis <i>et al.</i> , 2011) (Australia, Canada, France, Israel, New Zealand) NOS: 5	(1)Glioma & meningioma; (2) Histological confirmation	Population (sampling frame)	Glioma (553/1762), Meningioma (676/1911)	Glioma cases=42.4% ; Meningioma cases=56.4% Controls=39.5%	1)30-59; (2) both	Age, sex, region, education level, interaction between study region and time period of interview.	-Regular use compared to never regular use, cumulative call time. Further analysis based on RF exposure
(Lahkola <i>et al.</i> , 2008) (Denmark, Finland, Norway, Sweden, UK)- INTERPHONE NOS: 6	(1)Meningioma; (2) (ICD-O3 9530-9539)	Nordic countries= Population Register UK= General Practitioner's List	(1209/3299)	Cases=74% ; Controls=50%	(1)20-69; (2) both	Age, sex, residence, education, family history of meningioma, radiotherapy of head and neck (at least 10 yrs prior), diagnosis of neurofibromatosis and tuberous sclerosis	-Regular use, yrs since first use (1.5-4 yrs, 5-9 yrs, ≥ 10 yrs), lifetime years of use, cumulative number of calls and hours of use. Further stratified by laterality and type of phone (digital & analogue)

(Lahkola <i>et al.</i> , 2007) (Denmark, Finland, Norway, Sweden, UK)- INTERPHONE NOS: 5	(1)All gliomas and glioblastomas; (2) Glioma (ICD-O 3 codes 9380-9384, 9390-9394,9400,9401,9410,9411, 9420-9424,9430,9440-9444,9450-9451,9505)	Nordic countries= Population Register UK= General Practitioner's List	(1,521/3,301)	Cases=60%, Controls=50%	(1) Four Nordic countries- 20-69; UK-18-59; (2) both	Age, sex, residence, education, family history of meningioma, radiotherapy of head and neck (at least 10 yrs prior), diagnosis of neurofibromatosis and tuberous sclerosis	-Regular use, yrs since first use (1.5-4 yrs, 5-9 yrs, ≥ 10 yrs), , lifetime years of use, cumulative number of calls and hours of use. Further stratified by laterality and type of phone (digital & analogue)
(Hepworth <i>et al.</i> , 2006) (UK)- INTERPHONE	(1) Glioma; (2) ICD-O-3: C71 9380-9411, 9420-9460, 9480, 9505	General Practitioner's list of Patients	Glioma (966/1716)	Cases=51% , Controls=45%	(1)18-69; (2) both	Age, sex, general practice	-Regular use, year since first use (1.5-4 yrs, 5-9 yrs, ≥ 10 yrs), lifetime years of use, Cumulative hours of use and call time, and laterality.
(Klaeboe <i>et al.</i> , 2007) (Norway)- INTERPHONE	(1)Glioma & Meningioma; (2) Histological confirmation	Population register	Glioma & Meningioma (541/358)	Cases=74% Controls=69%	(1)19-69; (2) both	Age, sex, educational level and residential area.	-Regular use, duration of use (<2 yrs, 2-5 yrs, ≥6 yrs), cumulative use and number of calls, type of phone (digital & analogue). Laterality
(Schuz <i>et al.</i> , 2006)(Germany)- INTERPHONE	(1)Glioma & Meningioma; (2) Histological confirmation	Population register	Glioma (366/732); Meningioma (381/762)	Cases=80% Controls=60%	(1)30-59; (2) both	Gender, study center, age, SES	-Regular use, time since first use (never and <1, 1-4, 5-9, ≥10 yrs), lifetime number of calls and duration, intensity of use. Cordless data.
(Christensen <i>et al.</i> , 2005) (Denmark)- INTERPHONE	(1) High grade and low grade Glioma & Meningioma; (2)Glioma (ICD 191.0, 191.1, morphology codes 93803-94603);	Population register	(Glioma cases=252, Meningioma cases=175/822)	Glioma=71% Meningioma=74% Controls=64%	(1)20-69; (2)both	Sex, age, education level, hands free devices in cars.	-Regular use, time since first use (never and <1, 1-4, ≥5, 5-9, ≥10 yrs), lifetime number of calls and hours of use, intensity

	Meningioma (ICD 192.1, morphology codes 95300-95393)						
(Lonn <i>et al.</i> , 2005) (Sweden)- INTERPHONE	(1)Glioma & Meningioma; (2) Glioma=ICD 10 code 71, 2nd edition, codes 9380-9384, 9390-9394, 9400-9401, 9410-9411, 9420-9424, 9430, 9440-9443, 9450-9451, 9460, 9480-9481, 9505); Meningioma: ICD 10 code 70, 2nd edition, codes 9530-9505)	Population register	(Glioma cases=371, Meningioma cases=273/ all controls=674)	Glioma cases=74%, Meningioma cases=85%, Controls=71%	(1)20-69; (2)both	Age, gender, geographic region and education.	-Regular use, duration of use (<5, 5-9, ≥10 yrs), time since first regular use, cumulative use and number of calls. Type of phone (digital and analog). Laterality.
(Takebayashi <i>et al.</i> , 2008) (Japan) INTERPHONE	(1)Glioma & Meningioma; (2) Surgical Cases- Glioma ICDO-3- 9380-9384, 9390-9394, 9400-9401, 9410-9411, 9420-9424, 0430, 9440-9443, 9450-9451, 0460, 9480-9481;	Population based random digit dialling	Glioma (88/196); Meningioma (132/279)	Glioma- Cases=58.7 %/ Controls=5 2.5%, Meningioma- Cases=77.6 %/ Controls=5 1.6%	(1)30-69; (2)both	Age, sex, residence, education, marital status	-Regular use, cumulative years of and call time. Type of phone (analoge+digital, digital) and laterality.

	Meningioma-930-9539, MRI for remaining						
(Hours <i>et al.</i> , 2007)(France)	(1) Glioma & Meningioma; (2) Histological Confirmation	Electoral Roll	Glioma (96/96) Meningioma (145/145)	Glioma-60%, Meningioma-78.4%, Controls-74.7%	(1)30-59; (2) both	Sociodemographic variables, medical history of subject and family, use of radio systems, exposure to medical radiation	-Regular use, duration of use (<16, 16-27, 27-46, ≥46 months). Laterality.
HARDELL STUDIES							
(Hardell & Carlberg, 2009) (Sweden)- Further analysis of 1997-2000+2000-2003 <i>NOS: 7</i>	(1) Malignant tumours which include: Astrocytoma (I-IV), Oligodendroglioma, Other/Mixed gliomas; and Benign tumours which include: meningioma; (2) Histological confirmation	Population Register	(Malignant-905, Meningioma - 916/ All controls 900)	Malignant-90%, Benign-88%, Controls-89%	(1)≤80; (2) both	Age, gender, socioeconomic index, and year of diagnosis	Mobile phones and Cordless phones analyzed by latency (>1 year, > 10 year). Further analyzed by laterality.
(Hardell <i>et al.</i> , 2006) (Sweden)- Analysis of 1997-2000+2000-2003	(1)Malignant Tumours-(Astrocytoma (I-IV)); (2) Histological confirmation	Population Register	(1008/2437)	Cases-90%; Controls-89%	(1)20-80; (2) both	Age, gender, socioeconomic index, and year of diagnosis	Mobile phones and Cordless phones analyzed by latency (>1-5yr, >5-10 yr, >10 yr, Total >1 yr). Mobile phones and Cordless phones analyzed by laterality.

(Hardell <i>et al.</i> , 2006) (Sweden)- Analysis of 1997-2000+2000-2003	(1)Benign Tumours- Meningioma; (2) Histological confirmation	Population Register	(1429/2437)	Cases-88%, Controls-89%	(1)20-80; (2) both	Age, gender, socioeconomic index, and year of diagnosis	Mobile phones and Cordless phones analyzed by latency (>1-5yr, >5-10 yr, >10 yr, Total >1 yr). Mobile phones and Cordless phones analyzed by laterality.
(Hardell <i>et al.</i> , 2005) (Sweden)- Analysis of 2000-2003	(1)Malignant Tumours- (Astrocytoma (I-IV)); (2) Histological confirmation	Population Register	(317/692)	cases-88%, controls - 84%	(1)20-80; (2) both	Age, gender, socioeconomic index, and year of diagnosis	Mobile phones and Cordless phones analyzed by latency (>1-5yr, >5-10 yr, >10 yr, Total >1 yr). Mobile phones and Cordless phones analyzed by laterality.
(Hardell <i>et al.</i> , 2005) (Sweden)- Analysis of 2000-2003	(1)Benign Tumours- Meningioma	Population Register	(413/692)	cases-89%, controls-84%	(1)20-80; (2) both	Age, gender, socioeconomic index, and year of diagnosis	Mobile phones and Cordless phones analyzed by latency (>1-5yr, >5-10 yr, >10 yr, Total >1 yr). Mobile phones and Cordless phones analyzed by laterality.
(Hardell <i>et al.</i> , 2003) (Sweden) Further Analysis of 1997-2000	(1) Malignant tumours which include: Astrocytoma (I-IV),; and Benign tumours which include: meningioma; (2) Histological confirmation	Population Register	(1429/1470)	cases-88%, controls-91%	(1)20-80; (2) both	Sex, age Socioeconomic index code	Mobile phones and Cordless phones analyzed by latency >1, >5, >10 yr). Mobile phones and Cordless phones analyzed by laterality.
(Hardell <i>et al.</i> , 2002) (Sweden) Analysis of 1997-2000	(1)Malignant Tumours- (Astrocytoma (I-IV)); (2) Histological confirmation	Population Register	(529/529)	cases-91%, controls-90%	(1)20-80; (2) both	Socioeconomic status	Mobile phones and Cordless phones analyzed by latency (>1-6 yr, > 6 year). Further analyzed by laterality.
OTHER STUDIES							
(Inskip <i>et al.</i> , 2001) (USA) NOS: 6	(1)Glioma & Meningioma; (2)Glioma	Hospital-patients with non malignant	(782/799)	Cases=92% ; Controls=8	18+ yrs	Age, sex, race or ethnic group,	-Regular use, average daily use, duration of regular use (<0.5 yrs, 0.5 to <3.0yr, ≥3.0,

	(ICD-O-2) 9380 to 9473; Meningioma (ICD-O-2) 9530 to 9538	conditions		6%		hospital, distance from patient's residence to hospital, education, self reported annual household income, date of interview, and interview respondent.	≥5.0 yrs), cumulative use. Analysis by laterality.
(Auvinen <i>et al.</i> , 2002) (Finland)- <i>Subscriber data used.</i> NOS: 8	(1)Glioma & Meningioma; (2) A portion confirmed microscopicall y	Population register	(327/ with 5 age and sex matched controls for each case)	n/a	(1)Mean =50.5 yrs; (2)both	Urban residences, SES, occupation (farming exposure to electromagneti c fields)	Type of phone (analog and digital) stratified by duration of subscription (ever, <1 year, 1-2 years and >2 years)
(Frei <i>et al.</i> , 2011) (Denmark)- <i>-*Note: only cohort study*- Subscriber data used.UPDATE of Johansen et al., 2001- -follow-up up to 2007 NOS: 9</i>	(1)Glioma & meningioma; specific ICD- 10 codes for CNS tumours	Cellular Phone Subscribers	(10,729/358, 403)-cases include central nervous system tumours.	2.2%	(1)n/a; (2) both	Age, calendar year, level of education, disposable income.	Analysis provided for other cancers. For glioma, meningioma, IRR provided for subscription use in years (1-4, 5-9, ≥10, 10-12, ≥13) compared to non-subscribers.
(Johansen <i>et al.</i> , 2001) (Denmark) - <i>*Note: only cohort study*- Subscriber data used. -follow-up up to 1996 NOS: 5</i>	(1)Glioma & Meningioma; (2) Glioma: ICD-O codes: 93800–94603 [except 93923], 94403–94423, 94013, 93841, 94000–94003,	Cellular Phone Subscribers	(3,391/420,0 95)- cases include brain, nervous system, salivary glands and leukemia	Did not mention.	(1)Media n= 37.4 yrs for males, 38.4 for females; (2) both	Did not mention.	Detailed analysis for brain tumours in general. For glioma and meningioma, specifically, general SIR provided for use.

	94103–94213, and 94500– 94513; Meningioma: ICD-O Codes: 95300–95393.						
(Muscat <i>et al.</i> , 2000) (USA) NOS: 6	(1)Glioma & Oligodendrogl ioma/mixed gliomas; (2) ICD-9CM 191.0-191.9	Controls- Hospital patients with benign diseases, except at 2 centers- with mostly cancer patients.	Total Brain Tumours (469/422); Gliomas (cases=354); Oligodendro glioma/mixe d gliomas (cases=55)	Cases-82%, controls- 90%	(1)18-80; (2) both	age, years of education, sex, race, study center, proxy subject, and month and year of interview	Detailed analysis for brain tumours in general. For astrocytic tumours, specifically, general OR provided for use.

8.9.1. Description of Included Studies

A total of twenty-three relevant studies were identified and had satisfied the selection criteria. Of these, eleven were affiliated with the international INTERPHONE study, seven were affiliated with the Swedish Hardell studies, and the remaining five were conducted by independent study groups.

Seven of the eleven INTERPHONE publications were individual stand-alone manuscripts from differing centers involved in the international study (UK, Norway, Germany, Denmark, Sweden, Japan and France)(115-121). Two of the publications had provided pooled analyses by combining exposure estimates for five Nordic countries (UK, Norway, Denmark, Sweden, Finland) for glioma and meningioma, separately(122, 123). One publication had provided pooled analyses by combining the estimates of five other countries (Australia, Canada, France, Israel, New Zealand) with a specific focus on measured radiofrequency exposure from mobile phones and glioma/meningioma(124). The remaining larger INTERPHONE publication had pooled all of the thirteen participating countries exposure estimates together into a single analysis (Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden and UK)(125). The larger INTERPHONE publication was included in this SR and was not considered as a pooled MA, as all of the data from each center was considered part of the same study, following the same protocol, as such it has been treated as one study with a large sample size. Data from identified countries are provided in the table; however, since the larger INTERPHONE publication is more comprehensive, it will be used for analyses within this review.

For the Hardell studies, the group had conducted two case-control studies, one between the years 1997-2000, and the other 2000-2003. It was ensured that case subjects from the earlier study were not included in the latter study(126). As well, it was also ensured that INTERPHONE study subjects were not included since the Hardell group had sampled cases from another region of Sweden(127). The Hardell group had published several manuscripts analyzing the data for these two time periods, including an aggregated analysis combining data from both time periods together. As with the INTERPHONE studies above, this particular paper was included in the systematic review and will be considered for

analysis within this review and will not be considered a MA, as the same protocol was used for both time periods, and it can be seen as a single study.

The remaining five studies led by independent groups were also considered relevant for this review. Three of the studies had used subscriber data as a means to measure exposure(128-130). As such, care should be considered when interpreting these studies, as it cannot be assumed that the subscriber is the actual person using the mobile phone.

8.9.2. Quality Assessment

Only the all-encompassing Interphone study, the two pooled Interphone studies conducted by Lahkola and the larger Hardell & Carlberg study were quality assessed, as the smaller Interphone studies had followed the same international protocol. The same can be said for the other Hardell studies. The studies conducted by independent study groups were subjected to quality assessment. In total, ten studies were subjected to quality assessment using the NOS. NOS scores ranged from 5 to 9 out of a possible 9 points. Sub-group analysis based on quality scoring could not be completed as sufficient number of studies were lacking for the main analysis already.

8.9.3. LATENCY: Never User compared to Short-Term and Long-Term Users

Three studies were considered relevant for latency analysis. The estimates for the time periods of 1-1.9, 2-4 and 5-9 years were combined for the Interphone study group (125) to provide an overall estimate for short term use (1-9 years). An estimate was provided for long-term use (≥ 10 years). The estimates for the time periods of ≥ 3 years and ≥ 5 years were combined for Inskip *et al.*, (131) to provide an estimate of short term use as well. An estimate for long term use was not assessed. Hardell *et al.*,(113) had provided estimates for > 1 year latency (considered short-term) and >10 year latency (considered long-term).

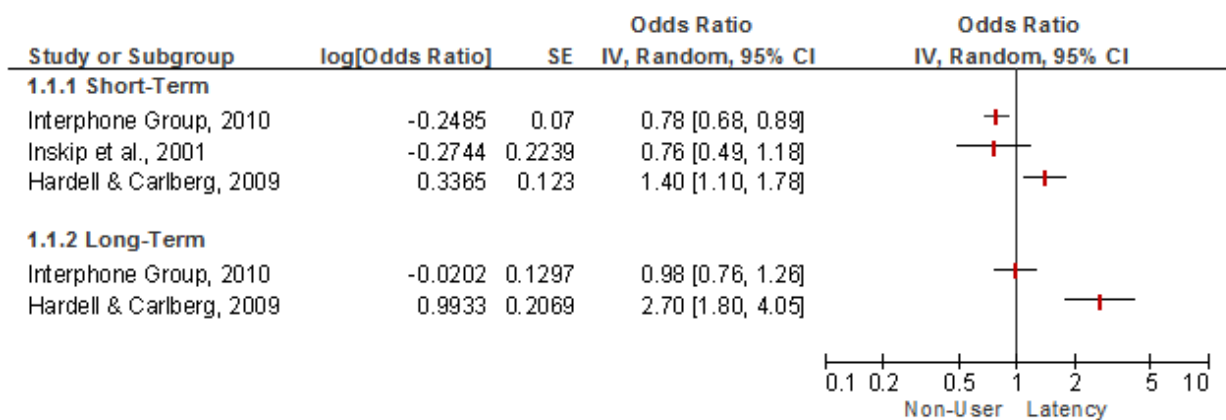
8.9.3.a. Glioma

For short-term use, (1-9 years) and its association with glioma, the three studies were combined in a MA using random effects modeling. As such, even with random effects modeling which takes into account the variation inherent in observational studies, the presence of heterogeneity between studies was significant. The I^2 test for heterogeneity

showed considerable heterogeneity ($I^2=89\%$), and the Cochrane's Q test ($p=0.0001$) was statistically significant for heterogeneity since it was ≤ 0.1 . The Hardell studies have shown a statistically significant positive association, whereas the Interphone study and Inksip *et al.* have demonstrated an inverse association, with the former being statistically significant.

For long-term use (≥ 10 years) and its association with glioma, two studies were included; however statistically significant heterogeneity was also present, I^2 ($I^2=94\%$), Cochrane's Q test ($p<0.0001$). Again, the Hardell studies have shown a statistically significant positive association, and the Interphone study has shown an inverse association; albeit not statistically significant.

Figure 11. Short-Term User and Long-Term User Compared to Non-User, Glioma, Adjusted

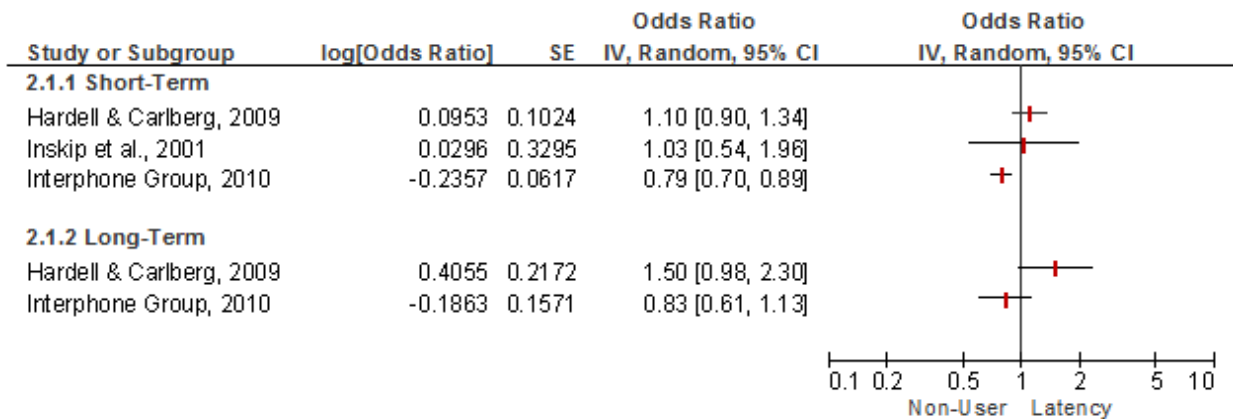


8.9.3.b. Meningioma

For short-term use, (1-9 years) and its association with meningioma, three studies were considered relevant and were combined using a random effects model. When pooled, the heterogeneity between studies was deemed as considerable heterogeneity as shown by the I^2 test for heterogeneity, $I^2=75\%$. The Cochrane's Q test also demonstrated significant heterogeneity ($p=0.02$). Both the Hardell studies and Inksip *et al.* studies have shown a positive association, albeit statistically non-significant; whereas the Interphone study has demonstrated a statistically significant inverse association.

For long-term use (≥ 10 years) and its association with glioma, two studies were considered relevant, however statistically significant heterogeneity was also present, I^2 ($I^2=79\%$), Cochrane's Q test ($p=0.03$). The Hardell studies have shown a positive association, and the Interphone study has shown an inverse association; both being non statistically significant.

Figure 12. Short-Term User and Long- Term Compared to Non- User- Meningioma, Adjusted



8.9.4. LATERALITY: Ipsilateral and Contralateral Use

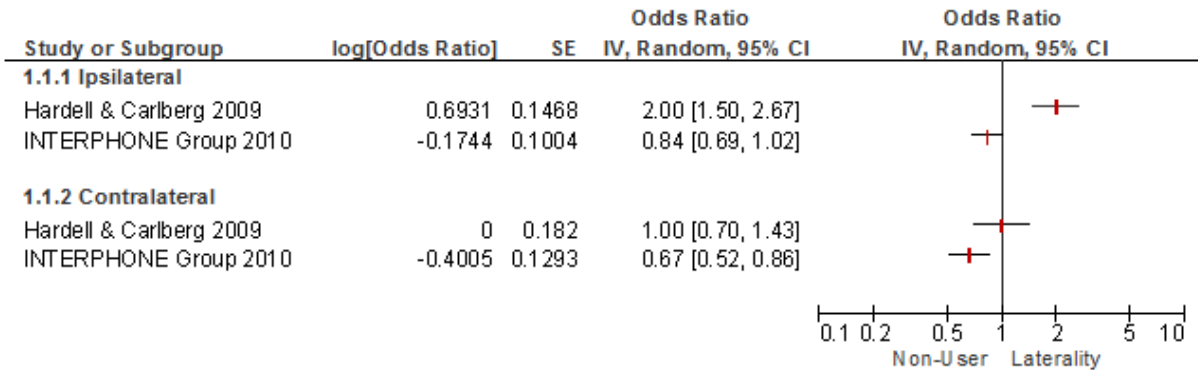
Two studies were considered for MA in regards to laterality, the larger INTERPHONE study, and the Hardell study which had pooled data from 1997-2000 and 2000-2003.

8.9.4.a. Glioma

As seen in **Figure 13**, for both ipsilateral and contralateral analyses, the presence of heterogeneity was evident. For ipsilateral use, there was considerable heterogeneity, I^2 (96%) and Cochrane's Q ($p<0.00001$). For contralateral use, there was substantial heterogeneity, I^2 (69%) and Cochrane's Q ($p=0.07$). As seen in other analyses, compared to the Interphone study, the Hardell studies have consistently demonstrated a positive association; and Interphone, an inverse association. In general, there seems to be a greater association between ipsilateral (use of mobile phone on same side as tumour location) use compared to

contralateral (use of mobile phones on opposite side of tumour location) use for the association between mobile phone use and glioma.

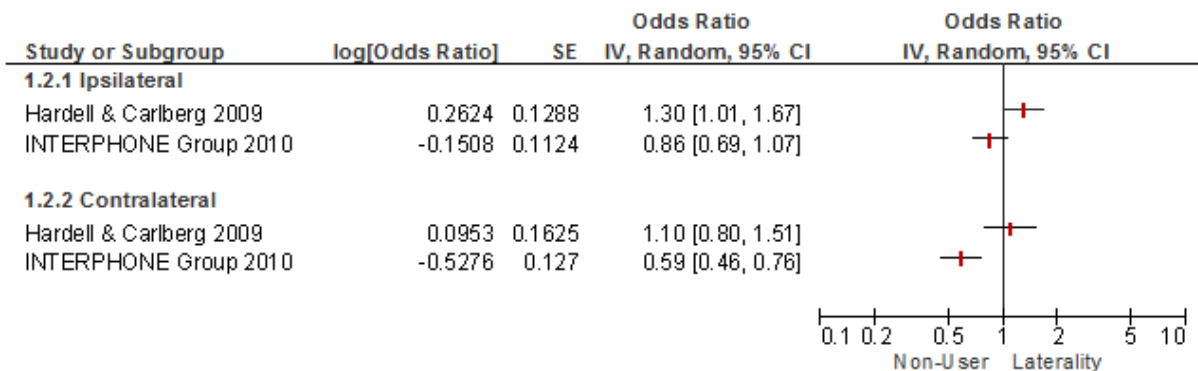
Figure 13. Ipsilateral and Contralateral User Compared to Non User- Glioma



8.9.4.b. Meningioma

As seen in **Figure 14**, for both ipsilateral and contralateral analyses, the presence of heterogeneity was evident. For ipsilateral use, there was considerable to substantial heterogeneity, I^2 (83%) and Cochrane's Q ($p=0.02$). For contralateral use, there was also considerable to substantial heterogeneity, I^2 (89%) and Cochrane's Q ($p=0.003$). Similar to the laterality analysis for glioma, the Hardell studies demonstrate a positive association in contrast to the Interphone studies, and there is a general trend with ipsilateral use having a greater influence on mobile phone use and meningioma.

Figure 14. Ipsilateral and Contralateral User Compared to Non User- Meningioma



8.9.5. TYPE OF PHONE: Analogue compared to Digital

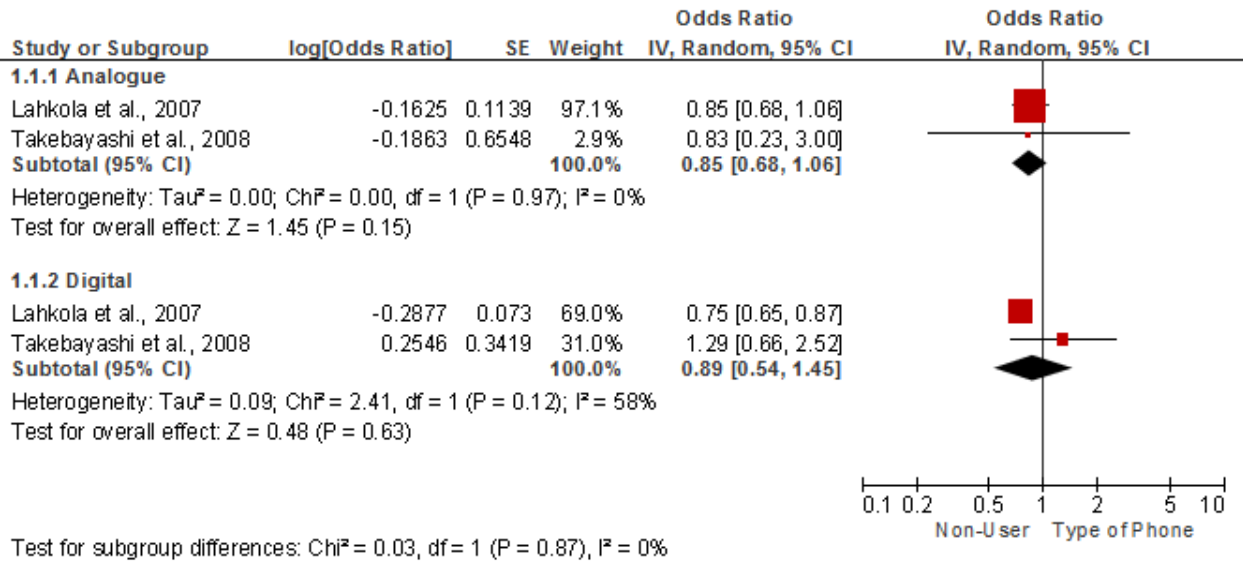
Only two studies were considered relevant for this particular analysis. The larger, all-encompassing Interphone study (125) did not provide this type of data and the larger Hardell & Carlberg, (113) study only provided cordless phone data. To this end, the Lohkola *et al.*, (122, 123) studies which pools the Interphone data for five Nordic countries (Denmark, Finland, Norway, Sweden, UK) and the Japanese Interphone study conducted by Takebayashi *et al.*, (120) provide odd estimates for analogue and digital mobile use and its association with glioma and meningioma. Auvinen *et al.*, (129) had also provided such data; however it was excluded for analysis based on the premise that subscriber data was used, where one cannot infer that the subscriber was the actual user of the mobile phone.

8.9.5.a. Glioma

For analogue use, when both studies were combined, there was little to no heterogeneity, $I^2=0\%$, Cochrane's Q ($p=0.97$). Based on these statistical tests, pooling of both studies were deemed appropriate, and the combined odds estimate was OR 0.85 (0.68-1.06). Thus, there seems to be no association between analogue mobile use and glioma.

For digital use, there seemed to be a moderate heterogeneity between both studies, as demonstrated by the I^2 test ($I^2=58\%$). Despite this moderate heterogeneity, the p-value for the Cochrane's Q test had not reached statistical significance for heterogeneity, as the p-value was >0.1 ($p=0.12$), and thus the data is considered homogeneous enough to pool. The pooled estimate was 0.89 (0.54-1.45), demonstrating no association between digital mobile use and glioma.

Figure 15. Analogue and Digital User Compared to Non User- Glioma, Adjusted

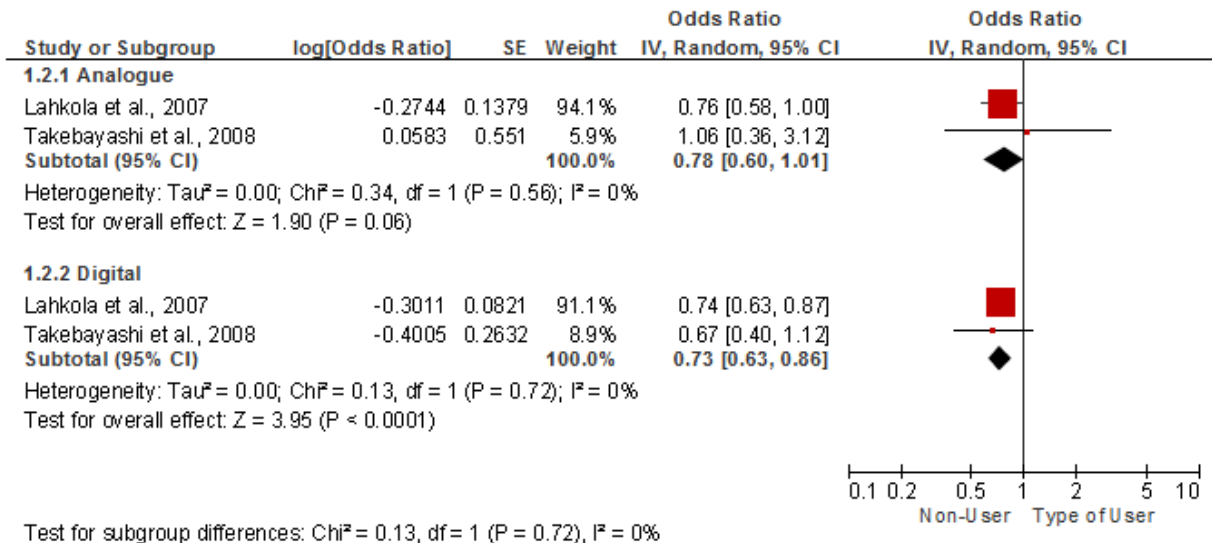


8.9.5.b. Meningioma

For analogue use, when both studies were combined, there was little to no heterogeneity, I²=0%, Cochran's Q (p=0.56). Based on these statistical tests, pooling of both studies were deemed appropriate, and the combined odds estimate was OR 0.78 (0.60-1.01). Thus, there seems to be no association between analogue mobile use and meningioma.

For digital use, there also seemed to be little to no heterogeneity, I²=0%, Cochran's Q (p=0.72). The pooled estimate was OR 0.73 (0.63-0.86), demonstrating an inverse association between digital mobile use and meningioma.

Figure 16. Analogue and Digital User Compared to Non User- Meningioma, Adjusted



8.9.6. CUMULATIVE CALL TIME

Cumulative call time was provided as an exposure category for the larger Interphone study(125); but not for the in depth larger analytical Hardell & Carlberg (113) study. It was, however, provided for the next two most appropriate studies conducted by Hardell *et al.*,(126, 127). Different studies have used different thresholds to form the categories for number of hours of cumulative call time. As such, due to this large difference between studies, it was considered inappropriate to attempt to pool the results as the exposure thresholds are considered to be heterogeneous.

The Interphone study(125), had separated their cumulative call time into deciles (starting from <5 hours and ending with ≥ 1640 hours). Only the tenth decile had provided significant results for glioma, OR 1.40 (1.03-1.89). The tenth decile resulted in a non-significant OR of 1.15 (0.81-1.62) for meningioma.

The Hardell *et al.*, (127) study which focused on malignant tumours such as high and low grade astrocytoma, had provided cumulative call time exposure categories based on type of phone used. Statistically significant results were derived for high grade astrocytoma and analogue cumulative call time of >85 hours, OR 2.2 (1.5-3.2); high grade astrocytoma and digital cumulative call time of ≤ 64 hours and >64 hours, OR 1.4 (1.04-1.8) and OR 1.7 (1.3-2.3), respectively and high grade astrocytoma and cordless cumulative call time of >195 hours, OR 1.9 (1.4-2.6). No statistically significant associations were found for low grade astrocytoma and any category of cumulative call time for this particular study.

The Hardell *et al.*, (126) study which focused on benign tumours such as meningioma had failed to find a statistically significant association for the three categories of cumulative call time, 1-500 h, 501-1000h, and >1000h with OR 1.0 (0.8-1.2), OR 1.3 (0.9-1.8), OR 1.3 (0.99-1.8), respectively.

9.0. PERSONAL HAIR DYE USE (PHASE2 : UPDATE OR *DE-NOVO* SYNTHESIS)

9.1. Brief Background/ Issues and Basis for Study Development

Personal use of hair dyes has been listed within plenty of narrative reviews as a potential risk factor associated with brain tumours. These literature reviews have not definitively concluded its positive association, as one can with ionizing radiation. However, its association is still questionable, and has not been addressed as a question in a systematic review; where one can place more confidence in the conclusions concerning its association with glioma and meningioma.

The prevalence of hair dye use is considerable. It has been reported that over 50% of women in developed countries use these products(132). Serious concern was presented in the 1970s when certain chemicals found in hair dyes (certain aromatic amines, p-phenylenediamine and aminophenylenyl in particular) were inducing tumours within animal models(133-135). As a result, certain chemicals were banned from these products, as a means to minimize risk(136). Despite these efforts, there are still over 5,000 chemicals used within hair dye products, and the safety of these formulations has not been confirmed(137). It has been shown in toxicological experiments that exposure to other amines from hair dyes are successful in percutaneous (dermal) absorption(138, 139).

There are essentially three types of hair dyes being used: permanent, semi-permanent, and temporary. Permanent dyes, making up majority of the use, are considered more damaging. An oxidative process is needed calling for the interaction between colourless precursors and couplers in the presence of hydrogen peroxide to produce a coloured dye which infiltrates the hairshaft(135).

Hair dye use has been proposed to be associated with several cancer sites within epidemiological studies, such as breast cancer, bladder cancer, and leukemia to name a few(140).

There have been no systematic reviews available which have satisfied the inclusion/exclusion criteria to be considered in Phase 1. Main reasons for exclusions of existing reviews are analyzing the outcome as "brain tumours" in a general term, and not considering them as separate histological sub-types, glioma and meningioma(138, 140).

Another reason for exclusion was the focus on maternal exposure and subsequent risk for childhood brain tumours, as opposed to personal use and risk in adulthood(138). Thus, a systematic review on personal hair dye use and the risk of adulthood glioma and meningioma, specifically, does not exist within the medical literature. An a priori protocol has already been developed and can be found in **Appendix O**.

9.2. Research Question and Objectives

Components of the intended research question can be constructed within a PICO framework.

- **Population:** Adults (≥ 18 years old, males and females)
- **Intervention/Exposure:** Personal hair dye use (ever, permanent, semi-permanent, temporary)
- **Comparator:** N/A
- **Outcomes:** Glioma sub-types (astrocytoma, glioblastoma, oligoastrocytoma, oligodendroglioma, ependymoma) and meningioma
- **Study Designs:** Case-control and cohort studies.

Research Question: Based on available case-control and cohort studies, is personal hair dye use (permanent, semi-permanent, and temporary) associated with adult onset of glioma sub-types (astrocytoma, glioblastoma, oligoastrocytoma, oligodendroglioma, ependymoma) and/or meningioma?

Objectives:

- To identify relevant observational studies (case-control and cohort) focusing on the effects of personal hair dye use and the onset of glioma and/or meningioma in an attempt to provide an overall conclusion regarding this association.
- If permissible (at least three separate study estimates), to conduct a MA on relevant studies (with data pertaining to Never vs. Ever, Never vs. Permanent, Never, vs. Semi-Permanent and Never vs. Temporary).
- To provide a current-up to date, high methodological quality SR and MA on the association between personal hair dye use and glioma/meningioma, as dictated by AMSTAR criteria, to be used by health policy makers and relevant stakeholders.

9.3. Literature Search Strategy

With the guidance of a health information specialist at the University of Ottawa, search strategies were developed and tailored for the following bibliographic databases: PubMed, Medline, Embase, CINAHL, TOXLINE and PsycINFO (see **Appendix P**). AARP Ageline was excluded as they were deemed irrelevant based on the searches conducted in Phase 1. Grey Literature sources, such as ProQuest Dissertation and Thesis Database, as well as Google and Google Scholar were searched. “Other sources” of literature were also considered. Bibliographies of included studies were searched, studies included in previous reviews were considered and hand-searching of disease-specific journals, such as Cancer Causes and Control and the International Journal of Cancer was completed as well.

All search strategies generally followed the same template. The following concept groups: Disease terms, risk terms, smoking terms, and a filter for identifying observational studies were all combined with the Boolean operator AND. Search terms within each concept group were combined the Boolean operator OR. Searches were conducted to include all published relevant articles up to January 25, 2013

9.4. A Priori Selection Criteria

Studies were included if they had satisfied all of the following inclusion criteria:

- Studies focused on the onset on at least one of the following brain tumours: glioma, astrocytoma, oligodendrolioma, oligoastrocytoma, ependymoma, glioblastoma, meningioma
- Studies focused on personal hair dye use as exposure and must provide risk estimates with 95% confidence intervals.
- Personal hair dye use had to be the main exposure variable, and could not be combined with another exposure variable as part of an interaction term.
- Studies had to be of either case-control or cohort study design.
- Studies had to be published in English or French.
- Full-text of studies had to be retrievable.

Studies were excluded if they had satisfied at least one of the following exclusion criteria:

- Studies focused on childhood primary brain tumours.

9.5. Study Selection Method

After the removal of duplicates, identified studies were subjected to two levels of screening (title/abstract and full text) using the same screening questions for each level within Distiller SR (Evidence Partners, Ottawa, Canada) (**See Appendix Q**). A method known as “liberal accelerated” screening was used whereby only one reviewer’s input is needed to advance an article to the next level; however decisions from two reviewers were needed to exclude an article. The first reviewer (PQ) screened 100% of the articles, and the second reviewer (RES) duplicate screened the excluded articles identified by the first reviewer. Any conflicts were resolved by consensus and a kappa statistic was determined for the strength of agreement for excluded studies between the two reviewers.

9.6. Data Extraction Method

Studies which satisfied the a priori selection criteria were subjected to the data extraction process. Information on study characteristics, participants, exposures, outcomes and results were recorded (**Appendix I**). The first reviewer extracted data from all relevant studies, and the second reviewer (MA) duplicate extracted a random 25% sample.

9.7. Study Quality Assessment

As recommended by the Cochrane Collaboration, quality assessment of observational studies were completed by using the NOS(57, 74). NOS was chosen since: it was widely used for quality assessing observational studies, was quick to implement, and it had established face and content validity, along with inter-rater reliability(57, 74).

Methodological issues between cohort and case control studies were evident, and the NOS accounted for such differences by subjecting both types of studies to different scales. The following components were addressed for both scales: selection (4 stars), comparability (2 stars) and ascertainment of exposure/outcome of interest (3 stars). The maximum score on

this scale is nine stars (57, 75).

Although standard scoring thresholds had yet to be determined, many studies had consistently used the threshold of ≥ 5 stars and <5 stars to represent studies of high and low quality(76-80).

9.8. Statistical Analysis

Quantitative summaries were considered for the following analyses: (a) never vs. permanent; (b) never, vs. semi-permanent; and (c) never vs. temporary. A MA was attempted if there were greater than three relevant studies per analysis and if heterogeneity tests determined that the pooling of numerous risk estimates was appropriate. Analysis was analyzed by cohort and case-control estimates separately.

Degree of heterogeneity was determined by conducting the following statistical tests, Cochrane's Q and I^2 (81). As outlined in the Cochrane Collaboration, I^2 percentages between 0%-40%, 30%-60%, 50%-90%, 75%-100% represents unimportant, moderate, substantial, and considerable heterogeneity, respectively(82). Due to the low power of the Cochrane's Q test to detect true heterogeneity, the threshold for significance was increased to $p=0.1$, meaning any p -value ≤ 0.1 was considered statistically significant for heterogeneity and any p -value >0.1 was considered homogeneous(82, 83).

Random effects models based on the DerSimonian and Laird Method (DLM), a variation of the inverse variance method was used to pool estimates together as opposed to using the fixed effects models(82, 84). Since variability is always present, random effects modeling generates more conservative estimates for determining significance by producing wider confidence intervals, allowing one to be more cautious in their conclusions. The standard errors and the log risk or odds ratios of eligible point estimates were inputted into Review Manager v.5, resulting in pooled adjusted point estimates(84). If sufficient data existed, sub-group analyses based sex and histological sub-type was attempted. Publication bias was assessed for symmetry through inverted funnel plots generated by Review Manager.

9.9. Results

Bibliographic database searching resulted in the identification of 23 potentially relevant articles. 9 additional articles were identified through searching other sources, such as grey literature, disease specific journals and studies included in existing reviews. Thus, a total of 32 potentially relevant articles were imported into Distiller SR (Evidence Partners, Ottawa, Canada). After the removal of duplicates, a total of 15 were subjected to Level 1 screening for relevancy based on title and abstract. No articles were in conflict. The kappa statistic for level of agreement based on the 9 excluded was 0.50, which represented moderate agreement(66). 6 studies had satisfied Level 1 screening, and the full-text was retrieved for further scrutiny in Level 2 screening.

Six full text articles were subjected to Level 2 screening. The kappa statistic for level of agreement based on the 2 excluded articles for the two reviewers was 1.00, which represented almost perfect agreement(66). For the excluded articles with reasons at level 2, see **Appendix R**.

The remaining 4 articles had satisfied the a priori inclusion/exclusion criteria and were subjected to 25% duplicate data extraction and quality assessment by the second reviewer (MA). Slight differences were noted in both extraction and quality assessment responses, and were promptly resolved by consensus.

Figure 17. PRISMA flow diagram of included/excluded studies

Source:

Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group. (2009). *Preferred Reporting Items for Systematic Review and Meta-Analyses: The PRISMA Statement*. PLoS Med 6(6): e1000097. Doi: 10.1371/journal.pmed1000097.

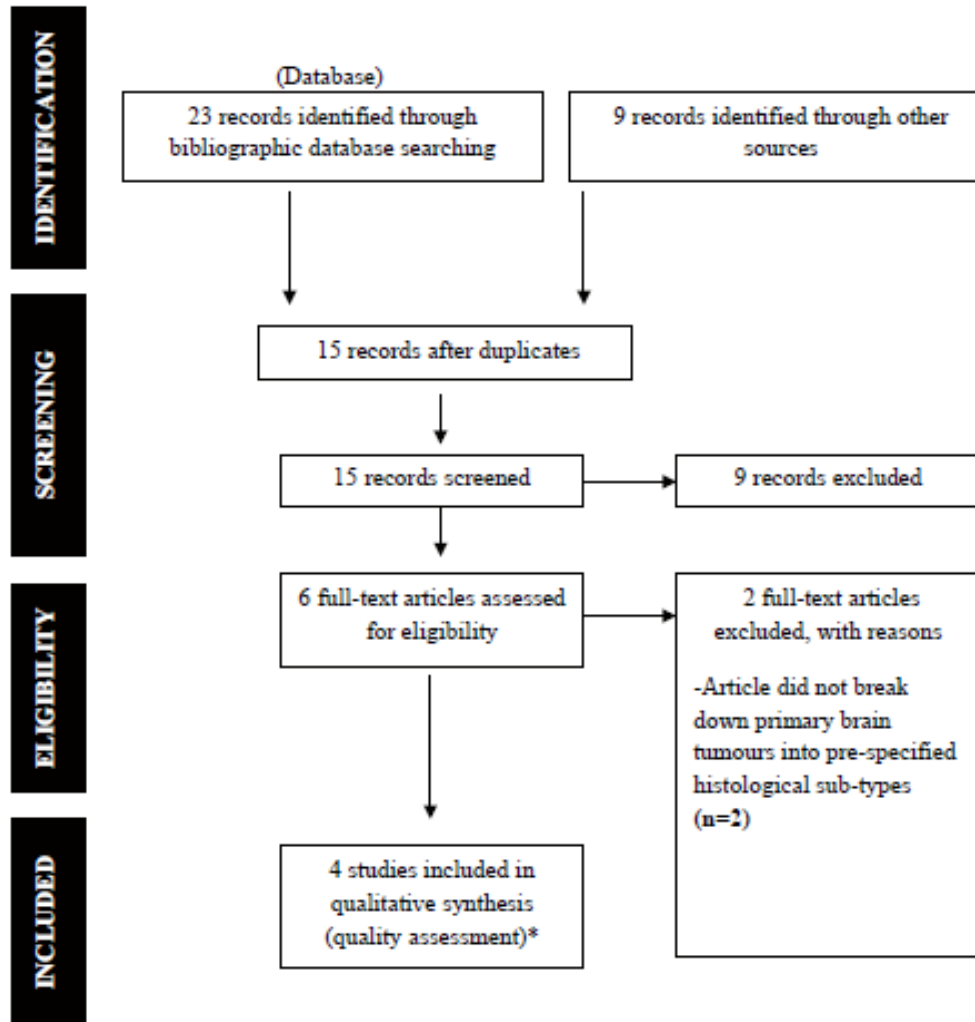


Table 9. Included studies identified for the association between personal hair dye use and glioma and meningioma.

CASE-CONTROL STUDIES								
Article	(1)Outcome; (2) Case ascertainment	Control Population	Sample Size	Response Rate	(1) Age; (2) Sex	Confounding Variables	Risk Estimates (Ever compared to Never, Permanent, Semi-Permanent, Temporary use of hair dyes)	Overall Conclusions
(Bluhm <i>et al.</i> , 2006) NOS: 6	(1) Glioma & Meningioma; (2)ICD-O codes-2nd edition: 9380-9473, 9490-9506	Hospital based	Cases: (Glioma=489; Meningioma=96); Controls=799	Cases-92%; Controls-86%	(1) 18+; (2) both	Matched on age, sex, race/ethnicity, hospital, and distance of residence from the hospital. Adjusted for marital status, education.	#1: Females, Glioma ,Ever, OR 1.0 (0.7-1.6) #2:Females, Glioma, Permanent, OR 1.0 (0.6-1.6) #3: Females, Glioma, Semi-Permanent, OR 1.0 (0.6-1.6) #4: Females, Glioma, Temporary, OR 0.8 (0.5-1.5) #5: Females, Glioblastoma, Ever, OR 1.0 (0.5-1.9) #6: Females, Glioblastoma, Permanent, OR 0.8(0.4-1.7) #7: Females, Glioblastoma, Semi-Permanent, OR 0.7 (0.4-1.5) #8: Females, Glioblastoma, Temporary, OR 0.6 (0.2-1.3) #9: Females, Meningioma, Ever, OR 0.8 (0.5-1.4) #10: Females, Meningioma, Permanent, OR 0.8 (0.5-1.4) #11: Females, Meningioma, Semi-Permanent, OR 0.8 (0.5-1.4) #12: Females, Meningioma, Temporary, OR 0.8 (0.4-1.5) #13: Males, Glioma, Ever, OR 0.9 (0.6-1.5) #14: Males, Glioma, Permanent, OR 1.4 (0.7-2.7). #15: Males, Glioma, Semi-Permanent, OR 0.8 (0.5-1.4) #16: Males, Glioma, Temporary, OR 1.7 (0.5-5.7)	No association between hair dye use and glioma/meningioma.

							#17: Males, Glioblastoma, Ever, OR 0.8 (0.4-1.6) #18: Males, Glioblastoma, Permanent, OR 2.1 (0.8-5.1) #19: Males, Glioblastoma, Semi-Permanent, OR 1.5 (0.4-5.0). #20: Males, Meningioma, Ever, OR 0.5 (0.1-1.4)	
(Heineman <i>et al.</i> , 2005) NOS: 7	(1) Glioma; (2) ICD-O: 938-948	Population based controls from another study	(112/215)	Cases-88%; Controls-82%	(1) 21+ years; (2) females	Year of birth, gender, education	#1: Glioma, Ever, OR 1.7 (1.0-2.9) #2: Glioma, Permanent, OR 2.4 (1.3-4.5) #3: Glioma, Non-Permanent, OR 1.0 (0.5-1.9) #4: Glioblastoma, Ever, OR 2.3 (1.2-4.3) #5: Glioblastoma, Permanent, OR 3.5 (1.7-7.3) #6: Glioblastoma, Non-Permanent, OR 1.3 (0.6-2.9)	There seems to be an association between permanent hair dye use and glioma and glioblastoma risk.
(Preston-Martin & Paganini-Hill, 1980) NOS: 5	(1) Meningioma; (2) histological confirmation	Population controls from same neighbourhood as cases.	(189/185)	cases-98%	(1) <65 years; (2) females	Matched on sex, race, and year of birth (within 5 years, SES	#1: Ever, OR 1.0 (p=0.91)	No Association.
(Ahlbom <i>et al.</i> , 1986) NOS: 6	(1) Astrocytoma; (2) diagnosis by medical record	Two types of controls: Hospital and population based.	Cases: 78; Controls: 197 clinical controls, and 92 population controls	Did not state explicitly	(1) 20-75; (2) both	age, sex, parish matched	#1: Ever, clinical controls, OR 0.8 (0.4-1.8) #2: Ever, population controls, OR 1.5 (0.6-3.7)	No Association.

9.9.1. Description of Identified Studies

Four case-control studies were identified overall. One study focused on glioma as an outcome(141). One study focused specifically on astrocytoma(142) . One study focused on meningioma(143). One study focused on both glioma and meningioma(144). Two studies had used actual ICD-O codes to identify diseased cases, whereas the remaining two had used either histological confirmation or referred to a medical record. All four studies had adjusted for various confounding variables, with the following being of the most common: age, sex, race/ethnicity, and education.

9.9.2. Quality Assessment

Quality assessment scores using the NOS were between 5 to 7 for all four studies out of a possible 9 points. Sub-group analyses based on quality scores could not be attempted, as there were not enough studies to stratify by similar quality score. As noted earlier, a cut-off score of 5 would be used to determine high compared to low quality; however, this may not be a good indicator, as all of the studies had scored above 5. If a sub-group analysis was plausible, then using the median score as a cut-off would be more appropriate.

9.9.3. Duration of use (years)

Bluhm *et al.*,(144) had looked at the following categories of use (<1 year, 1-9 years, 10-19 years, and ≥ 20 years) for glioma, glioblastoma, and meningioma risk. For all disease entities, a dose-response relationship was absent. It is hypothesized that as you increase the duration, you increase your risk. All estimates generally hovered around the null value of 1. Heineman *et al.*, (141) had looked at the following categories of use (<1-10 years, 11-20 years, 21+ years) for glioma and glioblastoma. Separate estimates were provided for permanent and non-permanent use. For permanent use, odd estimates tended to be higher than non-permanent. A dose response relationship was observed with permanent dye use and glioblastoma, with 21+ years associated with a statistically significant odds ratio, OR 4.9 (1.6-15.7).

9.9.4. Frequency of use

Two studies had assessed frequency of use per year and brain tumour risk. Bluhm *et al.*, (144) had looked at the following categories of use (<1, 1-3, 4-11, and 12-monthly) for glioma, glioblastoma and meningioma risk. As with duration of use, if the association is causal, one would expect a dose-response relationship with the greater number of use associated with greater risk. However, for all three disease entities this was not the case. No dose-response relationship was observed and all odd estimates tended to hover around the null value of 1. Heineman *et al.*, (141) had looked at the following categories for glioma and glioblastoma separately for permanent (<1-3, 4-6, 7+) and non-permanent use (<1-11, and 12+), respectively. For permanent use, there was no association for glioma, however for glioblastoma, the most elevated and statistically significant risk was for <1-3 and 4-6 times a year, OR 5.3 (1.2-24.1) and OR 9.4 (1.9-51.1). It should be noted that although these estimates are statistically significant, their confidence intervals are extremely wide. For non-permanent use, there was no significant association to report.

9.9.5. Colour of Permanent Hair Dye

Both Bluhm *et al.*, (144) and Heineman *et al.*, (141) had noted an elevated odds estimate for those who use permanent brown dyes. Estimates provided by Heineman for glioma and glioblastoma were statistically significant, whereas those provided by Bluhm for glioma, glioblastoma and meningioma, although elevated did not reach significance. For Heineman, the odds estimates for glioma and glioblastoma were OR 4.4 (1.7-11.4) and OR 6.5 (2.2-19.6), respectively. Although their 95% confidence intervals do not cross the null value of 1, one should note that the intervals are very wide. For red dyes, results are conflicting, as Bluhm has reported an elevated association for glioma, but an inverse association for glioblastoma; whereas Heineman has reported the opposite. Either way, all odds estimates for red dyes are not statistically significant. For blonde dyes, Bluhm has reported an inverse association for glioma, glioblastoma and meningioma; whereas Heineman has reported an elevated association for glioma and glioblastoma. Bluhm was the only study which had sufficient data for black hair dye use, and they had concluded null associations.

9.9.6. EVER VS. NEVER USE

For glioma, three case-control studies had analyzed the association between ever compared to never use of hair dyes, however one study had provided separate estimates for males and females (using separate control groups), and thus have two entries each into the analysis. Heterogeneity tests had shown the presence of unimportant heterogeneity based on I^2 test ($I^2 = 29\%$), and the Cochrane's Q test did not reach significance for heterogeneity ($p=0.24$). Based on the pooled adjusted odds estimates, there is a 13% increase in odds for ever users compared to never users; however this association is not statistically significant, as the 95% confidence intervals encompass the null value of 1. Based on **Figure 19**, the presence of publication bias was absent for this analysis, based on the symmetry of the inverted funnel plot.

Figure 18. Forest Plot for Glioma: Ever Vs. Never Use, Adjusted

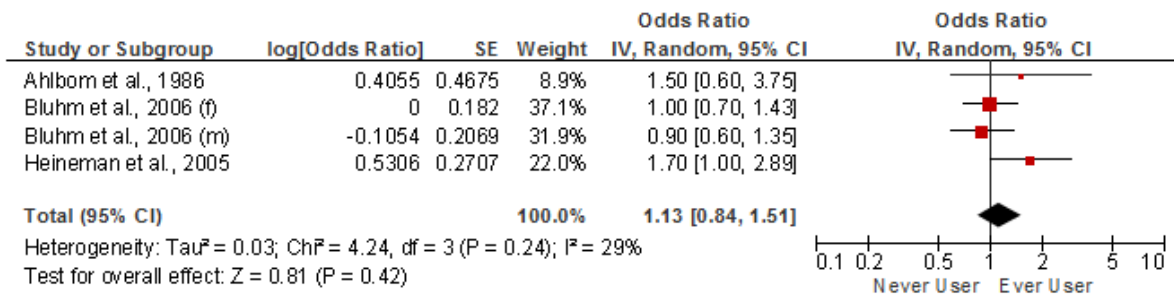
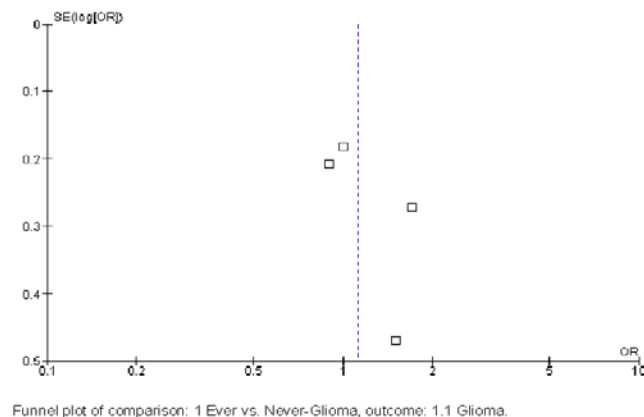
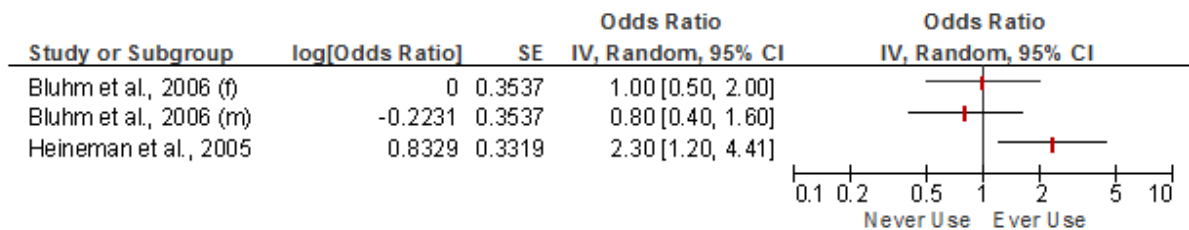


Figure 19. Inverted Funnel plot for Glioma: Ever vs. Never Use, Adjusted



For glioblastoma, two case-control studies had analyzed the association. Again, for one study, two separate estimates were provided for males and females. Heterogeneity tests had shown the presence of moderate heterogeneity based on I^2 test ($I^2=63\%$), and the Cochran's Q test had reached significance for heterogeneity ($p=0.07$). Thus, it was decided that the estimates were too statistically heterogeneous to pool. For both estimates provided for Bluhm *et al.*, (144), there was no association for ever use of hair dyes for females and males, OR 1.00 (0.50-2.00) and OR 0.80 (0.40-1.60), respectively. The remaining study by Heineman *et al.*, (141) had noted a 2.3 times statistically significant increase in risk with ever uses of hair dyes and glioblastoma for females. Publication bias was not assessed due to the small number of studies included in this particular analysis.

Figure 20. Forest Plot for Glioblastoma: Ever Vs. Never Use, Adjusted



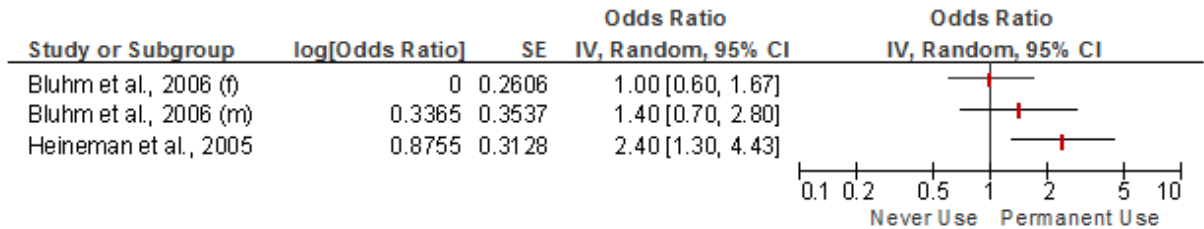
For meningioma, two case control studies had analyzed the association. Again, for one study, two separate estimates were provided for males and females. Since two estimates had provided confidence intervals, and the other study had provided a p-value to assess its certainty, it was decided that pooling would be inappropriate. For both estimates provided by Bluhm *et al.*, (144) there was no association for females and males, OR 0.8 (0.5-1.4) and 0.5 (0.1-1.4), respectively. The study conducted by Preston-Martin *et al.*, (143) had also found no association for females, OR 1.0 ($p=0.91$).

9.9.7. PERMANENT VS. NEVER USE

For glioma, two case control studies had analyzed the association. Again, for one study, two separate estimates were provided for males and females. Heterogeneity tests had shown the presence of moderate heterogeneity based on I^2 test ($I^2=57\%$), and the Cochran's Q test had reached significance for heterogeneity ($p=0.1$). Thus, it was decided that the estimates were too statistically heterogeneous to pool. Bluhm *et al.*, (144) had found a null

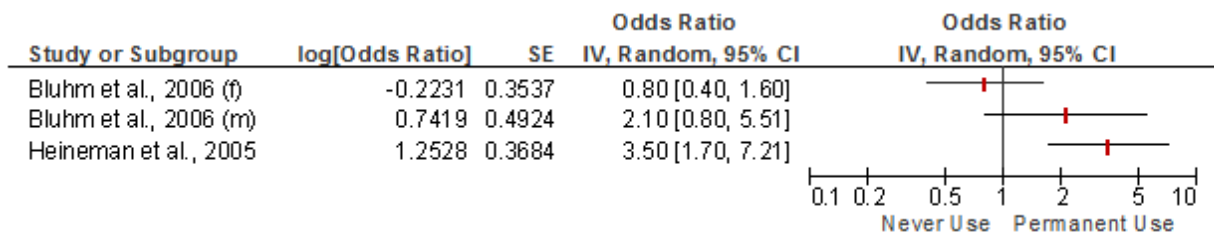
association for females, but had found a 40% increase in risk for men, albeit not statistically significant, OR 1.0 (0.6-1.6) and OR 1.4 (0.7-2.7), respectively. The remaining study by Heineman *et al.*, (141) had noted a 2.4 times statistically significant increase in risk with ever uses of hair dyes and glioma for females. Publication bias was not assessed due to the small number of studies included in this particular analysis.

Figure 21. Forest Plot for Glioma: Permanent Vs. Never Use, Adjusted



For glioblastoma, two case control studies had analyzed the association. Again, for one study, two separate estimates were provided for males and females. Heterogeneity tests had shown the presence of moderate heterogeneity based on I^2 test ($I^2=77\%$), and the Cochran's Q test had reached significance for heterogeneity ($p=0.01$). Thus, it was decided that the estimates were too statistically heterogeneous to pool. Bluhm *et al.*, (144) had found a null association for females, but had found a 2.1 times increase in risk for men, albeit not statistically significant, OR 0.80 (0.40-1.60) and OR 2.10 (0.80-5.51), respectively. The remaining study by Heineman *et al.*, (141), had noted a 3.5 times statistically significant increase in risk with ever uses of hair dyes and glioma for females. Publication bias was not assessed due to the small number of studies included in this particular analysis

Figure 22. Forest Plot for Glioblastoma: Permanent Vs. Never Use, Adjusted



For meningioma, Bluhm *et al.*, (144), had found no association for females, OR 0.8 (0.5-1.4).

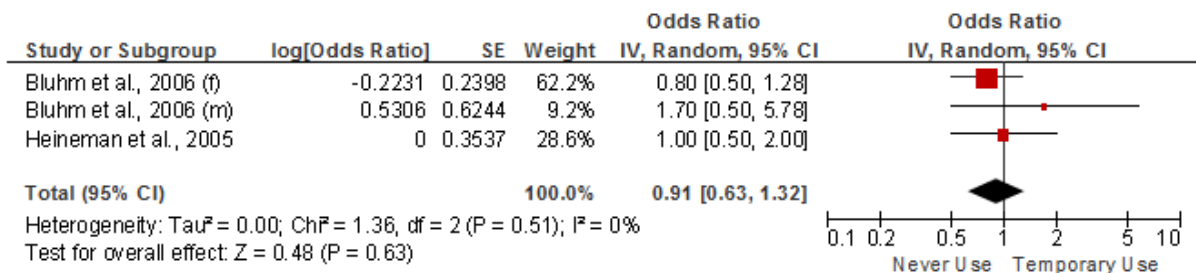
9.9.8. SEMI-PERMANENT VS. NEVER USE

For glioma, only one case-control had analyzed the association between semi-permanent use compared to never use of hair dyes, providing separate estimates for females and males. Both resulted in null findings, OR 1.0 (0.6-1.6) and OR 0.8 (0.5-1.4), respectively. This same study had analyzed its affects on glioblastoma, with null findings for females and a 50% increase in risk for males, albeit not statistically significant, OR 0.7 (0.4-1.5) and OR 1.5 (0.4-5.0), respectively. For meningioma, null findings were also found for females, OR 0.8 (0.5-1.4).

9.9.9. TEMPORARY/NON-PERMANENT VS. NEVER USE

For glioma, three case-control studies had analyzed the association between temporary use compared to never use of hair dyes, however one study had provided separate estimates for males and females (using separate control groups), and thus have two entries each into the analysis. Heterogeneity tests had shown the presence of unimportant heterogeneity based on I^2 test ($I^2 = 0\%$), and the Cochran's Q test did not reach significance for heterogeneity ($p=0.51$). Based on the pooled adjusted odds estimates, there is no association between permanent use of hair dyes and its risk of glioma, OR 0.91 (0.63-1.32). The presence of publication bias was absent for this analysis, based on the symmetry of the inverted funnel plot.

Figure 23. Forest Plot for Glioma: Temporary Vs. Never Use, Adjusted



For glioblastoma, two case-control studies had analyzed the association between temporary use compared to never use of hair dyes. Bluhm *et al.*, (144) had found no

association for females, OR 0.6 (0.2-1.3); whereas Heineman *et al.*, (141) had found a 30% increase in risk for females, however, it was not statistically significant, OR 1.3 (0.6-2.9). For meningioma, Bluhm *et al.*, (144), had found no association for females, OR 0.8 (0.5-1.4).

10.0 DISCUSSION

(PHASE 1: A Systematic Search of Existing Systematic Reviews and Meta-Analyses)

10.1 . Limitations at the Review Level

Limitations of the existing SRs were outlined below separated by differing items important in SR methodology. Further analyses of how these existing SRs compare and contrast with the three *de-novo* SRs completed in Phase 2 in regards to methods and results were reported in the discussion portion of each *de-novo* review, sections **10.4**, **10.5**, and **10.6**.

10.1.1. Comparable Outcomes through Common Disease Definitions

In order to provide a proper basis to pool multiple risk estimates, the studies must be similar enough in regards to the population, the intervention, and the outcomes (PIOs). By ensuring these four elements are homogeneous enough amongst studies, one can be confident that their pooled estimates describe the true association between exposure and outcome for a particular population(145). Regarding this topic, populations, interventions and comparators, are important. However, emphasis should be directed towards outcomes since brain tumours are a heterogeneous group of disease entities. Often times, many researchers' acknowledge brain tumours as a single entity, unaware that each histological sub-type may have differing etiologies(146). Care should be taken to ensure that similar brain tumour histologies are being compared.

Glioma is one of several types of brain tumour, and researchers often provide separate risk estimates from other types such as meningioma and medulloblastoma. It has been discovered, however, that certain sub-types of glioma possess differing molecular pathways, and thus potential differing etiologies(147). Since there is only a small number brain tumour cases as is, looking at glioma as a grouped entity is the most viable option at the present

moment. Ideally, there should be an overall glioma estimate and subsequent sub-group analyses for glioma sub-types should be provided when possible.

Authors of SRs and MAs should define a priori a disease classification system used to define glioma and meningioma. They should be using this classification system as an inclusion criterion to determine which individual observational studies should be included to ensure that disease outcomes are as similar as possible given the complexity of brain tumours as a disease itself. Ideally, the WHO's ICD codes (see **Table 1**) should be used. As noted previously, an overall glioma pooled estimate should be provided, but sub-group analysis for glioma sub-types should be attempted based on similar ICD codes. Although this is the ideal standard for SRs and is often applicable to most disease outcomes, for some diseases, such as brain tumours, this is difficult to accomplish. The main reasoning behind this is due to the numerous histological sub-types classified under the term "brain tumour", and the fact that there is no single agreed upon classification system to be used. Regardless, it is of great interest to see what other authors of systematic reviews focused on brain tumours have done to address this issue.

For the existing SRs and MAs which focused on mobile phone use, four out of five reviews had not referred to the use of a common disease classification system for defining glioma and meningioma(26, 92-94). It was implied that they had included any studies which focused on glioma and meningioma, regardless of whether a common classification system was used. The remaining review, although they had also not mentioned the use of a common disease classification system, they had done separate analyses for high grade and low grade gliomas(87). It can be implied that the authors had developed some sort of criteria for classifying glioma cases into one of these two categories. As such, one cannot be sure, as it was not reported in the review article.

The existing SR and MA on smoking conducted by Mandelzweig *et al.*, (95), had not explicitly stated the use of a common disease classification system to ensure that all observational studies included were considering the same disease entity. The authors did, however, ensure that each included study had medically confirmed cases of glioma. This does ensure some level of homogeneity, but using a standardized classification system would have been preferred.

For diet, Huncharek *et al.* (96) had not provided a common disease definition for what they had considered as homogeneous cases of glioma as reported within individual observational studies. Therefore, the cases of glioma which Huncharek *et al.*, (96) have considered may have been heterogeneous in nature.

10.1.2. Duplicate Screening and Extraction of Included Studies

It is highly recommended that screening and extraction for relevant articles be done in duplicate. Duplicate screening ensures that relevant articles are not being dismissed due to the opinions and biases of a single reviewer(148). In the same context, by conducting duplicate extraction, it can be re-assured that answers being extracted in correspondence to questions being asked are not interpreted differently by separate reviewers(148).

For existing SRs and MAs which focused on mobile phone use, only one review had addressed the issue of duplicate reviewers (93). This revelation is quite surprising as duplicate screening, at least, is considered an essential step when conducting a SR. Myung *et al.*, (93), had included two independent reviewers for screening and had consulted a third party when discordance was present. The authors did, however fail to mention whether duplicate extraction was conducted. The remaining three reviews did not mention whether duplicate screening and duplicate extraction were conducted(26, 87, 92, 94). Limited space allotted within manuscripts may have been a reason for excluding the description of whether duplicate screening and extraction were conducted; however, SR and MA are viewed as transparent methods of synthesizing information. As such, these important methodological steps should be reported nonetheless.

For smoking, Mandelzweig *et al.*, (95) had also failed to mention whether duplicate screening and extraction were considered.

For diet, Huncharek *et al.*, (96) had addressed the concept of duplicate reviewer to a certain degree. They had only one reviewer screen for relevant articles. They did, however, introduce duplicates within their extraction phase, where two independent reviewers extracted pertinent information, and disagreements were resolved by consensus.

10.1.3. Ensuring same Confounding Variables are Controlled for when Pooling

In order to ensure greater validity of results from a MA, it is imperative that confounding bias is limited as much as possible. Confounding bias within a MA occurs when the authors of a MA fail to include studies which control for the same confounding variables(149). Thus, when they pool the results together of multiple studies, heterogeneity is inherently present, and the results of the MA cannot be deemed reliable(149). Often times, it is difficult to find sufficient number of relevant studies which control for the exact same confounding variables, this is especially the case for observational studies as the study design is not as rigorous for controlling extraneous variables as would be a randomized controlled trial. Thus, many SRs include and pool studies which have adjusted for some important factors, irrespective of how many there are and which ones are controlled for. Usually, however, there are common variables which are common throughout the studies.

Socioeconomic status (SES) is an important confounding variable which may affect the estimates associated with lifestyle and behavioural risk factors and disease outcome. Some studies control for this; however some studies do not. A limitation of SRs especially consisting of observational studies, is that one cannot ensure that all included studies adjust for this confounding variable. However, with some studies controlling for this, one can assume that the extent of this variable on the estimate is taken care of to some extent.

For existing SRs and MAs, three reviews had not ensured that similar confounding variables were included within relevant studies(26, 93, 94). As such, their derived pooled estimates were likely to be affected by heterogeneity, as differing confounding variables were controlled for.

Kan *et al.*, (87), had listed the confounding variables taken into account for each included study. However, they did not ensure that these variables were similar before they had decided to pool the data. Kan *et al.*'s approach to this particular limitation was improved over Myung *et al.* (93) and Khurana *et al.*, (26), as they had listed these confounding variables to allow readers to interpret the results of the pooled analysis with their own discretion.

Out of the five reviews on mobile phone use, Lakhola *et al.*, (92) had done the most satisfactory job with attempting to control for confounding bias. The authors had ensured that the two important confounding variables age and sex were controlled for in all included studies. Although they had controlled for these two variables, other studies have also included other confounders which they have controlled for, which others have not. They had noted the implications of this in their discussion where they conclude that this may be a potential source of heterogeneity. Either way, heterogeneity cannot be fully eliminated, as it is rather difficult to find similar individual studies which control for the exact same confounding variables. It can, however, be minimized to a certain extent as demonstrated by Lakhola *et al.*, (92)

For smoking, similar to Kan *et al.*, 's (87) review on mobile phone use, Mandelzweig *et al.*,(93) had for each included study, listed the confounding variables which the study had controlled for. However, they did not attempt to ensure that these variables were similar before they had decided to pool the data. The authors did, however, address the lack of uniformity in confounding variables within included studies.

For diet, within their table of characteristics, Huncharek *et al.*,(96) had listed the confounding variables which each study had controlled for. Within their discussion, Huncharek *et al.* had stated that total energy intake was considered a very important confounding variable and that only two included studies had controlled for this. To determine the extent of the effect of this variable, the authors had conducted a sensitivity analysis by dropping the studies which had controlled for total energy intake, and the pooled estimate dropped significantly, thus supporting the assumption that this variable is contributing to confounding bias.

10.1.4. Quality Assessment of Included Studies

It has become common practice when conducting SRs, that a tool be used to quality assess the validity of the studies to be included within a review. This is an important step as including poor methodological quality studies, will more than likely introduce bias, often leading to exaggerated effect sizes (150).

Over the years, several tools and instruments have been developed for quality assessing observational studies. Some tools are more popular than others, however, it's up to the authors' discretion on which tool they believe would be best suited for their review. As well, theoretically, they should also be addressing the limitations involved when using that particular tool. As Armstrong *et al.*, (151) have noted, regardless of which tool is used, more often than not, the use of a tool ensures that the observational studies to be included are: ``...free from methodological biases (including selection bias, response bias, and observer bias).``

For the existing SRs and MA which focused on mobile phone use, three out of five reviews (26, 87, 92) had not used a tool to quality assess included observational studies. Therefore, it can be implied that their pooled analyses had incorporated both high and low quality studies, causing one to question the confidence one can place on their pooled estimates.

Repacholi *et al.*,(94) had used a quality assessment tool which they had developed themselves where certain domains of quality assessment had to be satisfied. Weights were given to each prompt. The remaining review by Myung *et al.*,(93) had used the Newcastle-Ottawa Scale (NOS) to quality assess its case-control studies. In response to the review, a commentary written by Stang *et al.*, (152) was published and had questioned Myung *et al.*'s use of the NOS and its validity. One criterion of the NOS states in particular that interviewers must be blinded to disease status, however, Stang *et al.*, argue that this is not likely possible unless structured, monitored interviews are taking place, which is not usually the case. They also question assigning low quality scores, when in fact the study might have actually satisfied certain NOS criteria, yet simply did not have enough manuscript space to describe their methods. They also question the arbitrary cut-off of seven stars to identify high quality versus low quality studies. In response to Stang *et al.*'s comments, the authors of this review had provided explanations for each criticism. In regards to validity of the NOS, they state that other quality assessment tools also have questionable validity, and that NOS was the most comprehensible. Myung *et al.* agree that more structured interview techniques should be in place to maintain blinding, however, if a study reported this action, it should still be considered high quality compared to studies which did not address this at all. Although lack

of reporting does not mean lack of action, Myung *et al* still feel that the only way to objectively quality assess a study is with the authors disclosure within their manuscripts. They had also used seven stars as a cut-off as no other criteria have been set.

For smoking, Mandelzweig *et al.*, (95) had also failed to quality assess its included studies. Thus, causing one to conclude that the authors had pooled both high and low quality studies together.

For diet, Huncharek *et al.* (96) had failed to quality assess their eligible observational studies. As such, they were unable to determine the effect high compared to low quality studies had on the review's conclusion.

10.1.5. Publication Bias Assessment

The presence of publication bias has the potential of influencing a review's conclusions(153). Publication bias usually occurs when reviews are more likely to include studies which report a positive association, have larger sample sizes, are of higher quality, are heavily influenced by funding companies, or a combination of all of the above(153). This happens most frequently since studies with negative and/or null findings are less likely to be submitted and published in reputable journals, and thus, are less likely to be identified within the medical literature. To correct for this, grey literature searching is encouraged to identify the studies which would have otherwise been missed. This includes searching through theses and dissertations, as well as conducting internet searches (Google, Google Scholar), for abstracts and governmental reports (63).

Several methods are available to assess the presence of publication bias. Visually, an inverted funnel plot is used. The symmetrical distribution of plots indicates the absence of publication bias. Statistically, one can determine its presence through two tests, Begg's and Egger's(153).

Sutton *et al.*, (153) were interested and carried out a study to determine whether the presence or absence of publication bias in a review did in fact influence a review's conclusion. Their findings suggest that the presence of publication bias had no effect(153). As such, the authors had noted that although several authors of SRs and MA fail to assess

publication bias, this step is still considered important and should still be done to ensure that studies are not selected in a non-random manner (153).

For the existing SRs and MAs which focused on mobile phone use, all but two review (26, 94) had assessed the presence of publication bias. Using a funnel plot, Lahkola *et al.*(92), had concluded that there was an absence of publication bias. Instead of a visual funnel plot, Kan *et al.*(87), had used Begg's and Egger's statistical test, with a p value <0.05, indicating the presence of such a bias. Although the authors had stated its use, they had failed to provide the results within their manuscript. Myung *et al.* (93) had used both methods to detect publication bias. The funnel plot which was symmetrical, indication lack of bias, and the Egger's statistical test had produced a p-value of 0.21, also indicating its absence.

For smoking, Mandelzweig *et al.*, (95) had assessed the presence of publication bias using both Begg's and Egger's statistical tests. They had provided separate results for both tests based on case-control studies, cohorts studies, and all together. All analyses presented with an absence of bias.

For diet, Huncharek *et al.*, (96) had failed to test for the presence of publication bias.

10.1.6. Proper Method of Pooling Estimates

When conducting MAs with randomized controlled trials, it is often easiest to assume with greater confidence that the studies being pooled are more likely to be homogeneous compared to MAs with observational studies(154, 155). With controlled trials, certain biases and confounders are more easily controlled. Thus, there is a greater probability that studies looking at a particular exposure and outcomes are more likely to be similar in RCTs, which leads to greater confidence in homogeneity of individual effect sizes which make up the pooled estimate(154). However, the pooling of observational studies is gaining greater popularity in the medical academia field, and is no longer viewed as inferior to the pooling of RCT estimates, quite to the extent as it had been before(156). The only caveat is that special attention should be paid to exploring the sources of heterogeneity within observational study estimates, should they exist(156).

There are two basic statistical models for pooling study estimates, fixed and random effects models. The fixed effects model assumes that the same effect is being measured

across all studies, and does not account for variability within the population(157, 158) . Thus the statistical model only includes a term for “within study” variation. The most common methods used to conduct fixed effects modeling are Mantel-Haenszel, Peto, General Variance-Based and Confidence Interval(158). The random effects model assumes that the studies included all possess a certain degree of variability since they are a random sample of the population, measuring an “average” effect(157, 158). Thus the statistical model includes terms for both “between study” and “within study” variation. The most common method used to conduct random effects modeling is DerSimonian and Laird(158).

Theoretically, one should be using a test to assess heterogeneity, such as Cochrane’s Q and/or I^2 . In the presence of heterogeneity, a random effects model should be used. In its absence a fixed effects model should be used. As explained prior, due to the greater likelihood of heterogeneity between studies of observational studies assessing the same population, exposure and outcome, a random effects model should be used, irrespective of the outcome from tests assessing heterogeneity(155). This is so, since random effects model are deemed more conservative providing wider confidence intervals. We therefore do not mistakenly place greater confidence on results, which inherently have a certain degree of heterogeneity present(155).

For the existing SRs and MAs which focused on mobile phone use, all reviews had approached the pooling of observational studies in different ways. Kan *et al.*,(87) and Repacholi *et al.*, (94) had used the most appropriate method for combining study estimates. Even though the authors had used a test for homogeneity to assess the degree of its presence they had opted for the use of a random effects model over a fixed effects model as it would have provided a more conservative estimate. This ideally, should be the standard when handling MAs with observational studies; one should use a random effects model, but should also use a test to assess the degree of heterogeneity present.

Both reviews by Myung *et al.*, (93) and Lahkola *et al.*,(92) had conducted the next best approach. They both had used a test to assess heterogeneity of included studies, (I^2 for Myung and Cochrane’s Q for Lahkola), and based on subsequent results; either a random or fixed effects model was used. Although the review by Khurana *et al.*, (26) had used a random

effects model, the authors had failed to conduct a test for heterogeneity to ascertain the degree of heterogeneity present.

For smoking, Mandelzweig *et al.*, (95) had used Cochrane's Q to assess the presence of homogeneity amongst the studies being pooled. Most appropriately, the authors had calculated pooled estimates using both fixed and random effects method. However, the authors had opted to report only those results derived from the random effects model as it is deemed more conservative.

For diet, Huncharek *et al.*, (96) had used Cochrane's Q test for homogeneity to determine whether heterogeneity was present among included studies. Based on their description within the methods section, it was assumed that the authors would have refrained from pooling study estimates if heterogeneity did indeed exist. However, based on the Cochrane's Q, study estimates were considered homogeneous, and therefore a fixed effect model, more specifically, the general variance based method was used.

10.2. Limitations of Methods used in Phase 1

10.2.1. Liberal Accelerated Method for Screening

The golden standard regarding methods of screening within the SR process is to conduct 100% duplicate screening of studies by two independent reviewers. Any conflicts are either settled by consensus by the two reviewers or a final decision is made by a third party. Although this method is largely encouraged within academic circles, often times, finite resources limit the ability to do so. As such, it is common for authors to streamline this process by either having only one author conduct screening or by having a second reviewer duplicate screen a random sample. The former certainly introduces selection bias, and the latter to a lesser extent. More recently, however, a new screening method has been recently cited within a publication by Khangura *et al.*, (159) and is currently being used by The Ottawa Hospital Research Institute (65) and is endorsed by the makers of Distiller SR.

This method is known as the "liberal accelerated method". One reviewer screens 100% of the articles. The articles excluded by the first reviewer are then screened in

duplicate by the second reviewer. Thus only one reviewer's input on an article's relevancy is needed to advance an article, and two reviewer's inputs are need to exclude an article(159). This creates a "safety-net" approach, where articles are not discarded from a relevant review by mistake. Since this a relatively new method, its implications have not yet been fully criticized. However, this method is a stream-lined approach and provides a middle ground between the two extremes of screening methods. Its use is promising as it has been gaining popularity within the medical literature.

10.2.2. Quantitative Aggregation of AMSTAR Scores.

The AMSTAR tool was developed as a means to identify certain methodological components which have been addressed or unaddressed in a SR and MA, thereby providing information on its methodological quality. Two SRs may have the same aggregated AMSTAR score, yet one may in fact be of higher quality than the other. This is possible such that certain criteria within AMSTAR carry heavier biases compared to others. For example, a review that did not use appropriate statistical methods would be deducted one point, and a review which simply had not provided a list of excluded studies would also be deducted one point. The former carries a heavier bias and certainly affects the methodological quality of a SR more so compared to the latter (27).

Quality assessment as with other aspect of SR methodology (screening, extraction), carries a significant level of subjectivity(21, 27). To avoid this subjectivity as much as possible, a random sample of studies will be subjected to duplicate quality assessment by a second reviewer.

Although there are obvious limitations to aggregating AMSTAR criteria, due to the nature of this thesis, it was considered the most appropriate way of characterizing the quality of a review. Without a numerical indicator, it is difficult to provide a bottom line summary about a review's quality. By assigning a quality score, the review if considered high quality could be further pursued to identify new evidence without replicating work that has already done.

Again, although aggregating AMSTAR scores is discouraged, many authors have done this, including the Canadian Agency for Drugs and Health (CADTH) for their Rx for

Change Database project(67). This agency is highly valued within public health circles and is used to inform policy on all three levels of government. Thus, we decided a priori to refer to their AMSTAR thresholds to assign low, moderate and high quality scores for relevant reviews (0-3, 4-7, 8-11).

(PHASE 2: Update or De-novo Synthesis)

10.3. Biases Based on Case-Control Study Designs

Within the field of Epidemiology, results from randomized controlled study designs is considered the most reliable source for evidence-based medicine (160). However, often times, when analyzing the etiological relationship between exposure and outcome, one cannot rely on randomized study designs due to severe ethical issues. It has been hypothesized that the certain risk factors (such as those discussed above, mobile phone use, smoking, diet and personal hair dye use) are associated with glioma and meningioma. Thus, based on this premise, it would be unethical to expose one arm of a controlled design to a risk factor which could potentially lead to the development of the disease in question (160).

Therefore, when studying the lifestyle and behavioural risk factors for glioma and meningioma, one must rely on observational study designs such as cohort and case-control studies. Next to randomized study designs, a well conducted cohort study is considered to have greater validity due its suggestive nature to infer temporality(160). The exposure clearly precedes the outcome, and this notion is one of nine of Bradford Hill's criteria for establishing causality(160). Although cohort studies on lifestyle and behavioural risk factors for glioma and meningioma have been conducted, they are few and far in between. Since brain tumours are rare, conducting a cohort study is often infeasible, resource wise, as long follow-up would be needed(160).

Due to the small number of incident and prevalent cases of glioma and meningioma, a large majority of etiological studies are based on case-control designs. Gathering data is more efficient, and one can be assured that there are enough cases to detect an effect(160). However, consequences of using such a design are its difficulty in inferring causation.

A common limitation mentioned amongst all six existing SRs and MAs was the potential influence that recall bias may have on all included individual studies. Simple aggregation of these estimates will not correct for these inherent recall biases present within the individuals studies, and is a limitation which must be acknowledged when interpreting pooled estimates.

Recall bias, a type of information bias, is a systematic (non-random) error which is commonly associated with case-control study designs(161). Often times when dealing with brain tumours, recall bias leads to differential misclassification of study subjects to exposure categories based on their disease outcomes. The misclassification is differential since the subjects are able to recall more or less of an exposure as a direct result of their disease status(161). With glioma and meningioma, the issue of recall is even more serious because these patients have brain tumours and with subsequent surgeries, their memories may be affected significantly(95). Since recall capabilities of these subjects are hindered, some case-control studies rely on proxies. The use of proxies is of concern since many are not aware of the true exposure dose which the subject has endured(95). Therefore risk estimates can either be over- or under-exaggerated since brain tumour cases can either over- or under-estimate their exposure(161).

For mobile phone use, it was noted that exposure ascertainment of most individual case-control studies lacked validity since the common method of gathering exposure data was through telephone interviews and questionnaires, resulting in a degree of subjectivity. A more objective way of gathering this data would be through mobile phone records; however, even then, one cannot be certain that the individual subscribed to such services is the individual using the mobile phone. Studies based on diet are also prone to such subjectivity with inaccurate recall of food intake through questionnaires.

10.4. Discussion of Smoking *De-novo* Review

10.4.1. Findings

When analyzing the effect of smoking patterns (age at initiation, duration of smoking, quantity of cigarettes per day and pack-years) on risk of glioma and/or meningioma, there did

not seem to be any inherent association. Since many of these smoking pattern variables are analyzed by increasing intervals, one would expect a dose-response relationship; however this was not evident. Exposure to passive smoking and brain tumour risk was also not evident.

However, when analyzing the above smoking pattern variables, the study conducted by Phillips *et al.*,(109) had consistently noted an increased risk of meningioma for males whereas females always displayed an inverse association. Although this is one study, Phillips *et al* have acknowledged that they have been the only study to observe such a pattern, and have acknowledged other studies such as Hu *et al.*,(110) , which have observed an opposite effect. However, a recent MA conducted by Claus *et al.*,(162) had concluded the same results, where males had a positive association, and females had an inverse association. Different studies were identified for this particular MA compared to the one conducted by Claus *et al.*,(162) as selection criteria and the search process itself may have differed since its process was not described fully within the manuscript.

A possible biological mechanism has been suggested to explain this finding. Irrespective of smoking status, incidence and prevalence of meningioma has always been higher amongst females, as meningioma has been hypothesized to be influenced by the female hormones, progesterone and estrogen(163). Based on these findings and that of Claus *et al.*, (162), the presence of effect modification by sex between smoking and meningioma seems to be present, with the male sex displaying an increased risk for meningioma based on the effects of smoking. This observed pattern may be biologically plausible, as smoking is known to have anti-estrogenic effects(164). Cigarette smoking converts active estradiol into inactive catechol estrogens(165). Thus, plausible binding of hormones to estrogen and progesterone receptors of the meninges may be significantly reduced amongst females. It has also been suggested that males have different patterns when smoking cigarettes compared to females with greater inhalation and greater frequency of puffs, leading to greater exposure irrespective to quantity of cigarettes smoked(109) .

Based on MAs, there is little to indicate that there is an association between ever and current smoker compared to never smoker for both glioma and meningioma. Although all adjusted pooled estimates were slightly elevated, none were of statistical significance. There

was however a statistically significant 20% increase in risk for past smokers compared to never smokers within cohort studies, RR 1.20 (1.04-1.38). The previous MA by Mandelzweig *et al.*,(95) identified in phase 1, had also noticed an elevated risk associated with past compared to never smokers, RR 1.16 (1.04-1.29). The same pattern between the current review and that conducted by Mandelzweig *et al.*, may be due to the inclusion of the same studies within the MA. There has been little evidence to support why such an association exists, as one would expect current smokers to have greater risk compared to past and ever smokers. This spurious association may be due to exposure misclassification, since studies have differing definitions for past, never, current. We kept these definitions broad as other studies within brain tumours and other diseases have used these categories for quantitative analysis(95, 166). The individual observational studies included within the MAs have also used these defining categories. However, one must keep in mind that the individual's study definitions within these categories may differ. As an example, Phillips *et al.*, (109) had defined ever smokers as those who have smoked at least 100 cigarettes within a lifetime 10 years prior to surgery date; otherwise they were classified as never smokers. At the individual study level, this misclassification bias may also be due to recall bias which is also possible in cohort studies of smoking, as participants would still have to self-report their exposures at baseline and follow-up data collection (likely without keeping a record of exposure).

A possible hypothesis for the lack of association can be attributed to the blood-brain barrier. It is known, as a result of several consistent studies, that maternal exposure to cigarette smoking can induce brain tumour formation in the child since the permeability of the blood-brain barrier is much less developed during fetal development(101). In adults, however, it has become questionable whether there can be such an effect, since the permeability of this barrier in adulthood is much more controlled(101, 167).

10.4.2. Strengths and Limitations

This MA has many strengths and limitations. In regards to strengths, this SR and MA was conducted in such a way that all eleven criteria of AMSTAR were satisfied, thus

rendering it of high methodological quality. This is of great importance when conducting a review, as failure to conduct certain methods can change the overall conclusions. As well, transparency by means of reporting is a fundamental concept within SRs since others should be able to replicate your work, and AMSTAR ensures that all steps are recorded in such a manner. Gliomas and meningiomas are rare diseases, and as such, individual studies usually have small number of cases, by conducting a pooled analysis, several studies are combined, thus increasing the number of cases and increasing the power to detect an association if present(168). Analyses were also separated by study design, which many reviews fail to do. Case-control and cohort studies are inherently differing study designs and have differing biases associated them.

In regards to limitations, a new method known as “liberal accelerated” screening was employed. Further discussion on this method can be found in **section 10.2.1**.

The primary limitation of this study would be the pooling of studies with differing adjustment for confounding variables. With observational studies, it is often times difficult to ensure that all studies control for the same confounding variables. Many studies provide unadjusted and adjusted pooled risk estimates. Unadjusted pooling was attempted; however several studies had lacked data to determine the number of cases and controls to calculate an estimate. Thus, adjusted pooled estimates were conducted. This is a practice conducted by many researchers conducting SRs and MA of observational studies(169, 170). The only caveat is that when interpreting such estimates, this obvious limitation should be considered.

10.4.3. Comparison with Existing Systematic Review

The review conducted by Mandelzweig *et al.*,(95) was deemed moderate quality with an AMSTAR score of 5. A major difference between the existing smoking review and this current review was the inclusion of meningioma in addition to glioma as outcome measures, and the inclusion of passive smoking as an exposure variable. As noted previously, certain AMSTAR criteria were not satisfied, whereas this review has ensured that all eleven AMSTAR criteria were fulfilled. Interestingly, we wanted to determine whether moderate to low quality reviews would change conclusions compared to a high quality reviews as per AMSTAR criteria.

Two things may cause a review to be considered moderate quality: (a) Either the authors had conducted essential SR steps and had failed to report them within their publications. As a result, the conclusions may be appropriate; however the confidence that the medical community and policy makers place on these conclusions may be hindered as they are not able to reference important steps taken to derive at such conclusions(171); (b) The authors had failed to conduct these essential SR steps all together. As a result, conclusions from these reviews may be misleading and inaccurate which may be problematic as health care providers and policy makers often base real-life decisions from these reviews. Transparency and accuracy of reporting are fundamental necessities of conducting SRs (171).

The existing review by Mandelzweig *et al.*, (95) had failed to refer to an a priori protocol. Duplicate screening and extraction was not discussed. A comprehensive literature search was not performed as only one bibliographic database was searched. The grey literature was not searched. The scientific quality of included studies was not assessed, and any potential conflicts of interests were not discussed.

In the end, conclusions for both reviews in regards to glioma did not differ. This was due to the fact that a large majority of included observational studies were the same for both reviews. Medline, the only database searched by Mandelzweig is the largest database containing indexed medical literature, and chances of identifying a large majority of relevant studies is very high(172). However, as per conventional SR methods, this review searched multiple databases to increase the probability of capturing all relevant studies. This review was novel compared to the existing review, in that an association with meningioma was found which was influenced by the variable, sex.

10.4.4. Overall Conclusion

Although there may be no overall association, it is suggestive that past smokers may have an elevated risk, although biases (such as misclassification, discussed previously) may be influencing this finding. As well, males are slightly more affected by smoking and glioma/meningioma risk compared to women; albeit its association needs further research.

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10.5. Discussion of Mobile Phone Use Review

10.5.1. Findings

For the main outcome analysis of latency, a quantitative summary estimate could not be derived as the heterogeneity between the three studies for glioma, and two studies for meningioma was considered too great. For both glioma and meningioma, the Hardell & Carlberg study (113) has consistently provided statistically significant positive associations, with the ≥ 10 year latency having a greater odds estimate compared to short-term use (1-9 years). The Interphone study(125) on the other hand, including the Inskip study(131) have consistently provided an inverse association. Based on the data, an association cannot be confirmed for both glioma and meningioma in regards to short and long term use.

For the secondary analysis of laterality, again, the presence of heterogeneity has inhibited the ability to pool the data. In general, ipsilateral use data provided by Hardell & Carlberg (113) and the Interphone Study (125) was more greatly associated with glioma and meningioma compared contralateral use. Based on the data, it is suggestive that ipsilateral use has a greater influence on glioma and meningioma development; although its impact may not be significant. It has been consistently cited in the literature that this general greater association for ipsilateral use compared to contralateral use could be partially explained by recall bias, and may not reflect a true association. Diseased cases are more likely to report greater use of mobile phones on the same side which their tumour are located (ipsilateral), in an attempt to positively explain mobile phone use as the causative agent for the disease state(173).

For the other secondary analysis, type of phone, heterogeneity did not pose such a problem, as studies which had used the same protocol were combined, the combined Interphone estimates of five Nordic countries conducted by Lahokla *et al.*,(122, 123) and the Japanese Interphone study data(120) . Based on the MA, there is no apparent association between analogue and digital use for glioma, OR 0.85 (0.68-1.06) and OR 0.89 (0.54-1.45), respectively. There is also no apparent association between analogue and digital use for meningioma, OR 0.78 (0.60-1.01) and OR 0.73 (0.63-0.86), respectively.

For cumulative call time, there only seemed to be a statistically significant association for glioma, for (a) the Interphone(125), at the 10th decile, and; (b) the Hardell *et al.*, (127) study , with all three types of phones, usually at the highest category of cumulative call time. No association was found for meningioma.

For the two major studies of interest for this review, Hardell & Carlberg (113) and the all encompassing Interphone study(125), the presence of inherent biases associated with each study could be the reason why both studies are deriving such conflicting results.

The inverse association observed within Interphone studies, could be attributed to the following reasons. Firstly, users of cordless phones were handled differently between the two major studies, a form of non differential misclassification bias of exposure, which usually causes a downward association(173, 174). For the Interphone study, cordless phone users were considered "unexposed" since they're exposure to electromagnetic radiation was deemed sufficiently lower compared to mobile phone users, and was considered to not have the same effect(26). Hardell *et al.*; however have argued the opposite, in which cordless phone users should be considered as exposed subjects when analyzing mobile phone use; albeit separately in a sub-group analysis(175). Since Interphone had included "exposed" subjects in the "non-exposed" group, the resulting odds estimates would have been driven away from a positive association, if present(175). This was verified when, the Hardell group themselves had used their data and had manipulated it, such that their cordless phone users were considered "unexposed", thus resulting in a lowered odds estimate(175).

Secondly, there was a significant difference in participation rates between the two studies which may lead to the presence of selection bias. Participation rates for Interphone were 64% for cases and 53% for controls; whereas 90% of cases and 89% of controls had participated in the Hardell studies(175). A validation study conducted for the Interphone study had noted that response bias (a form of selection bias) is deemed as one of the most heavily influenced biases inherent within Interphone. In order to determine whether non-responders differed from participants, non-responders were asked to fill out a short questionnaire on their mobile phone use habits. Surprisingly, non-responders reported less use compared to participants. Even when taking this into account, the odds estimates could not be fully explained by the presence of selection bias, as the resulting odds ratios would

have only increased to approximately 0.87-0.92 from 0.81 for glioma, still a downward association(176).

Thirdly, the issue of blinding could have partially explained the inverse association observed. The Interphone study had used computer-assisted questionnaires, where the facilitator was able to determine the participants' disease status when asking the relevant questions. As a result, the facilitator may have influenced how the participant's answers., which may have influence the downward bias, if the interviewers believe that mobile phone use does not cause brain tumours(177).

The positive associations consistently observed by the Hardell *et al.*, studies could be explained by many factors as well. It is also important to note that out of all of the epidemiological studies conducted on this topic, the Hardell studies have been the only group of studies to consistently present significant positive results, which has caused several scientists to critically evaluate the evidence presented by the Swedish group. Although there is a sense of questionability, scientists who have formed some sort of criticism have found it difficult to pinpoint certain biases involved. Differences in case definitions, exposure definitions and eligibility criteria between the three Hardell publications, 1994-1996, 1997-2000 and 2000 -2003 have been cited as a reason (173). A SSI report has criticized Hardell based on its 1997-2000 data, stating that interviewer bias could have played even if a mailed questionnaire was used. A nurse was asked to follow-up on patients who had not completed their questionnaires completely; this process was not fully described as being standardized, which indicates the possibility of interviewer bias. As well the SSI had stated that: "...with over 200 comparisons presented, it is likely that many of the "significant" findings are due to chance alone."(178).

Both the Interphone and Hardell studies were prone to recall bias. Recall bias is inherent within any case-control study. Those who have the disease may be more likely to over-estimate their exposure risk. Recall bias can also be used to explain the general increase in association for ipsilateral use over contralateral use, as diseased patients are more likely to recall using the mobile phone on the same side as their location for their tumour to explain their disease status.

10.5.2. Strengths and Limitations

This particular SR and MA differs from existing reviews such that a majority of AMSTAR criteria were fulfilled which would classify it as a high quality review. Five existing reviews were considered relevant in phase 1, with quality scores ranging from 3 to 7, thus classifying them as low to moderate. The most recent review, published by Repacholi *et al.*, (94) was well conducted; however several components essential within SRs and MA were either missing or were not alluded to. The authors did not complete a comprehensive search strategy as specific search strategy with Boolean operators (AND/OR) were not provided and external supplementary sources "grey literature" was not consulted. They had also failed to explicitly mention some form of duplicate screening or extraction within the review. As well, the authors had still decided to pool the data even though the heterogeneity tests conducted had proven that the study data were too different to combine. As well, the authors had defined a common exposure definition for pooling the Interphone and Hardell studies as regular user (at least 1 call/week for ≥ 6 months). Only the Interphone study had explicitly used this exposure definition for their study; whereas Hardell *et al.*, did not go into detail about their definitions and had simply alluded to mobile phone users as ever users. Thus, combining both studies would be misleading. This particular review had derived conclusions similar to those SRs and MA identified in phase 1. All reviews had concluded that there was no clear, concrete association between mobile phone use and glioma and meningioma. Although some reviews suggest that there may be the basis for a slight association, these conclusions are just suggestive and cannot be used to imply causation, as statistical significance is clearly lacking in all of the reviews.

Thus, a strength of this review was the satisfaction of all eleven AMSTAR criteria, thereby classifying it as a high quality review. Another strength would be the presence of an a priori protocol which many reviews either do not complete, or they fail to allude to one within their manuscripts. An exception would be the most recent review conducted by Rapecholi *et al.*, who had provided one within their supplementary materials. It was ensured that all processes involved in this review were transparent and documented, both fundamental when conducting reviews of this type.

In regards to limitations, a new method known as “liberal accelerated” screening was employed. Further discussion on this method can be found in **section 10.2.1**.

Many researchers have argued that there lacks a clear biological mechanism to explain how RF-EMFs from mobile phones can cause cancerous growths. As such, due to lack of biological mechanism, there is no basis to claim causation. However, there have been recent studies which have proposed that cells exposed to RF-EMFs alter the heat shock protein 70 (hsp70) causing damages to cells. However, these studies are inconclusive (179).

Despite the fact that the evidence provided has been conflicting and does not necessarily provide the basis for deriving a concrete solution, the International Agency for Research on Cancer (IARC) had gathered a working group of thirty expert scientists in an effort to classify what category of carcinogenic risk RF-EMFs fall into. The Hardell and Interphone studies were the main epidemiological studies used to inform their decisions. Although they are both conflicting, the working group had come to the consensus that RF-EMFs from mobile phones are considered '2b'- possibly carcinogenic, and had felt that the association with mobile phones could not be due solely to bias (114). Other carcinogens in 2b include chloroform and progestins, thus based on this one can see that this classification is not of immediate concern. However, the scientists wanted to ensure that the precautionary principle was in place, while further studies are conducted to provide more evidence for making a concrete conclusion.

10.5.3. Comparison with Previous Existing Systematic Review

Although there were multiple existing reviews on mobile phone use, Repacholi *et al's* (94) review will be used for comparison as it is the most recently published. The existing review was deemed moderate quality with an AMSTAR score of 5. As noted previously, certain AMSTAR criteria were not satisfied, whereas this review has ensured that all eleven AMSTAR criteria were fulfilled. It was not explicitly stated whether there was duplicate screening and extraction. A comprehensive search was not performed as extra supplementary sources were not considered and the grey literature was not searched. A list of excluded studies was not presented and neither was a table of characteristics of included studies. Publication bias was also not addressed.

In the end, conclusions for both reviews in regards to glioma and meningioma did not differ. Mandelzweig *et al.*,(95) had also noted the elevated risk associated with glioma use for ipsilateral cumulative use. However, an added benefit of our review is the transparency in reporting which the existing review lacks.

10.5.4. Overall Conclusion

Overall, there is no association for latency and type of phone use on glioma and meningioma risk. Both major studies in the field of mobile phone use research have agreed that ipsilateral use, and cumulative call time at the highest interval may increase overall risk. Based on this evidence, the association between mobile phone use and brain tumour risk is not entirely clear. More independent groups other than the two dominating the literature need to conduct research in this field to provide results from another perspective.

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10.6. Discussion of Personal Hair Dye Use Review

10.6.1. Findings

When analyzing the effect of hair dye use patterns (duration of use, frequency of use and type of permanent colour) on risk of glioma, glioblastoma and/or meningioma, based on the two studies which had provided information, there was no inherent association for duration and frequency. The authors did find an elevated association for glioblastoma risk and permanent hair dye use. Brown permanent hair dye seemed to be consistent in both studies as having the highest elevated odds ratio, and again, was statistically significant for glioblastoma, although very wide confidence intervals were an issue.

Based on the MA, due to the presence of significant heterogeneity in a number of comparisons, pooling of such results was discouraged. Two comparisons were considered homogeneous enough to pool: (a) ever compared to never use for glioma, where an elevated

odds estimate was detected; and (b) temporary compared to never use for glioblastoma, where an inverse odds estimate was detected. Both failed to reach statistical significance. For Ever compared to Never, Permanent compared to Never, Heineman *et al.*, (141) had consistently reported a statistically significant result for glioblastoma. Bluhm *et al.*, (144) had consistently reported a null result for glioblastoma, and therefore one cannot infer that there is a true effect on glioblastoma. Additional studies are needed to provide support.

As with all case-control studies, several biases could be affecting the reported results, such as recall bias. Hair dye as an exposure itself is very heterogeneous and increases the probability of measurement error tremendously (180) .

A possible explanation for observing no effect could be due to the phasing out of known carcinogens present in hair dyes in the 1980s, more specifically, 2,4-diaminotoluene and 2,4-diaminoanisole (140). The chemicals present in hair dyes after 1980 may not have a profound carcinogenic effect on disease risk. Heineman *et al.*, (141) had completed a subgroup analysis to assess disease risk before and after 1980, and the authors had found a statistically significant association for glioblastoma before 1980, OR 3.0 (1.3-6.7). However, for all other analyses, Heineman had included exposure data from all years, and so had the other three studies included in this SR. Therefore, any elevated effect caused by formulations of hair dyes before 1980 would have been included with a decreased effect caused by modern day hair dyes, thereby diluting any true effect if present.

As is seen with other carcinogenic substances, such as smoking, the biological mechanism whereby the substance is able to cross the well-developed and tightly controlled blood-brain barrier has not been proven. This may explain the lack of clear association, as there may not be a possible way for the substance to directly affect the brain tissue. Interestingly enough, one would hypothesize that with the blood brain barrier being less developed during pregnancy, that prenatal use of hair dyes would have an effect on the child. However, several studies have assessed this possible association with null results (181). Therefore, hair dye use may not play a role in brain tumour neurogenesis at all.

10.6.2. Strengths and Limitations

This MA has many strengths and limitations. In regards to strengths, this SR and MA was conducted in such a way that all eleven criteria of AMSTAR were satisfied, thus rendering it of high methodological quality. This is of great importance when conducting a review, as failure to conduct certain methods can change the overall conclusions. As well, transparency by means of reporting is a fundamental concept within SRs since others should be able to replicate your work, and AMSTAR ensures that all steps are recorded in such a manner. Gliomas and meningiomas are rare diseases, and as such, individual studies usually have small number of cases, by conducting a pooled analysis, several studies are combined, thus increasing the number of cases and increasing the power to detect an association if present(168).

In regards to limitations, a new method known as “liberal accelerated” screening was employed. Further discussion on this method can be found in **section 10.2.1**.

The primary limitation of this study would be the pooling of studies with differing adjustment for confounding variables. With observational studies, it is often times difficult to ensure that all studies control for the same confounding variables. Many studies provide unadjusted and adjusted pooled risk estimates. Unadjusted pooling was attempted; however several studies had lacked data to determine the number of cases and controls to calculate an estimate. Thus, adjusted pooled estimates were conducted. This is a practice conducted by many researchers conducting SRs and MA of observational studies(169, 170). The only caveat is that when interpreting such estimates, this obvious limitation should be considered.

10.6.3. Overall Conclusion

Based on the available studies which have assessed personal hair dye use and glioma and meningioma risk, it has been suggested that there is no overall association.

Funding was provided as part of the National Population Health Study on Neurological Conditions by the Public Health Agency of Canada.

11.0. CONCLUSION AND RECOMMENDATIONS

The following below are the overall conclusions for the three *de-novo* SRs and MA is conducted in Phase 2.

11.1. Smoking

No evident association was detected between particular smoking patterns (age at initiation, duration of smoking, quantity of cigarettes per day and pack-years) for glioma/meningioma risk. An interesting trend that warrants further research is the observed increased association between smoking and meningioma risk in males. For the MA, the only statistically significant elevated association was observed for passive smoking and glioma risk within cohort studies compared to never smokers. This finding is unusual and could be due to several biases.

11.2. Mobile Phone Use

Pooling of data for latency and laterality of mobile phone use was prohibited due to heterogeneity. Although both Interphone and Hardell studies had provided conflicting results for latency, they had both concluded that ipsilateral use was associated with increased risk. For both study groups, they had concluded that cumulative call time at the highest interval is usually associated with increased risk of glioma. For the MA, type of phone was not associated with glioma/meningioma risk. More independent groups other than the two dominating the literature need to conduct research in this field to provide results from another perspective.

11.3. Personal Hair Dye Use

No evident association between particular hair dye patterns (duration of use, frequency of use, and type of permanent colour) on glioma, glioblastoma, and meningioma risk. Based on the MA, ever, permanent, semi-permanent and temporary hair dye use compared to never use was not associated with increased risk.

Phase 1 was undertaken as a means to assess the methodological quality of existing SR and MAs on particular lifestyle and behavioural factors associated with glioma and meningioma risk. How one conducts a SR has the potential to change the overall derived conclusions. Based on this premise, a handful of existing reviews were considered relevant and were deemed moderate to low quality. Phase 2 was undertaken to conduct *de-novo* SRs of moderate to low quality reviews identified in phase 1, ensuring that high methodological standards were used according to the quality assessment tool, AMSTAR. Although rigorous SR methods were applied, the overall conclusion of no association was identified for all three risk factors, which was also noted in the phase 1 existing SRs. Thus, based on the evidence from high quality SRs, it has been suggested that these particular lifestyle and behavioural risk factors generally do not affect glioma and meningioma risk.

11.4. Recommendations for Observational Studies focusing on Lifestyle Risk Factors and Brain Tumour Research

When focusing on lifestyle risk factors associated with disease outcomes, observational studies are often sought as the only method to conduct epidemiological studies, since it has been deemed unethical to conduct randomized controlled trials on exposures that could impose harm(182). As demonstrated in this thesis, null associations are often common due to biases that could be inherently present in studies.

Generally, cohort studies are preferred over case-control designs(183). Case-control studies cannot infer temporality, thus one cannot be sure that exposure preceded the outcome. With cohort designs, temporality can be more easily determined(183).

Researchers are always limited by finite resources. If limited resources were not an obstacle, when conducting a cohort study, several suggestions could be considered: (a) Having the study participants actively record their exposures on a recording form and having several time-points over the course of the study period to collect exposure data (for example, sending out surveys monthly to collect contact with exposures). This would ensure that exposure information is kept up to date and that recall bias would be minimized; (b) if feasible, having more objective ways of measuring exposure. Subjective self-reporting is common. Objective methods of obtaining smoking levels, such as urinary cotinine would

increase internal validity(184); (c) Having a longer follow-up period for brain tumour development, which is considered a disease with long latency (for example, implementing decades of follow-up) (185).

11.5. Moving Forward in Brain Tumour Etiology Research

The Brain Tumor Epidemiology Consortium (BTEC), a group of prominent brain tumour epidemiology researchers, have agreed that the research in brain tumour and risk assessment is difficult as studies are usually heterogeneous in many aspects of study design, population and exposure assessments(16) . There needs to be consensus among brain tumour researchers in regards to the use of a common disease classification system.

However, the area which may influence brain tumour risk profoundly, in spite of this limitation, is the area of genetics(16). As part of the larger SR, being completed for PHAC, which is looking at all risk factors for primary brain tumours, a search for observational studies was conducted. A large majority of relevant observational studies published in the last two years have focused on genetic polymorphism, often times with either statistically significant elevated or inverse associations.

A lesson learned from this thesis, is that rigorous SR methods should be used according to quality assessment tools, such as AMSTAR, and that transparent reporting is essential and demonstrates good practice. Based on these high quality SRs, conclusions suggest that these particular risk factors are not associated with elevated risk. By following these quality guidelines, the various biases which may result from conducting SRs can be minimized as much as possible.

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13.0. APPENDICES

13.1. APPENDIX A

Phase 1-Search Strategies for Bibliographic Databases and Grey Literature Sources

Template source (for “overview” boxes” and “syntax guide”):

Kaunelis, D. and Farrah, K. “Lecture: Introduction to Literature Searching.” Canadian Agency for Drugs and Technologies in Health (CADTH). University of Ottawa. 12 May 2011.

OVERVIEW OF SEARCH STRATEGIES

Databases (bibliographic):	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations EMBASE PUBMED PsycINFO CINAHL TOXLINE AARP Ageline Cochrane Database of Systematic Reviews
Grey Literature:	ProQuest (Dissertations and Theses) GoogleScholar Google
Hand-Searching Journals:	Cancer Causes & Control (CCC) Cancer Epidemiology, Biomarkers & Prevention
Study Types:	Systematic reviews, Meta-Analyses (filters in place)

Search for Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

OVERVIEW

Databases (bibliographic):	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
Years Covered:	1948- December 31, 2011
Date of Search:	September 26, 2011 (with monthly alerts up to December 31, 2011)
Filter for SRs and MAs:	Lindsey Sikora (Librarian at McGill University)
Sources:	(Lindsey Sikora, personal communication, April 14, 2011)

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.

/	Searches the search term as a subject heading
.sh	Searches the search term as a subject heading
exp	Explodes a subject heading
adj	Search retrieves records containing search terms which are next to each other.
\$	Truncation (wildcard). Search retrieves all suffix variations of the search term.
.ti	Searches for the search term in the title.
.ab	Searches for the search term in the title.
.fs	Floating Subheadings. Used to help refine the meaning of a subject heading.
.pt	Publication type.
	Sources:
	Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations Database
	Field Guide (2008, January 9). Ovid MEDLINE ® Database Guide. Retrieved from: http://www.ovid.com/site/products/ovidguide/medline.htm#advanced .

Search for Embase

Line #	Strategy
1	exp Brain Neoplasms/
2	(primary adj brain adj tumo\$.ab,ti.
3	(brain adj cancer).ab,ti.
4	glioma/ or astrocytoma/ or glioblastoma/ or ependymoma/ or glioma, subependymal/ or oligodendroglioma/
5	meningioma/
6	(oligoastrocytoma\$ or glioma\$ or meningioma\$ or astrocytoma\$.ab,ti. or ependymoma\$.ab,ti. or glioblastoma\$.ab,ti.oastrocytoma\$.ab,ti
7	oligodendroglioma\$.ab,ti.
8	or/1-7
9	exp Risk/
10	etiology.fs.
11	Odds Ratio/
12	prevention& control.fs.
13	or/9-12
14	8 and 13
15	limit 14 to humans
16	Meta-Analysis/
17	(meta anal\$ or metaanal\$).ti,ab,sh.
18	16 or 17
19	(methodol\$ or systematic\$ or quantitativ\$).ti,ab,sh.
20	((methodol\$ or systematic\$ or quantitativ\$) adj (review\$ or overview\$ or survey\$)).ti,ab,sh.
21	20 and review.pt,sh.
22	18 or 21
23	15 and 22

OVERVIEW

Databases (bibliographic):	Embase Classic + Embase
Years Covered:	1947- December 31, 2011
Date of Search:	September 25, 2011 (with monthly alerts up to December 31, 2011)
Filter for SRs and MAs:	BMJ Clinical Evidence- Embase Systematic review strategy
	Source: BMJ Clinical Evidence. (n.d.). Default search strategies used for BMJ Clinical Evidence. Retrieved from http://clinicalevidence.bmj.com/ceweb/about/search_filters.jsp .

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.
/	Searches the search term as a subject heading
.sh	Searches the search term as a subject heading
exp	Explodes a subject heading
adj	Search retrieves records containing search terms which are next to each other.
adj#	Search retrieves records where the first search term is within <i>n</i> number of words to the second search term.
\$	Truncation (wildcard). Search retrieves all suffix variations of the search term.
.ti	Searches for the search term in the title.
.ab	Searches for the search term in the title.
.fs	Floating Subheadings. Used to help refine the meaning of a subject heading.
.pt	Publication type.
	Sources: Embase Classic + Embase Database
	Database Guide (2007, August 21). EMBASE: Excerpta Medica Database Guide. Retrieved from: http://www.ovid.com/site/products/ovidguide/embase.htm

Line #	Strategy
1	brain tumor/ or brain cancer/
2	(primary adj brain adj (tumo\$ or neoplasm\$ or cancer\$)).ti,ab.
3	(brain adj (tumo\$ or neoplasm\$ or cancer\$)).ti,ab.
4	astrocytoma/
5	glioma/ or ependymblastoma/ or ependymoma/ or glioblastoma/ or oligodendroglioma/
6	oligodendroglioma\$.ti,ab.
7	oligoastrocytoma\$.ti,ab.
8	glioma\$.ti,ab.
9	ependymoma\$.ti,ab.
10	glioblastoma\$.ti,ab
11	meningioma\$.ti,ab.
12	meningioma/ or malignant meningioma/
13	or/1-12

14	risk/ or attributable risk/ or high risk behavior/ or high risk population/ or population risk/ or risk assessment/ or risk factor/ or risk reduction/ or "prevention and control"/
15	cancer risk/
16	etiology/
17	or/14-16
18	13 and 17
19	limit 18 to humans
20	exp review/
21	(literature adj3 review\$).ti,ab
22	exp meta analysis/
23	exp "Systematic Review"/
24	20 or 21 or 22 or 23
25	(medline or medlars or embase or pubmed or cinhal or amed or psychlit or psyclit or psychinfo or psyinfo or scisearch or cochrane).ti,ab
26	retracted article/
27	25 or 26
28	24 and 27
29	(systematic\$ adj2 (review\$ or overview)).ti,ab.
30	(meta?anal\$ or meta anal\$ or meta-anal\$ or metaanal\$ or metanal\$).ti,ab.
31	28 or 29 or 30
32	19 and 31

Search for PubMed

OVERVIEW

Databases (bibliographic):	PubMed
Years Covered:	1951-December 31, 2011
Date of Search:	September 25, 2011 (with monthly alerts up to December 31, 2011)
Filter for SRs and MAs:	McMaster University-Health Information Unit (Evidence-Based Health Informatics)

Source:

McMaster University-Health Information Unit (Evidence-Based Health Informatics). (2011, February). Search Filters for MEDLINE in Ovid Syntax and PubMed translation. Retrieved from:http://hiru.mcmaster.ca/hiru/HIRU_Hedges_MEDLINE_Strategies.aspx#Therapy.

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.
*	Truncation (wildcard). Search retrieves all suffix variations of the search

Mesh	term.
MeSH Terms	Medical Subject Heading
Subheading	Medical Subject Heading term
Title/Abstract	Used to further refine a Medical Subject Heading Search retrieves records which contain search terms in the title and abstract.
	Sources: PubMed Database

JEFFLINE (Jefferson University). (2010, March). Searching PubMed. Retrieved from:
http://jeffline.jefferson.edu/Ask/Help/Handouts/Searching_PubMed.pdf

(((((("Brain Neoplasms"[Mesh] OR "Astrocytoma"[Mesh]) OR "Glioma, Subependymal"[Mesh]) OR "Oligodendroglioma"[Mesh]) OR "Glioblastoma"[Mesh]) OR "Ependymoma"[Mesh]) OR "Meningioma"[Mesh]) OR "Glioma"[Mesh]) OR ((primary brain tumor[Title/Abstract] OR primary brain tumors[Title/Abstract] OR Brain cancer[Title/Abstract]) OR (brain tumo*[Title/Abstract] OR oligoastrocytoma[Title/Abstract] OR brain tumors[Title/Abstract] OR brain tumourigenesis[Title/Abstract])) AND (((MEDLINE[Title/Abstract] OR systematic[Title/Abstract]) AND review[Title/Abstract]) OR meta analysis[Publication Type]) AND (((("risk"[MeSH Terms] OR "risk factors"[MeSH Terms]) OR "odds ratio"[MeSH Terms]) OR "causality"[MeSH Terms]) OR "prevention and control"[Subheading])

Search for COCHRANE

OVERVIEW

Databases (bibliographic):	The Cochrane Library Included: Cochrane Database of Systematic Reviews (Cochrane Reviews); Database of Abstracts and Review of Effects (DARE); Cochrane Central Register of Controlled Trials (clinical trials); The Cochrane Methodology Register (method studies); Health Technology Assessment Database (technology assessments); The NHS Economic Evaluation Database (economic evaluations)
Years Covered:	1972-December 31, 2011
Date of Search:	September 25, 2011 (with monthly alerts up to December 31, 2011)
Filter for SRs and MAs:	No filter

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.
*	Truncation (wildcard). Search retrieves all suffix variations of the search term.
MeSH	Medical Subject Headings
Explode	Searches all Medical Subject Headings in the MeSH tree.

ti, ab, kw.	Searches for search term in title, abstract, and as a key word. Sources: The Cochrane Library. (n.d.). Search Manual. Retrieved from: http://www.thecochranelibrary.com/view/0/SearchManual.html .
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Line #	Strategy
1	MeSH descriptor Brain Neoplasms explode all trees
2	MeSH descriptor Glioma explode all trees
3	MeSH descriptor Glioblastoma explode all trees
4	MeSH descriptor Ependymoma explode all trees
5	MeSH descriptor Oligodendroglioma explode all trees
6	MeSH descriptor Meningioma explode all trees
7	MeSH descriptor Risk explode all trees
8	MeSH descriptor Causality explode all trees
9	MeSH descriptor Primary Prevention explode all trees
10	(brain tumo*):ti,ab,kw or (brain cancer):ti,ab,kw or (brain neoplasm):ti,ab,kw
11	(glioma):ti,ab,kw or (meningioma):ti,ab,kw or (astrocytoma):ti,ab,kw or (oligoastrocytoma):ti,ab,kw or (oligodendroglioma):ti,ab,kw or (glioblastoma):ti,ab,kw or (ependymoma):ti,ab,kw
12	(#7 OR #8 OR #9)
13	(#1 OR #2 OR #3 OR #4OR #5OR #6OR #10 OR #11)
	(#12 AND #13)

Search for CINAHL

OVERVIEW

Databases (bibliographic):	CINAHL- Cumulative Index to Nursing & Allied Health Literature Database Guide
Years Covered:	1982- December 31, 2011
Date of Search:	September 26, 2011 (with monthly alerts up to December 31, 2011)
Filter for SRs and MAs:	SIGN (Scottish Intercollegiate Guidelines Network) Source: SIGN (Scottish Intercollegiate Guidelines Network). (2011, September 16). Search Filters. Retrieved from: http://www.sign.ac.uk/methodology/filters.html#systematic .

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.
NOT	Search retrieves records which contains the first search term but not the second.
*	Truncation (wildcard). Search retrieves all suffix variations of the search term.
PT	Publication type.

MH	Exact Subject Heading
TX	All Text
Sources:	
CINAHL—Cumulative Index to Nursing & Allied Health Literature Database Guide Database	
Database Guide (2007, April 4). CINAHL—Cumulative Index to Nursing & Allied Health Literature Database Guide. Retrieved from:	
http://www.ovid.com/site/products/ovidguide/nursing.htm .	

Line #	Strategy
1	(MH "Brain Neoplasms") OR (MH "Glioma") OR (MH "Meningeal Neoplasms") OR (MH "Meningioma")
2	"brain cancer" OR "brain tumo*" OR "primary brain tumo*" OR "astrocytoma" OR "glioblastoma" OR "oligodendroglioma" OR "oligoastrocytoma" OR "ependymoma"
3	(MH "Attributable Risk") OR (MH "Risk Factors") OR "etiology" OR "causation" OR "risk" OR "risk factor" OR "prevention and control"
4	S1 or S2
5	MH meta analysis
6	TX meta analys*
7	TX metaanaly*
8	(MH "Literature Review+")
9	TX systematic review
10	TX systematic overview
11	S5 or S6 or S7 or S8 or S9 or S10
12	PT commentary
13	PT Letter
14	PT editorial
15	(MH "Animals")
16	S12 or S13 or S14 or S15
17	S11 not S16
18	S17 and S3 and S4

Search for AgeLine (AARP)

OVERVIEW

Databases (bibliographic):	AgeLine (AARP- American Association of Retired Persons)
Years Covered:	1978- December 31, 2011
Date of Search:	September 26, 2011(with monthly alerts up to December 31, 2011)
Filter for SRs and MAs:	No filter

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
-----	--

OR	Search retrieves records which contain at least one search term.
*	Truncation (wildcard). Search retrieves all suffix variations of the search term.
TX	All Searchable fields
DE	Descriptor (subject heading)
	Sources:
	AgeLine (AARP) Database
	ProQuest. (n.d.). AgeLine. Retrieved from http://www.csa.com/factsheets/ageline-set-c.php

Line #	Strategy
1	TX brain cancer
2	TX brain tumo*
3	TX brain neoplasm
4	TX primary brain tumo*
5	TX glioma
6	TX astrocytoma
7	TX glioblastoma
8	TX ependymoma
9	TX oligodendroglioma
10	TX meningioma
11	TX oligoastrocytoma
12	DE "Risk Factors" OR DE "Predictive Factors" OR DE "At Risk Populations" OR DE "Disease Susceptibility" OR DE "Etiology"
13	DE "Preventive Medicine" OR DE "Immunization" OR DE "Health Behavior" OR DE "Health Promotion" OR DE "Health Services" OR DE "Prevention" OR DE "Screening"
14	DE "Meta Analyses"
15	TX systematic review
16	Or/ S1-10
17	(S12 or S13)
18	(S14 or S15)
	S16 and S17 and S18

Search for PsycINFO

OVERVIEW

Databases (bibliographic):	PsycINFO
Years Covered:	1806- December 31, 2011
Date of Search:	September 26, 2011 (with monthly alerts up to December 31, 2011)
Filter for SRs and MAs:	Alison Weightman-Health Evidence Bulletin (Wales Project)
	Source:

Alison Weighthman-Health Evidence Bulletin (Wales Project). (n.d.).
 Search
 filter for pyschlit/clin psych/psychinfo. Retrieved from:
<http://heb.w.cf.ac.uk/methodology/appendix2.htm>.

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.
*	Truncation (wildcard). Search retrieves all suffix variations of the search term.
/	Searches the search term as a subject heading
.ab, ti.	Searches for the search term in the abstract and title
.sh	Searches the search term as a subject heading
.id	Searches the search term as a key concept.

Sources:

PsycINFO Database

Line #	Strategy
1	brain neoplasms/
2	"primary brain tumo*" .ab,ti.
3	brain cancer.ab,ti.
4	"brain tumo*" .ab,ti.
5	glioma/
6	astrocytoma.ab,ti.
7	glioblastoma.ab,ti.
8	ependymoma.ab,ti
9	oligodendroglioma.ab,ti.
10	meningioma.ab,ti.
11	oligoastrocytoma.ab,ti.
12	glioma.ab,ti.
13	or/1-12
14	risk factors/ or at risk populations/ or causality/ or predisposition/ or protective factors/ or psychosocial factors/ or risk assessment/ or sociocultural factors/ or "susceptibility (disorders)"/
15	meta analysis.sh.
16	meta-anal:.ab,ti
17	metaanal:.ab,ti.
18	meta analysis.id.
19	(systematic: and (review: or overview)).ab,ti.
20	(critical: and apprais:).ab,ti.
21	(critical: and review:).ab,ti.
22	or/15-21
23	literature review.sh
24	literature review.id
25	or/23-24
26	22 or 25
27	case report.sh
28	22 not 27

29	26 not 27
30	13 and 14 and 28
32	13 and 14 and 29

Search for TOXLINE

OVERVIEW

Databases (bibliographic):	TOXLINE
Years Covered:	1838- December 31, 2011
Date of Search:	September 26, 2011 (with monthly alerts up to December 31, 2011)
Filter for SRs and MAs:	No filter

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.
*	Truncation (wildcard). Search retrieves all suffix variations of the search term.
adj	Search retrieves records containing search terms which are next to each other.
ab	Searches for search terms in abstract

Sources:

TOXLINE database

[ab\(brain cancer or brain neoplasms or brain tumour or astrocytoma or glioma or glioblastoma or ependymoma or oligodendroglioma or meningioma or oligoastrocytoma\) AND ab\(\(risk* or risk factor or etiology or causation or prevention\)\) AND ab\(\(systematic adj review or meta-analysis or metaanalysis or meta-analy*\)\)](#)

Search for PROQUEST Dissertations & Theses (PQDT)

OVERVIEW

Databases (bibliographic):	ProQuest Dissertations & Theses
Years Covered:	1861- December 31, 2011
Date of Search:	September 26, 2011 (with monthly alerts up to December 31, 2011)
Filter for SRs and MAs:	No filter

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.
*	Truncation (wildcard). Search retrieves all suffix variations of the search term.
ab	Search retrieves records which contain search terms in abstract.

Sources:

ProQuest Dissertations & Theses Database

ab(brain tumo* OR brain cancer OR brain neoplasm OR glioma OR astrocyoma OR glioblastoma OR ependymoma OR oligodendroglioma OR oligoastrocytoma OR meningioma) AND ab((risk* OR risk factor OR etiology OR causation OR OR prevention)) AND ab((systematic review OR meta-analysis))

Cancer Causes & Control (CCC)- Volume 1/1990-Voume 22/2011:

OVERVIEW

Academic Journal:	Cancer Causes & control (CCC)
Years Covered:	1990-2011
Date of Search:	September 21, 2011 (with monthly alerts up to December 31, 2011)
Filter for SRs and MAs:	No Filter

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.

“Brain tumor and meta-analysis”
“Brain tumor and systematic review”
“glioma and systematic review”
“meningioma and systematic review”
“glioma and meta-analysis”

Cancer Epidemiology, Biomarkers & Prevention- November 1991-present:

OVERVIEW

Academic Journal:	Cancer Epidemiology, Biomarkers & Prevention
Years Covered:	1991-2011
Date of Search:	September 22, 2011 (with monthly alerts up to December 31, 2011)
Filter for SRs and MAs:	No filter

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.

“Brain tumor and meta-analysis”
 “Brain tumor and systematic review”
 “glioma and meta-analysis”
 “meningioma and meta-analysis”
 “glioma and systematic review”
 “meningioma and systematic review”

Google Scholar:

OVERVIEW

Database:	Google Scholar
Years Covered:	?
Date of Search:	September 22, 2011 (with monthly checks up to December 31, 2011)

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.
*	Truncation (wildcard). Search retrieves all suffix variations of the search term.

“Brain tumor and risk meta-analysis”
 “Brain tumor and risk and systematic review”
 “glioma and risk and meta-analysis”
 “glioma and risk and systematic review”
 “meningioma and risk and meta-analysis”
 “meningioma and risk and systematic review”

“(Brain tumo* OR glioma OR meningioma) AND phone AND (systematic review OR "meta analysis")”
 “(Brain tumo* OR glioma OR meningioma) AND smoking AND (systematic review OR "meta analysis")”
 “(Brain tumo* OR glioma OR meningioma) AND drinking AND (systematic review OR "meta analysis")”
 “(Brain tumo* OR glioma OR meningioma) AND diet AND (systematic review OR "meta analysis")”
 “(Brain tumo* OR glioma OR meningioma) AND (supplements OR vitamins) AND (systematic review OR "meta analysis")”

“(Brain tumo* OR glioma OR meningioma) AND head trauma AND (systematic review OR "meta analysis")”

“(Brain tumo* OR glioma OR meningioma) AND artificial sweeteners AND (systematic review OR "meta analysis")”

Google:

OVERVIEW

Database:	Google
Years Covered:	
Date of Search:	September 26, 2011 (With monthly checks up to December 31, 2011)

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.
*	Truncation (wildcard). Search retrieves all suffix variations of the search term.

“(brain tumo* OR glioma OR meningioma) AND risk AND (systematic review OR meta-analysis)”

“(brain tumo* OR glioma OR meningioma) AND phone AND (systematic review OR meta-analysis)”

“(brain tumo* OR glioma OR meningioma) AND smoking AND (systematic review OR meta-analysis)”

“(brain tumo* OR glioma OR meningioma) AND drinking AND (systematic review OR meta-analysis)”

“(brain tumo* OR glioma OR meningioma) AND diet AND (systematic review OR meta-analysis)”

“(brain tumo* OR glioma OR meningioma) AND (supplements OR vitamins) AND (systematic review OR meta-analysis)”

“(brain tumo* OR glioma OR meningioma) AND head trauma AND (systematic review OR meta-analysis)”

“(brain tumo* OR glioma OR meningioma) AND artificial sweeteners AND (systematic review OR meta-analysis)”

13.2. APPENDIX B

Phase 1- Level 1 Title and Abstract Screening Forms

Level 1 SCREENING- TITLE AND ABSTRACT

1. **Is this article related to brain tumours[more specifically, must include ONE or more of the following: GLIOMA, ASTROCYTOMA, OLIGODENDROGLIOMA, OLIGOASTROCYTOMA, EPENDYMOMA, GLIOBLASTOMA, MENINGIOMA]?** *-*Note*-*

Include articles which address brain tumours--in a general term-- for further scrutiny

If needed, please refer to accompanying 2007 WHO Classification System for CNS tumours for relevant ICD-O codes (for reference only- do not exclude review articles which use different classification systems or those who do not mention a classification system at all)

Yes

No

Can't Tell

2. **Is this article related to lifestyle/behavioural etiological risk factors (modifiable ones at the individual level) for developing (or protecting against) brain tumours?**

Examples: mobile phone use, smoking, alcohol consumption, vitamin supplements, etc) If unsure select "can't tell"

Yes

No

Can't Tell

3. **Does the article consist of childhood primary brain tumours? (exclusion criteria)**
(Ex: childhood medulloblastoma, using the term "pediatric")

Yes

No

Can't Tell

4. **Does this article focus solely on any of the following outcomes or factors? (exclusion criteria)**

Focuses on other Primary Brain Tumor subtypes that are NOT considered Glioma, Astrocytoma, Oligodendroglioma, Oligoastrocytoma, Ependymoma, Glioblastoma, Meningioma OR does not use the general term "brain tumors".

Secondary Tumours (also known as metastatic) * (Note-DEFINED AS DEVELOPED ELSEWHERE AND SPREAD TO THE BRAIN)

Diagnostic Focus

Prognostic Risk Factors (Includes therapeutic agents which affects the progression of PBT itself in an already diagnosed patient)

- Etiological Risk Factors that are NOT Lifestyle/Behavioural
- Irrelevant Outcomes. Please specify
- Focuses on mainly metastatic tumours (Note-* DEFINED AS SPREADING FROM THE BRAIN TO OTHER SITES-FOCUS IS ON OTHER TUMOUR SITES)
- None of the Above

5. Can the study be classified as any of the following methodological designs (exclusion criteria)?

- Observational study
- Randomized Controlled Trial
- Literature review (not systematic in nature)
- Commentaries and Editorials
- Guidelines (without a systematic review portion)
- None of the above

6. Is this abstract presented in English or French?

- Yes
- No
- Uncertain

7. Is this article a systematic review and/or meta-analysis?

- Systematic Review with possible meta-analysis
- Systematic Review AND Meta-Analysis
- Neither
- Can't Tell

8. COMMENTS?

13.3. APPENDIX C

Phase 1- Level 2 Full Article Screening Forms

Level 2 SCREENING- FULL ARTICLE REVIEW

1. Is this article related to primary brain tumours [more specifically, must include ONE or more of the following: GLIOMA, ASTROCYTOMA, OLIGODENDROGLIOMA, OLIGOASTROCYTOMA, EPENDYMOMA, GLIOBLASTOMA, MENINGIOMA]? *Note-If the Full Article doesn't break down the term "brain tumour" into sub-types, then exclude

If needed, please refer to accompanying 2007 WHO Classification System for CNS tumours for relevant ICD-O codes (for reference only- do not exclude review articles which use different classification systems or those who do not mention a classification system at all)

Yes

No

Can't Tell

2. Is this article related to lifestyle/behavioural etiological risk factors (modifiable actions at the individual level) for developing (or protecting against) brain tumours? (Examples: mobile phone use, smoking, alcohol consumption, vitamin supplements, etc)

Yes

No

Can't Tell

3. Does the article consist of childhood primary brain tumours? (exclusion criteria) (Examples: childhood medulloblastoma, using the term "pediatric")

Yes

No

Can't Tell

4. Does this article focus solely on any of the following outcomes or factors? (exclusion criteria)

Focuses on other major primary brain tumours that are NOT considered Glioma, Astrocytoma, Oligodendroglioma, Oligoastrocytoma, Ependymoma, Glioblastoma or Meningioma

Secondary Tumours (also known as metastatic) * (Note- DEFINED AS DEVELOPED ELSEWHERE AND SPREAD TO THE BRAIN)

Diagnostic Focus

Prognostic Risk Factors (includes therapeutic agents which affects the progression of PBT in patients already diagnosed)

Etiological Risk Factors that are NOT Lifestyle/Behavioural

- Irrelevant outcomes. Please specify
- Focuses on mainly metastatic tumours (Note-* DEFINED AS SPREADING FROM THE BRAIN TO OTHER SITES-FOCUS IS ON OTHER TUMOUR SITES)
- None of the Above

5. Can this study be classified as any of the following methodological designs? (exclusion criteria)

- Observational study
- Randomized Control trial
- Literature Review (not systematic in nature)
- Commentaries and Editorials
- Guidelines (without a systematic review portion)
- None of the Above

6. What are the risk factors considered?

- Mobile Phone Use
- Smoking
- Alcohol Consumption
- Personal Hair Dye Use
- Diet
- Vitamins and Supplements
- Head Trauma *Must be caused from leisure/recreational activities*
- Not Specified

7. What type of Primary Brain Tumour? *Note- Some reviews will address more than one PBT*

- Glioma
- Astrocytoma
- Oligodendroglioma
- Oligoastrocytoma
- Glioblastoma
- Ependymoma
- Meningioma

8. Is the abstract presented in English or French?

- Yes
- No
- Uncertain

Is this article a systematic review and/or meta-analysis? *Note-To be considered a systematic review, the methodology employed must be developed a priori. More specifically, for the purpose of this

9. complex review, to be considered a systematic review, the study must: (1) indicate that a computerized literature search was conducted, (2) have an inclusion/exclusion criteria→ If it is vague/implied still include.

- Systematic Review and possible meta-analysis
- Both Systematic Review AND Meta-Analysis
- Neither

10. Is the full publication available? *Note-If article is being ordered through RACER, do not complete Level 2 screening until the article is available for review. If article cannot be ordered and is not accessible, complete Level 2 screening and select "no" (article will be excluded from the study)

- Yes
- No
- Can't Tell

11. COMMENTS?

**13.4. Appendix D
Phase 1- Extraction Form**

POPULATION					
Sex:					
Age (range):					
Co-Morbidities:					
Race:					
Country of Study:					

Disease Status/Entities being considered:					
What classification system (and ICD codes) did the authors use for the disease status/entities listed above?					
Exposure(s) being considered:					
Duration of exposure(s):					
Target population of the study:					
Setting of the study (community, institutional care, residential setting)?					
METHODS					
What was the research question/aim stated in the review article?					
What type of study designs were included in the review?					
What were the stated inclusion criteria of the review?					
What were the stated exclusion criteria of the review?					
What years were included in the search strategy?					
Which databases were searched?					
What were the MeSH terms included in the search strategy?					
What were the keywords included in the search strategy?					
Did they use a quality assessment tool/instrument to assess the methodological quality of the included studies? If yes, list the tool:					
If they conducted a meta-analysis, what type of statistical model did they use to pool the results?					
RESULTS					
What were the sample sizes of included studies (n)? (provide as a range)					
If a systematic review was done (qualitative), what were the individual risk estimates from the included studies of the SR? Format: #1 [author, risk factor, disease outcome (if applicable), any sub-groups considered (if applicable)], risk estimate (confidence intervals)] Example: #1 [Smoking, Glioma, African American, RR 1.23 (1.00-1.45)]					
If a meta-analysis (quantitative) was done, what were the pooled risk estimates resulting from the MA? Format: #1 [author, risk factor, disease outcome (if applicable), any sub-groups considered (if applicable)], statistic for					

consistency (estimate), risk estimate (confidence intervals) Example: #1 [Smoking, Glioma, African American, $I^2(0.3)$, RR 1.02 (0.98-1.06)]					
What are the main conclusions of the Meta-Analysis?					
If publication bias was addressed, did they perform any graphical aids (such as funnel plots) or statistical tests? Format: #1 [risk factor, disease outcome (if applicable), any sub-groups considered (if applicable)], type of graphical aid, (publication bias-yes/no) Example: #1 [Smoking, Glioma, African American, funnel plot, publication bias-yes]					
What were the limitations noted at the individual study level?					
What were the limitations at the review level?					
Overall main conclusion of review (2-3 sentences)					

13.5. Appendix E

Phase 1- List of Excluded Studies at Level 2 Screening

- 1. Is this article related to brain tumours-must include sub-types of interest? (answer: no)**

Merill RM., Fugal S., Novilla LB, et al. (2005). Cancer risk associated with early and late maternal age at first birth. *Gynecol Oncol*, 96(3): 583-93.

Ortega-Garcia JA., Martin M., Navarro-Camba E., et al. (2009). Pediatric Health Effects of Chronic Exposure to Extremely Low Frequency Electromagnetic Fields. *Current Pediatric Reviews*, 5(4):234-240.

Moulder JE., Foster KR., Erdreich LS., et al. (2005). Mobile phones, mobile phone base stations and cancer: a review. *Int J. Radiat Biol*, 81(3): 189-203.

Ischibe N., Wlordarczyk RC., Fulco C. (2009). Overview of the institute of medicine`s committee search strategy and review process for gulf war and health: long-term consequences of traumatic brain injury. *J. Head Trauma Rehabil*, 24(6): 424-9.

Smith PCK. (2002). The role of the primary care advanced practice nurse in evaluating and monitoring childhood cancer survivors for a second malignant neoplasm. *Journal of Pediatric Oncology Nursing*, 19: 84-96.

2. Is this article related to lifestyle/behavioural etiological risk factors for developing (or protecting against) brain tumours? (answer: no)

Kamp MA., Beseoglu K., Eicker S., et al., (2011). Secretory meningiomas: systematic analysis of epidemiological, clinical, and radiological features. *Acta Neurochir*, 153 (3): 457-65.

Li CY., Lin RS., Sung FC. (2003). Elevated residential exposure to power frequency magnetic field associated with greater average age at diagnosis for patients with brain tumors. *Bioelectromagnetics*, 24(3): 218-21.

Rutherford GW., Wlodarczyk RC. (2009). Distant sequelae of traumatic brain injury: premature mortality and intracranial neoplasms. *J. Head Trauma Rehabil*, 24(6): 468-74.

3. Does this article consist of childhood primary brain tumours (answer: yes)

Rollison DE., Helzlsouer KJ., Pinney SM. (2006). Personal hair dye use and cancer: a systematic literature review and evaluation of exposure assessment in studies published since 1992. *J Toxicol Environ Health B Crit Rev*, 9(5): 413-39.

4. Article focuses on etiological risk factors that are not lifestyle/behavioural (answer: yes)

Miller RD, Neuberger JS.& Gerald KB. (1997). Brain cancer and leukemia and exposure to power-frequency (50- to 60- Hz) electric and magnetic fields. *Epidemiol Rev*, 19(2): 273-93.

5. Article is a literature review (answer: yes)

Kundi M. (2010). The controversy about a possible relationship between mobile phone use and cancer. *Cien Saude Colet*, 15(5): 2415-30.

Dubey RB., Hanmandlu M. & Gupta SK. (2010). Risk of brain tumors from wireless phone use. *J. Comput Assist Tomogr*, 34(6): 799-807.

6. Article is a commentary or editorial) (answer: yes)

Samkange-Zeeb F., Schuz J., Schlehofer B., et al. (2010). Comparison of studies on mobile phone use and risk of tumors. *J Clin Oncol*, 28(7): 124-5.

7. Article does not focus on brain tumour sub-types of interest (answer: yes)

Takkouche B., Etminan M & Montes-Martinez A. (2005). Personal use of hair dyes and risk of cancer: a meta-analysis. *JAMA*, 293(20): 2516-25.

Alper BS.(2008). Limited evidence on cell phones and brain tumors. *Evidence-Based Medicine*.

8. Article is neither a systematic review and/or meta-analysis (answer: yes)

Croft RJ., McKenzie RJ., Inyang I et al. (2008). Mobile phones and brain tumours: a review of epidemiological research. *Australas Phys Eng Sci Med*, 31(4): 255-67.

Hashibe M., Straif K., Tashkin DP et al., (2005). Epidemiologic review of marijuana use and

cancer risk. *Alcohol*, 35(3): 265-75.

Biglia N., Gadducci A., Ponzone R., et al. (2004). Hormone replacement therapy in cancer survivors. *Maturitas*, 48(4): 333-46.

Hardell L., Carlberg M., Hansson MK., (2009). Epidemiological evidence for an association between use of wireless phones and tumor diseases. *Pathophysiology*, 16(2-3): 113-22.

Kohli DR., Sachdev A., Vats HS. (2009). Cell phones and tumor: still in no man's land. *Indian J Cancer*, 46(1): 5-12.

Repacholi MH., Lerchl A., Roosli M., et al. (2012). Systematic review of wireless phone use and brain cancer and other head tumors. *Bioelectromagnetics*, 33(3): 187-206.

Swerdlow AJ., Feychting M., Green AC., et al., (2011). Mobile phones, brain tumors, and the interphone study: where are we now? *Environ Health Perspect*, 119(11): 1534-8.

9. Article is a meta-analysis only (answer: yes)

McCarthy BJ., Rankin KM., Aldape K., et al. (2011). Risk factors for oligodendroglial tumors: a pooled international study. *Neuro Oncol*, 13(2): 242-50.

Hardell L., Carlberg M., Soderqvist F., et al. (2008). Meta-analysis of long-term mobile phone use and the association with brain tumours. *Int J Oncol*, 32(5): 1097-103.

Hardell L., Carlberg M., Soderqvist et al. (2007). Long-term use of cellular phones and brain tumours: increased risk associated with use for ≥ 10 years. *Occup Environ Med*, 64: 626-632.

Hardell L., Carlberg M., Hansson MK. (2006). Pooled analysis of two case-control studies on use of cellular and cordless telephones and the risk for malignant brain tumours diagnosed in 1997-2003. *Int Arch Occup Environ Health*, 79(8): 630-9.

Levis AG., Minicuci N., Ricci P., et al. (2011). Mobile phones and brain tumours. The discrepancies in cause-effect relationships in the epidemiological studies-how do they arise? *Environ Health*, 10: 59.

13.6. Appendix F

Phase 2- Smoking Systematic Review Protocol

Brief Background/ Issues and Basis for Development of Study

Cigarette smoking has long been considered a possible risk factor for the onset of primary brain tumours. The biological mechanism for this association has not been clearly defined. Plausible hypotheses have been proposed, but have yet to be definitively proven (Lachance et al, 2011). N-nitroso compounds are found within cigarettes and these compounds are generally considered carcinogenic (Holick et al., 2007). Using animal models within controlled laboratory settings, researchers who have injected N-nitroso compounds intravenously into rats and have observed brain tumour formation (Holick et al., 2007; Silvera et al., 2006). As such, researchers have been interested in determining whether cigarette exposure to N-Nitroso compounds will have the same effect on brain tumour formation in humans. It is known, as a result of several consistent studies, that maternal exposure to cigarette smoking can induce brain tumour formation in the child since the permeability of the blood-brain barrier is much greater during fetal development (Silvera et al., 2006). In adults, however, it has become questionable whether there can be such an effect, since the permeability of this barrier in adulthood is much more controlled (Il'yasova et al., 2011; Silvera et al., 2006). Alternatively, it has been suggested that rather than having to penetrate the blood-brain barrier, N-Nitroso compounds provided by cigarette smoking, can enter the brain through other mechanisms such as the routes taken by therapeutic medications for brain related diseases (Mandelzweig et al., 2009).

As indicated in Phase 1, the only available systematic review and meta-analysis on smoking and onset of brain tumours published before December 31, 2011 is that conducted by Mandelzweig et al., 2009. With an AMSTAR score of 6 (moderate methodological quality) it is considered eligible to be subjected to de-novo processes. The purpose of this current review to address certain aspects within AMSTAR which Mandelzweig and colleagues had failed to address. As a result, certain conclusions from the review in question may or may not change. Mandelzweig et al. had also looked at glioma specifically; our aim is to also include meningioma as a primary outcome.

1. Research Question and Objectives

Components of the intended research question can be constructed within a PICO framework.

- **Population:** Adults (≥ 18 years old, males and females)
- **Intervention/Exposure:** Tobacco smoking as risk factor (Active, Passive)
- **Comparator:** N/A
- **Outcomes:** Glioma sub-types (astrocytoma, glioblastoma, oligoastrocytoma, oligodendroglioma, ependymoma) and meningioma
- **Study Designs:** Case-control and cohort studies.

Research Question: Based on available case-control and cohort studies, is tobacco smoking (active/passive) associated with adult onset of glioma sub-types (astrocytoma, glioblastoma, oligoastrocytoma, oligodendroglioma, ependymoma) and/or meningioma?

Objectives:

- To identify relevant observational studies (case-control and cohort) focusing on the effects of tobacco smoking and the onset of glioma and/or meningioma in an attempt to provide an overall conclusion regarding this association.
- If permissible (at least three study estimates), to conduct a meta-analysis on relevant studies (with data pertaining to Never vs. Ever Smoker, Never, vs. Current Smoker and Never vs. Past Smoker).
- To provide a current-up to date, high methodological quality systematic review and meta-analysis on the association between smoking and glioma/meningioma, as dictated by AMSTAR criteria, to be used by health policy makers and relevant stakeholders.

2. Methods

2.1.Literature Search Strategy

With the guidance of a health information specialist at the University of Ottawa, search strategies were developed for the Medline bibliographic database (see Appendix). Using this as a template, similar search strategies will be developed for the following databases as well: PubMed, Embase, CINAHL and PsycINFO. AARP Ageline and TOXLINE were excluded as they were deemed irrelevant based on the searches conducted in Phase 1. Grey Literature sources, such as ProQuest Dissertation and Thesis Database, as well as Google and Google Scholar will be searched. “Other sources” of literature will also considered: Hand searching of bibliographies of included studies, studies included in previous reviews and of disease-specific journals, such as Cancer Causes and Control and the International Journal of Cancer will be completed as well.

2.2.Selection Criteria

Studies will be included if they satisfy all of the following inclusion criteria:

- Studies have to focus on the onset on at least one of the following brain tumours: glioma, astrocytoma, oligodendroglioma, oligoastrocytoma, ependymoma, glioblastoma, meningioma
- Studies have to focus on smoking (tobacco-either active or passive) as exposure and must provide risk estimates with 95% confidence intervals.
- Smoking have to be the main exposure variable, and cannot be combined with another exposure variable as part of an interaction term.
- Studies have to be of either case-control or cohort study design.
- Studies have to be published in English or French.

- Full-text of studies needs to be retrievable.
- Studies have to be published before December 31, 2011.

Studies will be excluded if they satisfy at least one of the following exclusion criteria:

- Studies which focus on childhood primary brain tumours.

2.3. Study Selection Method

Similar to screening processed conducted in Phase 1, a liberal accelerated method will be utilized. In order to ensure feasibility while retaining the integrity of a SR, a method known as “liberal accelerated” will be selected for the screening process. This method is opted for due to the sheer number of collected articles and the issue of limited resources. Based on this method, a unanimous decision by two reviewers (MH or RES and PQ) is needed for an article to be excluded. This ensures that articles excluded by the first reviewer (PQ) are re-assessed by a second reviewer. A safety net is essentially created when two opinions were needed to exclude an article. A kappa statistic, to determine inter-rater reliability is calculated to determine agreement for exclusion between the two reviewers. The second reviewer does not need to review the included articles since only one reviewer’s decision is required to advance the article to the next level. The first reviewer then retrieves the full text and subjects the article to further scrutiny, and any non relevance will have been detected further on in the process. Any discordance between the two reviewers will be resolved by consensus.

2.4. Data Extraction Strategy

Data extraction forms have been developed a priori (see appendix). These forms have already been used widely for a national neurological project looking at risk factors for the onset of fourteen neurological conditions. Briefly, the first reviewer will extract all relevant data from the identified studies, and the second reviewer will duplicate extract a random 25% sample.

2.5. Study Quality Assessment

As recommended by the Cochrane Collaboration, quality assessment of observational studies will be completed by using the Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Non-Randomised Studies in Meta-Analyses (Reeves et al., 2008; Wells et al., Agency for Healthcare Research and Quality (AHRQ), 2011) (see appendix). NOS was chosen since: it is widely used for quality assessing observational studies, quick to implement, and it has established face and content validity, along with inter-rater reliability (Reeves et al., 2008; Wells et al., Agency for Healthcare Research and Quality (AHRQ), 2011). Methodological issues between cohort and case control studies are evident, and the NOS accounts for such differences by subjecting both types of studies to different scales. The following components are addressed for both scales: selection (4 stars), comparability (2 stars) and ascertainment of exposure/outcome of interest (3 stars). The maximum score on this scale is nine stars (Wells et al., Castillo et al., 2010).

Although standard scoring thresholds have yet to be determined, many studies have consistently used the threshold of ≥ 5 stars and <5 stars to represent studies of high and low quality (Regwan et al., 2010; Wai et al., 2010; Tilney et al., 2007; Yeung et al., 2011; Lui et al., 2010).

2.6. Data Analysis Methods

A quantitative summary (the MA portion) will be attempted if:

- (1) There are greater than three relevant studies and;
- (2) Heterogeneity tests determine that the pooling of numerous point estimates is appropriate.

Relevant information from each study will be inputted RevMan which will generate funnel plots and their associated heterogeneity statistics, I^2 and Cochrane's Q (Ioannidis, 2008).

As outlined by the Cochrane Collaboration, I^2 percentages between 0%-40%, 30%-60%, 50%-90%, 75%-100% represents unimportant heterogeneity, moderate heterogeneity, substantial heterogeneity and considerable heterogeneity, respectively (Higgins & Green, 2008). Due to the low power of the Cochrane's Q test to detect true heterogeneity, the threshold for significance has been increased to $p=0.1$, meaning any p -value ≤ 0.1 will be considered statistically significant for heterogeneity and any p -value >0.1 will be considered homogeneous (Higgins & Green, 2008; Higgins et al., 2003).

After testing for heterogeneity, there are many options:

- (1) If the studies are homogeneous, then the studies may be similar enough for their estimates to be pooled using a random effects model resulting in an overall pooled estimate;
- (2) (a) if the studies are heterogeneous, it may be inappropriate to pool studies that are too dissimilar and a qualitative summary would suffice or;
(b) one can pool, using a random effects model, however, as described below, a subgroup analysis to explain the sources of heterogeneity must be attempted if there are sufficient number of articles available to do so (Higgins & Green, 2008).

Random effects models based on the DerSimonian and Laird method (DLM) (Higgins & Green, 2008) will be used to pool estimates together as opposed to using fixed effects models. Between study variances will always be present, and the random effects model accounts for this by including Tau squared (T^2) into the calculation (Higgins & Green, 2008; Deeks et al., 2001). Since variability is always present, random effects modeling generates more conservative estimates for determining significance by producing wider confidence intervals, allowing one to be more cautious in their conclusions. In regards to weights, a fixed effects model based on the inverse variance approach assigns heavier weights to studies with more precision (larger sample sizes and smaller standard errors) (Higgins & Green, 2008). Conversely, in a random effects model, the DLM method (variation of the inverse variance approach) assigns slightly more weight to smaller sized studies. This allows for smaller studies, with inherent variations, to have greater contribution to the model, since a common sized effect (fixed effects model) is disregarded (Higgins & Green, 2008).

Upon generating a forest plot, RevMan is also able to produce an inverted funnel plot which addresses the influence of publication bias. An asymmetrical plot generally indicates the presence of publication bias, whereas a symmetrical plot generally indicates its absence (Higgins & Green, 2008).

2.7. Planned Sensitivity/Subgroup Analyses

It has been decided a priori from previous studies in the field, that if substantial heterogeneity exists and sufficient data is available, sub-group analysis will be attempted. All included studies will be pooled by study design to determine the presence of heterogeneity. Sub-group analyses will then be attempted by pooling studies with similar histological sub-types, disease classification systems (ICD codes, simple histological confirmation) sex, and exposure categories. (Harder et al., 2008; Bondy et al., 2008; Tan et al., 2010; Kan et al., 2008; Egger et al., 2001; Huss et al., 2008; Melnyk & Fineout-Overholt, 2010). By doing so, effect estimates which may differ based on certain characteristics will be identified and interpreted.

3. Presentation of Findings

Again, MOOSE guidelines will be used for reporting SRs and MAs (Stoup et al., 2000). The process of identifying, including and excluding relevant articles will be documented through the PRISMA flow diagram (Moher et al., 2009). Evidence tables derived from data extraction and subsequent qualitative summaries will be presented. If a MA is attempted, a forest plot with the pooled estimate and corresponding 95% confidence intervals, along with statistical values for heterogeneity (Cochrane's Q and I^2) will be provided. An inverted funnel plot will also be provided to address publication bias.

13.7. Appendix G

Phase 2- Smoking: Search Strategies for Bibliographic Databases and Grey Literature Sources

Template source (for “syntax guide” and “overview” boxes):

Kaunelis, D. and Farrah, K. “Lecture: Introduction to Literature Searching.” Canadian Agency for Drugs and Technologies in Health (CADTH). University of Ottawa. 12 May 2011.

OVERVIEW OF SEARCH STRATEGIES	
Databases (bibliographic):	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations EMBASE PUBMED PsycINFO CINAHL
Grey Literature:	ProQuest (Dissertations and Theses) GoogleScholar Google
Hand-Searching Journals:	Cancer Causes & Control (CCC) International Journal of Cancer
Study Types:	Cohort studies and Case-Control studies (filters in place)

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

OVERVIEW	
Databases (bibliographic):	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
Years Covered:	1946- December 31, 2011
Date of Search:	June 26, 2012
Filter:	SIGN (Scottish Intercollegiate Guidelines Network)
	Sources: http://www.sign.ac.uk/methodology/filters.html#obs
SYNTAX GUIDE	
AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.
/	Searches the search term as a subject heading
.sh	Searches the search term as a subject heading
exp	Explodes a subject heading
adj	Search retrieves records containing search terms which are next to each other.
\$	Truncation (wildcard). Search retrieves all suffix variations of the search term.
.ti	Searches for the search term in the title.
.ab	Searches for the search term in the title.
.fs	Floating Subheadings. Used to help refine the meaning of a subject heading.
.pt	Publication type.

Sources:

Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations Database

Field Guide (2008, January 9). Ovid MEDLINE ® Database Guide. Retrieved from:
<http://www.ovid.com/site/products/ovidguide/medline.htm#advanced>.

Line #	Strategy
1	exp Brain Neoplasms/
2	(primary adj brain adj tumo\$.ab,ti.
3	(brain adj cancer).ab,ti.
4	glioma/ or astrocytoma/ or glioblastoma/ or ependymoma/ or glioma, subependymal/ or oligodendroglioma/
5	meningioma/
6	(oligoastrocytoma\$ or glioma\$ or meningioma\$ or astrocytoma\$.ab,ti. or ependymoma\$.ab,ti. or glioblastoma\$.ab,ti.oastrocytoma\$.ab,ti
7	oligodendroglioma\$.ab,ti.
8	or/1-7
9	exp Risk/
10	etiology.fs.
11	Odds Ratio/
12	prevention& control.fs.
13	or/9-12
14	Smoking/
15	8 and 13 and 14
16	limit 15 to humans
17	epidemiologic Studies/
18	exp Case-Control Studies/
19	exp Cohort Studies/
20	case control.tw.
21	(cohort adj (study or studies)).tw.
22	cohort analy\$.tw.
23	(follow up adj (study or studies)).tw.
24	(observational adj (study or studies)).tw.
25	longitudinal.tw.
26	retrospective.tw.
27	or/17-26
28	16 and 27

Embase

OVERVIEW

Databases (bibliographic):	Embase
Years Covered:	1980- December 31, 2011
Date of Search:	June 26, 2012
Filter:	SIGN (Scottish Intercollegiate Guidelines Network)
	Source: http://www.sign.ac.uk/methodology/filters.html#obs

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.
/	Searches the search term as a subject heading
.sh	Searches the search term as a subject heading
exp	Explodes a subject heading
adj	Search retrieves records containing search terms which are next to each other.
adj#	Search retrieves records where the first search term is within <i>n</i> number of words to the second search term.
\$	Truncation (wildcard). Search retrieves all suffix variations of the search term.
.ti	Searches for the search term in the title.
.ab	Searches for the search term in the title.
.fs	Floating Subheadings. Used to help refine the meaning of a subject heading.
.pt	Publication type.
	Sources: Embase Classic + Embase Database
	Database Guide (2007, August 21). EMBASE: Excerpta Medica Database Guide. Retrieved from: http://www.ovid.com/site/products/ovidguide/embase.htm

Line #	Strategy
1	brain tumor/ or brain cancer/
2	(primary adj brain adj (tumo\$ or neoplasm\$ or cancer\$)).ti,ab.
3	(brain adj (tumo\$ or neoplasm\$ or cancer\$)).ti,ab.
4	astrocytoma/
5	glioma/ or ependymblastoma/ or ependymoma/ or glioblastoma/ or oligodendroglioma/
6	oligodendroglioma\$.ti,ab.
7	oligoastrocytoma\$.ti,ab.
8	glioma\$.ti,ab.
9	ependymoma\$.ti,ab.
10	glioblastoma\$.ti,ab
11	meningioma\$.ti,ab.
12	meningioma/ or malignant meningioma/
13	or/1-12
14	risk/ or attributable risk/ or high risk behavior/ or high risk population/ or population risk/ or risk assessment/ or risk factor/ or risk reduction/ or "prevention

	and control"/
15	cancer risk/
16	etiology/
17	or/14-16
18	exp smoking/ or exp cigarette smoking/
19	smoking\$.ti,ab.
20	or/18-19
21	13 and 17 and 20
22	limit 21 to humans
23	clinical study/
24	case control study/
25	family study/
26	longitudinal study/
27	retrospective study/
28	prospective study/
29	randomized controlled trials/
30	28 not 29
31	cohort analysis/
32	(cohort adj (study or studies)).tw.
33	(case control adj (study or studies)).tw.
34	(follow up adj (study or studies)).tw.
35	(observational adj (study or studies)).tw.
36	(epidemiologic\$ adj (study or studies)).tw.
37	(cross sectional adj (study or studies)).tw.
38	or/23-27, 30-37
39	22 and 38

PubMed

OVERVIEW

Databases (bibliographic):	PubMed
Years Covered:	1951-December 31, 2011
Date of Search:	June 26, 2012
Filter:	n/a

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.
*	Truncation (wildcard). Search retrieves all suffix variations of the search term.
Mesh	Medical Subject Heading
MeSH Terms	Medical Subject Heading term
Subheading	Used to further refine a Medical Subject Heading
Title/Abstract	Search retrieves records which contain search terms in the title and abstract.
Sources:	

PubMed Database

JEFFLINE (Jefferson University). (2010, March). Searching PubMed. Retrieved from:
http://jeffline.jefferson.edu/Ask/Help/Handouts/Searching_PubMed.pdf

((((((((((brain neoplasms[MeSH Terms])) OR (astrocytoma[MeSH Terms])) OR (Glioma[MeSH Terms])) OR (oligodendroglioma[MeSH Terms])) OR (glioblastoma[MeSH Terms])) OR (ependymoma[MeSH Terms])) OR (meningioma[MeSH Terms])) OR (primary brain tumor*[Title/Abstract])) OR (oligoastrocytoma[MeSH Terms])) AND ((((((risk[MeSH Terms])) OR (risk factors[MeSH Terms])) OR (odds ratio[MeSH Terms])) OR (causality[MeSH Terms])) OR (prevention and control[MeSH Subheading])) AND (((smoking[MeSH Terms])) OR (smoking[Title/Abstract]))

CINAHL

OVERVIEW

Databases (bibliographic):	CINAHL- Cumulative Index to Nursing & Allied Health Literature Database Guide
Years Covered:	1982- December 31, 2011
Date of Search:	June 26, 2012
Filter:	SIGN (Scottish Intercollegiate Guidelines Network) Source: http://www.sign.ac.uk/methodology/filters.html#obs

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.
NOT	Search retrieves records which contains the first search term but not the second.
*	Truncation (wildcard). Search retrieves all suffix variations of the search term.
PT	Publication type.
MH	Exact Subject Heading
TX	All Text

Sources:

CINAHL—Cumulative Index to Nursing & Allied Health Literature Database Guide Database

Database Guide (2007, April 4). CINAHL—Cumulative Index to Nursing & Allied Health Literature Database Guide. Retrieved from:

<http://www.ovid.com/site/products/ovidguide/nursing.htm>.

Line #	Strategy
1	(MH "Brain Neoplasms") OR (MH "Glioma") OR (MH "Meningeal Neoplasms") OR (MH "Meningioma")
2	TX "brain cancer" OR TX "brain tumor*" OR TX "primary brain tumor*" OR TX

	"astrocytoma" OR TX "glioblastoma" OR TX "oligodendroglioma" OR TX "oligoastrocytoma" OR TX "ependymoma"
3	(MH "Attributable Risk") OR (MH "Risk Factors") OR TX "etiology" OR TX "causation" OR TX "risk" OR TX "risk factor" OR TX "prevention and control"
4	MH smoking OR TX "smok"
5	S1 or S2
6	S3 and S4 and S5
7	MM "Prospective Studies"
8	MH "Case Control Studies +"
9	MM "Correlational Studies"
10	MM "Noncurrent Prospective Studies"
11	MM "Cross Sectional Studies"
12	TX "cohort study" OR TX "cohort studies"
13	TX "observational study" OR TX "observational studies"
14	S7 or S8 or S9 or S10 or S11 or S12 or S13
15	S6 and S14
16	
17	
18	

PsycINFO

OVERVIEW

Databases (bibliographic):	PsycINFO
Years Covered:	1806- December 31, 2011
Date of Search:	June 26, 2012
Filter:	University of Texas School of Public Health. Search filters for case-control studies, cohort studies, cross-sectional studies, clinical trials. Accessed 26 June 2012. [Ovid] Source: https://sph.uth.tmc.edu/charting/Ovid_PsycINFO_filters.htm

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.
*	Truncation (wildcard). Search retrieves all suffix variations of the search term.
/	Searches the search term as a subject heading
.ab, ti.	Searches for the search term in the abstract and title
.sh	Searches the search term as a subject heading
.id	Searches the search term as a key concept.
	Sources: PsycINFO Database

Line #	Strategy
1	brain neoplasms/

2	"primary brain tumo*" .ab,ti.
3	brain cancer.ab,ti.
4	"brain tumo*" .ab,ti.
5	glioma/
6	astrocytoma.ab,ti.
7	glioblastoma.ab,ti.
8	ependymoma.ab,ti
9	oligodendroglioma.ab,ti.
10	meningioma.ab,ti.
11	oligoastrocytoma.ab,ti.
12	glioma.ab,ti.
13	or/1-12
14	risk factors/ or at risk populations/ or causality/ or predisposition/ or protective factors/ or psychosocial factors/ or risk assessment/ or sociocultural factors/ or "susceptibility (disorders)"/
15	Tobacco smoking/
16	"smok*" .ab,ti.
17	Or/15-16
18	13 and 14 and 17
19	((case* adj5 control*) or (case adj3 comparison*) or case-comparison or control group*).ti,ab. Not "Literature Review".md.
20	((cohort or longitudinal or prospective or retrospective).ti,ab,id. or longitudinal study.md. or prospective study.md. or retrospective study.md.) not "Literature Review".md.
21	19 or 20
22	18 and 21

PROQUEST Dissertations & Theses (PQDT)

OVERVIEW

Databases (bibliographic): ProQuest Dissertations & Theses
Years Covered: 1861- December 31, 2011
Date of Search: June 26, 2012

Filter: No filter

SYNTAX GUIDE

AND Search retrieves records which contain all search terms.
OR Search retrieves records which contain at least one search term.
* Truncation (wildcard). Search retrieves all suffix variations of the search term.
ab Search retrieves records which contain search terms in abstract.

Sources:

ProQuest Dissertations & Theses Database

[ab\(brain tumo* OR brain cancer OR brain neoplasm OR glioma OR astrocyoma OR glioblastoma OR ependymoma OR oligodendrogloma OR oligoastrocytoma OR meningioma\) AND ab\(\(risk* OR risk factor OR etiology OR causation OR prevention\)\) AND ab\(\(smoking OR smoke\)\)](#)

Cancer Causes & Control (CCC)- Volume 1/1990-Voume 22/2011:

OVERVIEW	
Academic Journal:	Cancer Causes & control (CCC)
Years Covered:	1990-2011
Date of Search:	June 26, 2012
Filter:	n/a

SYNTAX GUIDE	
AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.

“Brain tumor and smoking”

“Glioma and smoking”

“meningioma and smoking”

International Journal of Cancer- Volume 1/1966- Volume 129/2011:

OVERVIEW	
Academic Journal:	International Journal of Cancer
Years Covered:	1966-2011
Date of Search:	June 26, 2012
Filter:	n/a

SYNTAX GUIDE	
AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.

“Brain tumor and smoking (abstract)”

“Glioma and smoking (abstract)”

“meningioma and smoking (abstract)”

Google Scholar:

OVERVIEW	
Database:	Google Scholar
Years Covered:	?
Date of Search:	June 12, 2012

SYNTAX GUIDE	
AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.
*	Truncation (wildcard). Search retrieves all suffix variations of the search term.

“Brain tumor and smoking”

Google:

OVERVIEW	
Database:	Google
Years Covered:	?
Date of Search:	June 12, 2012

SYNTAX GUIDE	
AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.
*	Truncation (wildcard). Search retrieves all suffix variations of the search term.

“Brain tumor and smoking”

13.8. Appendix H

Phase 2- Smoking:Screening- Level 1: Title and Abstract & Level 2: Full Article

- Does the article include ONE or more of the following (focus of onset): GLIOMA, ASTROCYTOMA, OLIGODENDROGLIOMA, OLIGOASTROCYTOMA, EPENDYMOMA, GLIOBLASTOMA, MENINGIOMA]? ***Note*-if the article does not break down primary brain tumours, then exclude.**
1. Yes
 No
 Can't Tell
 2. Is this article related to smoking (ie. cigarettes/ tobacco- active/passive)? Must provide risk estimates and 95% CIs.
 Yes
 No
 Can't Tell
 3. Does the article consist of childhood primary brain tumours (exclusion criteria) (Ex: childhood medulloblastoma, using the term "pediatric")
 Yes
 No
 Can't Tell
 4. Is smoking the main exposure variable being analyzed? (ie. if it is analyzed in conjunction with an interaction exposure term, then exclude)
 Yes
 No
 Can't Tell
 5. Is the following either a case-control or cohort study?
 Yes
 No
 Can't Tell
 6. What type of primary brain tumour?
 Glioma

- Astrocytoma
- Oligodendrogloma
- Oligoastrocytoma
- Glioblastoma
- Ependymoma
- Meningioma
- Not Applicable

7. Is this article presented in English or French?

- Yes
- No
- Can't Tell

8. Is the full article published before December 31, 2011?

- Yes
- No
- Can't Tell

9. Is the full publication available? *Note- if article is being ordered through RACER, do not complete Level 2 screening until the article is available for review. If article cannot be ordered and is not accessible, complete level 2 screening and select "no" (article will be excluded)

- Yes
- No
- Can't Tell

13.9. Appendix I

Phase 2- Smoking: Extraction Form

Provide information pertaining to the relevant characteristics in the studies analyzed: NB: If the article does not state a particular characteristic, indicate "N/A" in the textbox.					
STUDY CHARACTERISTICS					
Does the article refer to a classification system used to define disease outcomes?					
Location:					
Race/Ethnicity:					
Study design type:					
Period of recruitment (case-control and cohort):					
Average follow-up (cohort studies)					
PARTICIPANTS					
Sample size Cohort studies (# cases/final cohort size) Case-control (# cases/# controls)					
Source of participants (ex: community, hospital/institution, population). Ensure that source of BOTH cases and controls (for case-control studies) is specified.					
Age (mean age or range):					
Sex:					
Response rate (%):					
EXPOSURES					
Risk factor:					
Ascertainment (ex: serum levels, self report):					
Categorization of exposure (ex: quartile 1 vs quartile 4, exposed vs. unexposed, 250 mg vs. 0mg, etc):					
OUTCOME AND RESULTS					
Outcome (ex: glioma, meningioma, etc):					
Ascertainment/case definitions (DSM, ICD-10, etc):					
Confounding adjustments (variables):					
Risk estimates & 95% CI (for each comparison):					
Limitations noted:					
Conclusion (few sentences summarizing the overall conclusion of the study):					

13.10. Appendix J

Phase 2- Smoking: List of Excluded Studies at Level 2 Screening

1. Is this article related to brain tumours-must include sub-types of interest? (answer: no)

Benson, V. S., Green, J., Pirie, K., & Beral, V. (2010). Cigarette smoking and risk of acoustic neuromas and pituitary tumours in the Million Women Study. *British journal of cancer*, 102(11), 1654-1656.

Schlehofer, B., Kunze, S., Sachsenheimer, W., Blettner, M., Niehoff, D., & Wahrendorf, J. (1990). Occupational risk factors for brain tumors: results from a population-based case-control study in Germany. *Cancer Causes & Control*, 1(3), 209-215.

Brownson, R. C., Reif, J. S., Chang, J. C., & Davis, J. R. (1990). An analysis of occupational risks for brain cancer. *American journal of public health*, 80(2), 169-172.

Chuang, S. C., Gallo, V., Michaud, D., Overvad, K., Tjønneland, A., Clavel-Chapelon, F., ...& Vineis, P. (2011). Exposure to environmental tobacco smoke in childhood and incidence of cancer in adulthood in never smokers in the European prospective investigation into cancer and nutrition. *Cancer Causes & Control*, 22(3), 487-494.

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Bray, F., & Atkin, W. (2004). International cancer patterns in men: geographical and temporal variations in cancer risk and the role of gender. *The journal of men's health & gender*, 1(1), 38-46.

Ausman, J.I. In this Issue..

Pang, D., McNally, R., & Birch, J. M. (2003). Parental smoking and childhood cancer: results from the United Kingdom Childhood Cancer Study. *British journal of cancer*, 88(3), 373-381.

Tsai, S. P., Wendt, J. K., Cardarelli, K. M., & Fraser, A. E. (2003). A mortality and morbidity study of refinery and petrochemical employees in Louisiana. *Occupational and environmental medicine*, 60(9), 627-633.

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Kleihues, P. (1996). The etiology of human cancers. *Prev. Med*, 25 (1): 13.

Wrensch, M., Bondy, M. L., Wiencke, J., & Yost, M. (1993). Environmental risk factors for

primary malignant brain tumors: a review. *Journal of neuro-oncology*, 17(1), 47-64.

Richardson, R. S., Chilmonczyk, B. A., Salmun, L. M., & Megathlin, K. N. (1993). The hazards of active and passive smoking. *N Engl J Med*, 328(23), 1665-9.

Kobaashi, N., Hanawa, Y., Nagahara, N., Akatsuka, J., & Matsui, I. (1990). A study of environmental factors before and during pregnancy in childhood malignancy]. *Ganno rinsho. Japan journal of cancer clinics*, 370.

Hirayama, T. (1990). [A large scale cohort study on the effect of life styles on the risk of cancer by each site]. *Gan no rinsho. Japan journal of cancer clinics*, 233.

Hirayama, T. (1985). Passive smoking--a new target of epidemiology. *The Tokai journal of experimental and clinical medicine*, 10(4), 287.

Efird, J. T. (2003). *Epidemiologic Issues in Squamous Cell Skin Cancer, Primary Adult-onset Brain Cancer, and Parkinson's Disease* (Doctoral dissertation, Stanford University).

Chiu, C. H. (1997). *Cigarette Smoking and Selected Cancers in Iowa* (Doctoral dissertation, University of Iowa).

2. Is this article related to smoking (ie. cigarettes/ tobacco- active/passive)? Must provide risk estimates and 95% CIs.) (answer: no)

MUSICCO, M., FILIPPINI, G., BORDO, B. M., MELOTTO, A., MORELLO, G., & BERRINO, F. (1982). Gliomas and occupational exposure to carcinogens: case-control study. *American journal of epidemiology*, 116(5), 782-790.

Anderson, L. M. (2008). Environmental genotoxicants/carcinogens and childhood cancer: filling knowledge gaps. *Current problems in pediatric and adolescent health care*, 38(2), 50.

Hashibe, M., Straif, K., Tashkin, D. P., Morgenstern, H., Greenland, S., & Zhang, Z. F. (2005). Epidemiologic review of marijuana use and cancer risk. *Alcohol*, 35(3), 265-275.

CHOI, N. W., SCHUMAN, L. M., & GULLEN, W. H. (1970). EPIDEMIOLOGY OF PRIMARY CENTRAL NERVOUS SYSTEM NEOPLASMS II: CASE-CONTROL STUDY. *American journal of epidemiology*, 91(5), 467-485.

3. Does the article consist of childhood brain tumours (answer: yes)

Ferrence, R. (2010). Passive smoking and children. *BMJ*, 340.

4. Is smoking the main exposure variable being analyzed? (ie. if it is analyzed in conjunction with an interaction exposure term, then exclude) (answer: yes)

Flint-Richter, P., Mandelzweig, L., Oberman, B., & Sadetzki, S. (2011). Possible interaction between ionizing radiation, smoking, and gender in the causation of meningioma. *Neuro-oncology*, 13(3), 345-352.

Hogervorst, J. G., Schouten, L. J., Konings, E. J., Goldbohm, R. A., & van den Brandt, P. A. (2009). Dietary acrylamide intake and brain cancer risk. *Cancer Epidemiology Biomarkers & Prevention*, 18(5), 1663-1666.

Bardakci, F., Arslan, S., Bardakci, S., Binatli, A. O., & Budak, M. (2008). Sulfotransferase 1A1 (SULT1A1) polymorphism and susceptibility to primary brain tumors. *Journal of cancer research and clinical oncology*, 134(1), 109-114.

Lin, H. (1998). Relationships between the alterations of tumor suppressor genes, risk factors and clinical outcomes of gliomas.

5. Is the full publication available? (answer: no)

Smokeless Tobacco

Second-hand tobacco smoke

Gousias, K., Markou, M., Voulgaris, S., Goussia, A., Voulgari, P., Bai, M., ... & Alamanos, Y. (2009). Descriptive epidemiology of cerebral gliomas in northwest Greece and study of potential predisposing factors, 2005–2007. *Neuroepidemiology*, 33(2), 89-95.

Wu, M. (2007). A case-control study on risk factors of intracranial tumors in Shandong Province. *Dissertation*

13.11. Appendix K

Phase 2- Mobile Phone Use Systematic Review Protocol

1. Brief Background/Issues and Basis for Study Development

Several reviews have analyzed the association between mobile phone use (non-ionizing radiofrequency fields) and primary brain tumours with inconsistent findings. It has been hypothesized that the head's increased exposure to radiofrequencies due to the proximity of mobile phone devices may have an effect on tumour formation (Hossman & Hermann, 2003). This concern has become increasingly prevalent as the level of Megahertz (MHz) exposure has increased over the years due to technological advances. The 1980s were dominated by analogue phones which emitted 450 and 900 MHz, then came digital phones in the 1990s which emitted 900 and 1,800 MHz, then followed 3G mobile phones in 2003, which emit 1,900 MHz (Hardell & Carlberg, 2009). The pattern of increasing MHz is concerning as MHz exposure had almost doubled within a 10 year span, and it has only been increasing with the introduction of the 3G network. This topic is an area which needs to be of great focus, as the use of mobile phones has become a norm within society. As well, despite the conflicting results, the International Agency for Research on Cancer (IARC) have agreed to classify radiofrequency electromagnetic fields (those associated with mobile phone use) as a category 2B, possibly carcinogenic to humans (IARC, 2011). It would be of great interest to determine whether conducting a systematic review and meta-analysis on the world literature concerning mobile phone using proper systematic review methods would support this decision made by IARC.

As indicated in Phase 1, there are five low to moderate quality systematic review and meta-analysis on mobile phone use and onset of brain tumours published before December 31, 2011. With AMSTAR scores ranging from 3 to 7 (low to moderate), reviews on this specific topic are considered eligible to be subjected to de-novo processes. The purpose of this current review is to address certain aspects within AMSTAR which these authors have failed to address. As a result, certain conclusions from the review in question may differ.

2. Research Question and Objectives.

Components of the intended research question can be constructed within a PICO framework.

- **Population:** Adults (≥ 18 years old, males and females)
- **Intervention/Exposure:** Mobile phone use and/or cordless phone use
- **Comparator:** non regular users
- **Outcomes:** Glioma sub-types (astrocytoma, glioblastoma, oligoastrocytoma, oligodendroglioma, ependymoma) and meningioma
- **Study Designs:** Case-control and cohort studies.

Research Question: Based on available case-control and cohort studies, are mobile phone use and /or cordless phone use associated with adult onset of glioma sub-types (astrocytoma, glioblastoma, oligoastrocytoma, oligodendroglioma, ependymoma) and/or meningioma?

Objectives:

- To identify relevant observational studies (case-control and cohort) focusing on the effects of mobile phone use and the onset of glioma and/or meningioma in an attempt to provide an overall conclusion regarding this association.
- If permissible (at least three study estimates), to conduct a meta-analysis on relevant studies (with data pertaining to Never vs. regular user, Never, vs. short term and Never vs. long term.
 - Short term: “ Ever having been a user for 1-9 years”
 - Long term: “ Ever having been a user for ≥ 10 years”
- To provide a current-up to date, high methodological quality systematic review and meta-analysis on the association between mobile phone use and glioma/meningioma, as dictated by AMSTAR criteria, to be used by health policy makers and relevant stakeholders.

4. Methods

4.1.Literature Search Strategy

With the guidance of a health information specialist at the University of Ottawa, search strategies were developed for the Medline bibliographic database (see Appendix). Using this as a template, similar search strategies will be developed for the following databases as well: PubMed, Embase, CINAHL and PsycINFO. AARP Ageline and TOXLINE were excluded as they were deemed irrelevant based on the searches conducted in Phase 1. Grey Literature sources, such as ProQuest Dissertation and Thesis Database, as well as Google and Google Scholar will be searched. “Other sources” of literature will also considered: Hand searching of bibliographies of included studies, studies included in previous reviews and of disease-specific journals, such as Cancer Causes and Control and the International Journal of Cancer will be completed as well.

4.2.Selection Criteria

Studies will be included if they satisfy all of the following inclusion criteria:

- Studies have to focus on the onset on at least one of the following brain tumours: glioma, astrocytoma, oligodendroglioma, oligoastrocytoma, ependymoma, glioblastoma, meningioma
- Studies have to focus on mobile phone use (cellular) and cordless as exposure and must provide risk estimates with 95% confidence intervals.
- Mobile phone use had to be the main exposure variable, and cannot be combined with another exposure variable as part of an interaction term.
- Studies have to be of either case-control or cohort study design.
- Studies have to be published in English or French.

- Full-text of studies needs to be retrievable.
- Studies have to be published before December 31, 2011.

Studies will be excluded if they satisfy at least one of the following exclusion criteria:

- Studies which focus on childhood primary brain tumours.

4.3. Study Selection Method

Similar to screening processes conducted in Phase 1, a liberal accelerated method will be utilized. In order to ensure feasibility while retaining the integrity of a SR, a method known as “liberal accelerated” will be selected for the screening process. This method is opted for due to the sheer number of collected articles and the issue of limited resources. Based on this method, a unanimous decision by two reviewers (MH or RES and PQ) is needed for an article to be excluded. This ensures that articles excluded by the first reviewer (PQ) are re-assessed by a second reviewer. A safety net is essentially created when two opinions were needed to exclude an article. A kappa statistic, to determine inter-rater reliability is calculated to determine agreement for exclusion between the two reviewers. The second reviewer does not need to review the included articles since only one reviewer’s decision is required to advance the article to the next level. The first reviewer then retrieves the full text and subjects the article to further scrutiny, and any non-relevance will have been detected further on in the process. Any discordance between the two reviewers will be resolved by consensus.

4.4. Data Extraction Strategy

Data extraction forms have been developed a priori (see appendix). These forms have already been used widely for a national neurological project looking at risk factors for the onset of fourteen neurological conditions. Briefly, the first reviewer will extract all relevant data from the identified studies, and the second reviewer will duplicate extract a random 25% sample.

4.5. Study Quality Assessment

As recommended by the Cochrane Collaboration, quality assessment of observational studies will be completed by using the Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Non-Randomised Studies in Meta-Analyses (Reeves et al., 2008; Wells et al., Agency for Healthcare Research and Quality (AHRQ), 2011) (See Appendix). NOS was chosen since: it is widely used for quality assessing observational studies, quick to implement, and it has established face and content validity, along with inter-rater reliability (Reeves et al., 2008; Wells et al., Agency for Healthcare Research and Quality (AHRQ), 2011). Methodological issues between cohort and case control studies are evident, and the NOS accounts for such differences by subjecting both types of studies to different scales. The following components are addressed for both scales: selection (4 stars), comparability (2 stars) and ascertainment of exposure/outcome of interest (3 stars). The maximum score on this scale is nine stars (Wells et al., Castillo et al., 2010).

Although standard scoring thresholds have yet to be determined, many studies have consistently used the threshold of ≥ 5 stars and < 5 stars to represent studies of high and low quality (Regwan et

al., 2010; Wai et al., 2010; Tilney et al., 2007; Yeung et al., 2011; Lui et al., 2010).

4.6.Data Analysis Methods

A quantitative summary (the MA portion) will be attempted if:

- (3) There are greater than three relevant studies and;
- (4) Heterogeneity tests determine that the pooling of numerous point estimates is appropriate.

Relevant information from each study will be inputted RevMan which will generate funnel plots and their associated heterogeneity statistics, I^2 and Cochrane's Q (Ioannidis, 2008).

As outlined by the Cochrane Collaboration, I^2 percentages between 0%-40%, 30%-60%, 50%-90%, 75%-100% represents unimportant heterogeneity, moderate heterogeneity, substantial heterogeneity and considerable heterogeneity, respectively (Higgins & Green, 2008). Due to the low power of the Cochrane's Q test to detect true heterogeneity, the threshold for significance has been increased to $p=0.1$, meaning any p -value ≤ 0.1 will be considered statistically significant for heterogeneity and any p -value >0.1 will be considered homogeneous (Higgins & Green, 2008; Higgins et al., 2003).

After testing for heterogeneity, there are many options:

- (3) If the studies are homogeneous, then the studies may be similar enough for their estimates to be pooled using a random effects model resulting in an overall pooled estimate;
- (4) (a) if the studies are heterogeneous, it may be inappropriate to pool studies that are too dissimilar and a qualitative summary would suffice or;
(b) one can pool, using a random effects model, however, as described below, a subgroup analysis to explain the sources of heterogeneity must be attempted if there are sufficient number of articles available to do so(Higgins & Green, 2008).

Random effects models based on the DerSimonian and Laird method (DLM) (Higgins & Green, 2008) will be used to pool estimates together as opposed to using fixed effects models. Between study variances will always be present, and the random effects model accounts for this by including Tau squared (T^2) into the calculation(Higgins & Green, 2008; Deeks et al., 2001). Since variability is always present, random effects modeling generates more conservative estimates for determining significance by producing wider confidence intervals, allowing one to be more cautious in their conclusions. In regards to weights, a fixed effects model based on the inverse variance approach assigns heavier weights to studies with more precision (larger sample sizes and smaller standard errors) (Higgins & Green, 2008). Conversely, in a random effects model, the DLM method (variation of the inverse variance approach) assigns slightly more weight to smaller sized studies. This allows for smaller studies, with inherent variations, to have greater contribution to the model, since a common sized effect (fixed effects model) is disregarded(Higgins & Green, 2008).

Upon generating a forest plot, RevMan is also able to produce an inverted funnel plot which addresses the influence of publication bias. An asymmetrical plot generally indicates the presence of publication bias, whereas a symmetrical plot generally indicates its absence (Higgins & Green, 2008).

4.7.Planned Sensitivity/Subgroup Analyses

It has been decided a priori from previous studies in the field, that if substantial heterogeneity

exists and sufficient data is available, sub-group analysis will be attempted. All included studies will be pooled by study design to determine the presence of heterogeneity. Sub-group analyses will then be attempted by pooling studies with similar histological sub-types, disease classification systems (ICD codes, simple histological confirmation) sex, and exposure categories. (Harder et al., 2008; Bondy et al., 2008; Tan et al., 2010; Kan et al., 2008; Egger et al., 2001; Huss et al., 2008; Melnyk & Fineout-Overholt, 2010). By doing so, effect estimates which may differ based on certain characteristics will be identified and interpreted.

Presentation of Findings

Again, MOOSE guidelines will be used for reporting SRs and MAs (Stoup et al., 2000). The process of identifying, including and excluding relevant articles will be documented through the PRISMA flow diagram (Moher et al., 2009). Evidence tables derived from data extraction and subsequent qualitative summaries will be presented. If a MA is attempted, a forest plot with the pooled estimate and corresponding 95% confidence intervals, along with statistical values for heterogeneity (Cochrane's Q and I^2) will be provided. An inverted funnel plot will also be provided to address publication bias.

13.12. Appendix L

Phase 2- Mobile Phone Use: Search Strategies for Bibliographic Databases and Grey Literature Sources

Template source (for “syntax guide” and “overview” boxes):

Kaunelis, D. and Farrah, K. “Lecture: Introduction to Literature Searching.” Canadian Agency for Drugs and Technologies in Health (CADTH). University of Ottawa. 12 May 2011.

OVERVIEW OF SEARCH STRATEGIES	
Databases (bibliographic):	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations EMBASE PUBMED PsycINFO CINAHL
Grey Literature:	ProQuest (Dissertations and Theses) GoogleScholar Google
Hand-Searching Journals:	Cancer Causes & Control (CCC) International Journal of Cancer
Study Types:	Cohort studies and Case-Control studies (filters in place)

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

OVERVIEW	
Databases (bibliographic):	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
Years Covered:	1946- December 31, 2011
Date of Search:	October 12, 2012
Filter:	SIGN (Scottish Intercollegiate Guidelines Network)
	Sources: http://www.sign.ac.uk/methodology/filters.html#obs
SYNTAX GUIDE	
AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.
/	Searches the search term as a subject heading
.sh	Searches the search term as a subject heading
exp	Explodes a subject heading
adj	Search retrieves records containing search terms which are next to each other.
\$	Truncation (wildcard). Search retrieves all suffix variations of the search term.
.ti	Searches for the search term in the title.
.ab	Searches for the search term in the title.
.fs	Floating Subheadings. Used to help refine the meaning of a subject heading.
.pt	Publication type.
	Sources:

Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations Database

Field Guide (2008, January 9). Ovid MEDLINE ® Database Guide. Retrieved from:
<http://www.ovid.com/site/products/ovidguide/medline.htm#advanced>.

Line #	Strategy
1	exp Brain Neoplasms/
2	(primary adj brain adj tumo\$).ab,ti.
3	(brain adj cancer).ab,ti.
4	glioma/ or astrocytoma/ or glioblastoma/ or ependymoma/ or glioma, subependymal/ or oligodendroglioma/
5	meningioma/
6	(oligoastrocytoma\$ or glioma\$ or meningioma\$ or astrocytoma\$).ab,ti. or ependymoma\$.ab,it. or glioblastoma\$.ab,ti.oastrocytoma\$.ab,ti
7	oligodendroglioma\$.ab,ti.
8	or/1-7
9	exp Risk/
10	etiology.fs.
11	Odds Ratio/
12	prevention& control.fs.
13	or/9-12
14	Cellular phone/
15	Mobile phone.ab,ti.
16	Mobile telephone.ab,ti.
17	Cell phone.ab,ti.
18	Cellular phone.ab,ti.
19	Or/14-18
20	8 and 13 and 19
21	limit 20 to humans
22	epidemiologic Studies/
23	exp Case-Control Studies/
24	exp Cohort Studies/
25	case control.tw.
26	(cohort adj (study or studies)).tw.
27	cohort analy\$.tw.
28	(follow up adj (study or studies)).tw.
29	(observational adj (study or studies)).tw.
30	longitudinal.tw.
31	retrospective.tw.
32	or/22-31
33	21 and 32

Embase

OVERVIEW

Databases (bibliographic):	Embase
Years Covered:	1980- December 31, 2011
Date of Search:	October 12, 2012
Filter:	SIGN (Scottish Intercollegiate Guidelines Network)
	Source: http://www.sign.ac.uk/methodology/filters.html#obs

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.
/	Searches the search term as a subject heading
.sh	Searches the search term as a subject heading
exp	Explodes a subject heading
adj	Search retrieves records containing search terms which are next to each other.
adj#	Search retrieves records where the first search term is within <i>n</i> number of words to the second search term.
\$	Truncation (wildcard). Search retrieves all suffix variations of the search term.
.ti	Searches for the search term in the title.
.ab	Searches for the search term in the title.
.fs	Floating Subheadings. Used to help refine the meaning of a subject heading.
.pt	Publication type.
	Sources: Embase Classic + Embase Database
	Database Guide (2007, August 21). EMBASE: Excerpta Medica Database Guide. Retrieved from: http://www.ovid.com/site/products/ovidguide/embase.htm

Line #	Strategy
1	brain tumor/ or brain cancer/
2	(primary adj brain adj (tumo\$ or neoplasm\$ or cancer\$)).ti,ab.
3	(brain adj (tumo\$ or neoplasm\$ or cancer\$)).ti,ab.
4	astrocytoma/
5	glioma/ or ependymblastoma/ or ependymoma/ or glioblastoma/ or oligodendroglioma/
6	oligodendroglioma\$.ti,ab.
7	oligoastrocytoma\$.ti,ab.
8	glioma\$.ti,ab.
9	ependymoma\$.ti,ab.
10	glioblastoma\$.ti,ab
11	meningioma\$.ti,ab.
12	meningioma/ or malignant meningioma/
13	or/1-12
14	risk/ or attributable risk/ or high risk behavior/ or high risk population/ or population risk/ or risk assessment/ or risk factor/ or risk reduction/ or "prevention

	and control"/
15	cancer risk/
16	etiology/
17	or/14-16
18	Mobile phone/
19	Cellular phones\$.ti,ab.
20	Cell phone\$.ti,ab.
21	Mobile phone\$.ti,ab.
22	Or/18-21
23	13 and 17 and 22
24	limit 23 to humans
25	clinical study/
26	case control study/
27	family study/
28	longitudinal study/
29	retrospective study/
30	prospective study/
31	randomized controlled trials/
32	30 not 31
33	cohort analysis/
34	(cohort adj (study or studies)).tw.
35	(case control adj (study or studies)).tw.
36	(follow up adj (study or studies)).tw.
37	(observational adj (study or studies)).tw.
38	(epidemiologic\$ adj (study or studies)).tw.
39	(cross sectional adj (study or studies)).tw.
40	or/25-29, 32-39
41	24 and 40

PubMed

OVERVIEW

Databases (bibliographic):	PubMed
Years Covered:	1951-December 31, 2011
Date of Search:	October 12, 2012
Filter:	n/a

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.
*	Truncation (wildcard). Search retrieves all suffix variations of the search term.
Mesh	
MeSH Terms	Medical Subject Heading
Subheading	Medical Subject Heading term
Title/Abstract	Used to further refine a Medical Subject Heading

Search retrieves records which contain search terms in the title and abstract.

Sources:

PubMed Database

JEFFLINE (Jefferson University). (2010, March). Searching PubMed. Retrieved from:
http://jeffline.jefferson.edu/Ask/Help/Handouts/Searching_PubMed.pdf

((((((((((brain neoplasms[MeSH Terms])) OR (astrocytoma[MeSH Terms])) OR (Glioma[MeSH Terms])) OR (oligodendroglioma[MeSH Terms])) OR (glioblastoma[MeSH Terms])) OR (ependymoma[MeSH Terms])) OR (meningioma[MeSH Terms])) OR (primary brain tumor*[Title/Abstract])) OR (oligoastrocytoma[MeSH Terms])) AND (((((risk[MeSH Terms])) OR (risk factors[MeSH Terms])) OR (odds ratio[MeSH Terms])) OR (causality[MeSH Terms])) OR (prevention and control[MeSH Subheading])) AND (((mobile phones[MeSH Terms])) OR (cellular phones[Title/Abstract]) OR (cell phones [Title/Abstract]))

CINAHL

OVERVIEW

Databases (bibliographic):	CINAHL- Cumulative Index to Nursing & Allied Health Literature Database Guide
Years Covered:	1982- December 31, 2011
Date of Search:	October 12, 2012
Filter:	SIGN (Scottish Intercollegiate Guidelines Network) Source: http://www.sign.ac.uk/methodology/filters.html#obs

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.
NOT	Search retrieves records which contains the first search term but not the second.
*	Truncation (wildcard). Search retrieves all suffix variations of the search term.
PT	Publication type.
MH	Exact Subject Heading
TX	All Text

Sources:

CINAHL—Cumulative Index to Nursing & Allied Health Literature Database Guide Database

Database Guide (2007, April 4). CINHAL—Cumulative Index to Nursing & Allied Health Literature Database Guide. Retrieved from:

<http://www.ovid.com/site/products/ovidguide/nursing.htm>.

Line #	Strategy
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1	(MH "Brain Neoplasms") OR (MH "Glioma") OR (MH "Meningeal Neoplasms") OR (MH "Meningioma")
2	TX "brain cancer" OR TX "brain tumo*" OR TX "primary brain tumo*" OR TX "astrocytoma" OR TX "glioblastoma" OR TX "oligodendroglioma" OR TX "oligoastrocytoma" OR TX "ependymoma"
3	(MH "Attributable Risk") OR (MH "Risk Factors") OR TX "etiology" OR TX "causation" OR TX "risk" OR TX "risk factor" OR TX "prevention and control"
4	MH mobile phones OR TX "cellular phone*" OR TX "cell phone*" OR TX "mobile phone*"
5	S1 or S2
6	S3 and S4 and S5
7	MM "Prospective Studies"
8	MH "Case Control Studies +"
9	MM "Correlational Studies"
10	MM "Noncurrent Prospective Studies"
11	MM "Cross Sectional Studies"
12	TX "cohort study" OR TX "cohort studies"
13	TX "observational study" OR TX "observational studies"
14	S7 or S8 or S9 or S10 or S11 or S12 or S13
15	S6 and S14
16	
17	
18	

PsycINFO

OVERVIEW

Databases (bibliographic):	PsycINFO
Years Covered:	1806- December 31, 2011
Date of Search:	October 12, 2012
Filter:	University of Texas School of Public Health. Search filters for case-control studies, cohort studies, cross-sectional studies, clinical trials. Accessed 26 June 2012. [Ovid] Source: https://sph.uth.tmc.edu/charting/Ovid_PsycINFO_filters.htm

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.
*	Truncation (wildcard). Search retrieves all suffix variations of the search term.
/	Searches the search term as a subject heading
.ab, ti.	Searches for the search term in the abstract and title
.sh	Searches the search term as a subject heading
.id	Searches the search term as a key concept.
	Sources: PsycINFO Database

PROQUEST Dissertations & Theses (PQDT)

Line #	Strategy
1	brain neoplasms/
2	"primary brain tumo*".ab,ti.
3	brain cancer.ab,ti.
4	"brain tumo*".ab,ti.
5	glioma/
6	astrocytoma.ab,ti.
7	glioblastoma.ab,ti.
8	ependymoma.ab,ti
9	oligodendroglioma.ab,ti.
10	meningioma.ab,ti.
11	oligoastrocytoma.ab,ti.
12	glioma.ab,ti.
13	or/1-12
14	risk factors/ or at risk populations/ or causality/ or predisposition/ or protective factors/ or psychosocial factors/ or risk assessment/ or sociocultural factors/ or "susceptibility (disorders)"/
15	Cellular Phones/
16	"mobile phone*".ab,ti.
17	"cell phone*".ab,ti.
18	"cellular phone*".ab,ti.
19	Or/15-18
20	13 and 14 and 19
21	((case* adj5 control*) or (case adj3 comparison*) or case-comparison or control group*).ti,ab. Not "Literature Review".md.
22	((cohort or longitudinal or prospective or retrospective).ti,ab,id. or longitudinal study.md. or prospective study.md. or retrospective study.md.) not "Literature Review".md.
23	21 or 22
	20 and 23

OVERVIEW

Databases (bibliographic):	ProQuest Dissertations & Theses
Years Covered:	1861- December 31, 2011
Date of Search:	October 12, 2012
Filter:	No filter

[ab\(brain tumo* OR brain cancer OR brain neoplasm OR glioma OR astrocyoma OR glioblastoma OR ependymoma OR oligodendrogloma OR oligoastrocytoma OR meningioma\) AND ab\(\(risk* OR risk factor OR etiology OR causation OR prevention\)\) AND ab\(\(mobile phones OR cellular phone OR](#)

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.
*	Truncation (wildcard). Search retrieves all suffix variations of the search term.
ab	Search retrieves records which contain search terms in abstract.
Sources:	
ProQuest Dissertations & Theses Database	

[cell phones\)\)](#)

Cancer Causes & Control (CCC)- Volume 1/1990-Voume 22/2011:

OVERVIEW

Academic Journal:	Cancer Causes & control (CCC)
Years Covered:	1990-2011
Date of Search:	October 11, 2012
Filter:	n/a

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.

"Brain tumor and mobile phones"

"Brain tumor and cellular phones"

"glioma and mobile phones"

"meningioma and mobile phones"

International Journal of Cancer- Volume 1/1966- Volume 129/2011:

OVERVIEW

Academic Journal:	International Journal of Cancer
Years Covered:	1966-2011
Date of Search:	October 11, 2012
Filter:	n/a

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.

“Brain tumor and mobile phone (abstract)”

“Brain tumor and cellular phone (abstract)”

“glioma and mobile phone (abstract)”

"meningioma and mobile phone (abstract)"

Google Scholar:

OVERVIEW

Database:	Google Scholar
Years Covered:	?
Date of Search:	October 12, 2012

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.
*	Truncation (wildcard). Search retrieves all suffix variations of the search term.

“Brain tumor and mobile phones”

Google:

OVERVIEW

Database:	Google
Years Covered:	?
Date of Search:	October12, 2012

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.
*	Truncation (wildcard). Search retrieves all suffix variations of the search term.

"Brain tumor mobile phones"

13.13. Appendix M

Phase 2- Mobile Phones: Screening- Level 1: Title and Abstract & Level 2: Full Article

- Does the article include ONE or more of the following (focus of onset): GLIOMA, ASTROCYTOMA, OLIGODENDROGLIOMA, OLIGOASTROCYTOMA, EPENDYMOMA, GLIOBLASTOMA, MENINGIOMA]? ***Note*-if the article does not break down primary brain tumours, then exclude.**
1. Yes
 No
 Can't Tell
 2. Is this article related to mobile phone use (ie. cellular, include cordless)
 Yes
 No
 Can't Tell
 3. are risk/odds estimates provided with 95% CI?
 Yes
 No
 Can't Tell
 4. Does the article consist of childhood primary brain tumours (exclusion criteria) (Ex: childhood medulloblastoma, using the term "pediatric")
 Yes
 No
 Can't Tell
 5. Is mobile phone use the main exposure variable being analyzed? (ie. if it is analyzed in conjunction with an interaction exposure term, then exclude)
 Yes
 No
 Can't Tell
 6. Is the following either a case-control or cohort study?
 Yes
 No
 Can't Tell

7. What type of primary brain tumour?

- Glioma
- Astrocytoma
- Oligodendrogloma
- Oligoastrocytoma
- Glioblastoma
- Ependymoma
- Meningioma
- Not Applicable

8. Is this article presented in English or French?

- Yes
- No
- Can't Tell

9. Is the full article published before December 31, 2011?

- Yes
- No
- Can't Tell

10. Is the full publication available? *Note- if article is being ordered through RACER, do not complete Level 2 screening until the article is available for review. If article cannot be ordered and is not accessible, complete level 2 screening and select "no" (article will be excluded)

- Yes
- No
- Can't Tell

13.14. Appendix N

Phase 2- Mobile Phones: List of Excluded Studies at Level 2 Screening

1. Is this article related to brain tumours-must include sub-types of interest? (answer: no)

- Hardell, L., & Carlberg, M. (2010). Mobile phone use and the risk for malignant brain tumors: a case-control study on deceased cases and controls. *Neuroepidemiology*, 35(2), 109-114.
- Hardell, L., Mild, K. H., Carlberg, M., & Hallquist, A. (2004). Cellular and cordless telephone use and the association with brain tumors in different age groups. *Archives of Environmental Health: An International Journal*, 59(3), 132-137.
- Hardell, L., Mild, K. H., Pålsson, A., & Hallquist, A. (2001). Ionizing radiation, cellular telephones and the risk for brain tumours. *European Journal of Cancer Prevention*, 10(6), 523-529.
- Hardell, L., Nasman, A., Pahlson, A., & Hallquist, A. (2000). Case-control study on radiology work, medical X-ray investigations, and use of cellular telephones as risk factors for brain tumors. *MedGenMed*, 2(2), E2.
- Hardell, L., Näsman, A., Pålsson, A., & Hallquist, A. (1999). Use of cellular telephones and the risk for brain tumours: A case-control study. *International journal of oncology*, 15(1), 113.
- Hardell, L., Hallquist, A., Mild, K. H., Carlberg, M., Pålsson, A., & Lilja, A. (2002). Cellular and cordless telephones and the risk for brain tumours. *European Journal of Cancer Prevention*, 11(4), 377-386.
- Is there a link between cell phone use and cancer? (2011) *Mayo Clin Womens Healthsource*, 15(5): 8.
- Printz, C. (2010). Jury still out on cell phone—Cancer connection. *Cancer*, 116(9), 2067-2067.
- Muscat, J. E., Malkin, M. G., Thompson, S., Shore, R. E., Stellman, S. D., McRee, D., ...& Wynder, E. L. (2000). Handheld cellular telephone use and risk of brain cancer. *JAMA: the journal of the American Medical Association*, 284(23), 3001-3007.
- Hardell, L., Carlberg, M., & Mild, K. H. (2005). Use of cellular telephones and brain tumour risk in urban and rural areas. *Occupational and environmental medicine*, 62(6), 390-394.

2. Is this article related to mobile phone use (ie. cellular, include cordless)? (answer: no)

- Schüz, J., Böhler, E., Schlehofer, B., Berg, G., Schlaefter, K., Hettinger, I., ...& Blettner, M. (2009). Radiofrequency electromagnetic fields emitted from base stations of DECT cordless phones and the risk of glioma and meningioma (Interphone Study Group, Germany).

3. Are risk/odd ratios provided with corresponding 95% CIs? (answer: no)

Milham, S. (2010). Meningioma and mobile phone use. *International journal of epidemiology*, 39(4), 1117-1119.

Kundi, M. (2010). Mobile phone use and brain cancer: is the association biased?. *Neuroepidemiology*, 35(2), 115-116.

Hocking, B. (2008). Japanese mobile phone study. *British journal of cancer*, 98(11), 1879-1879.

Gale, B. D., & Juran, D. (2006). Cellular telephones and risk for brain tumors: A population-based, incident case-control study. *Neurology*, 66(5), 781-781.

Hardell, L., Mild, K. H., & Kundi, M. (2005). RE:" LONG-TERM MOBILE PHONE USE AND BRAIN TUMOR RISK". *American journal of epidemiology*.

Nelson, N. J. (2001). Recent studies show cell phone use is not associated with increased cancer risk. *Journal of the National Cancer Institute*, 93(3), 170-172.

Ahlbom, A., & Feychting, M. (2011). Mobile telephones and brain tumours. *BMJ*, 343.

Ahlbom, A., Feychting, M., Cardis, E., & Elliott, P. (2007). Re: Cellular telephone use and cancer risk: update of a nationwide Danish cohort study. *Journal of the National Cancer Institute*, 99(8), 655-655.

Ahlbom, A., & Feychting, M. (1999). Re: Use of cellular phones and the risk of brain tumours: a case-control study. *International journal of oncology*, 15(5), 1045.

Milham, S. (2006). Mobile phone use and risk of glioma in adults: case-control study. *British Journal of Cancer*, 94(9), 1351-1351.

Mir, L. (2009). Meningioma and mobile phones: a large European study, *Envir Risques Sante*, 8: 384-385.

OKTAR, N. (2001). <http://www.jns.dergisi.org/text.php3?id=417> Editorial Cell Phones and Brain Tumors. *Science*, 294, 1440-2.

Ahearn, A. (2011). Assessing the Science of Cell Phone Safety, with David Savitz. *Environmental health perspectives*, 119(11), 2-p.

Cardis, E., & Sadetzki, S. (2011). Indications of possible brain-tumour risk in mobile-phone studies: should we be concerned?. *Occupational and Environmental Medicine*, 68(3), 169-171.

Morgan, L. (2005). RE:“LONG-TERM MOBILE PHONE USE AND BRAIN TUMOR RISK”. *American Journal of Epidemiology*, 162(6), 599-600.

Milham, S. (2005). Re: "Long-term mobile phone use and brain tumor risk." *Am J Epidemiol*, 162 (6): 599.

4. Are they either of case-control or cohort study design? (answer: no)

Hardell, L., Mild, K. H., Carlberg, M., & Soderqvist, F. (2006). Tumour risk associated with use of cellular telephones or cordless desktop telephones. *World J Surg Oncol*, 4(74), 74.

Nicolle-Mir, L. Mobile telephones and brain tumors: Final results of the INTERPHONE study. [French]

Help desk. Is mobile phone use associated with increased risk of brain tumors?

4. Is the full publication available? (answer: no)

Momoli, F., Parent, M.-E., Siemiatycki, J., Platt, R., Richardson, L., Bedard, D., Cardis, E., McBride, M., and Krewski, D. A probabilistic multiple-bias model applied to a study of mobile phone use and risk of glioma

13.15. Appendix O

Phase 2- Personal Hair Dye Use Systematic Review Protocol

Brief Background/ Issues and Basis for Study Development

Personal use of hair dyes has been listed within plenty of narrative reviews as a potential risk factor associated brain tumours. These literature reviews have not definitively concluded its positive association, as one can with ionizing radiation; however its association is still questionable, and has not been addressed as a question in a systematic review; where one can place more confidence in the conclusions concerning its association with glioma and meningioma.

The prevalence of hair dye use is considerable. It has been reported that over 50% of women in developed countries use these products (Sosted et al., 2004). Serious concern was presented in the 1970s when certain chemicals found in hair dyes (certain aromatic amines, p-phenylenediamine and aminophenyl) in particular) were inducing tumours within animal models (Hennekens et al., 1979; Zhang et al., 2012; Bolt & Golka, 2007). As a result, certain chemicals were banned from these products, as a means to minimize risk (Rauscher et al., 2004). Despite these efforts, there are still over 5,000 chemicals used within hair dye products, and the safety of these formulations has not been confirmed (National Cancer Institute, 2011). It has been shown in toxicological experiments that exposure to other amines from hair dyes are successful in percutaneous (dermal) absorption (Rollison et al., Huncharek & Kupelnick., 2005).

There are essentially three types of hair dyes being used: permanent, semi-permanent, and temporary. Permanent dyes, making up majority of the use, are considered more damaging. An oxidative process is needed calling for the interaction between colourless pre-cursors and couplers in the presence of hydrogen peroxide to produce a coloured dye which infiltrates the hairshaft (Bolt & Golka., 2007).

Hair dye use has been proposed to be associated with several cancer sites within epidemiological studies, such as breast cancer, bladder cancer, and leukemia to name a few (Takkouche et al., 2005).

There have been no systematic reviews available which have satisfied the inclusion/exclusion criteria to be considered in Phase 1. Main reasons for exclusions of existing reviews are analyzing the outcome as "brain tumours" in a general term, and not considering them as separate histological sub-types, glioma and meningoma (Takkouche et al., 2005; Rollison et al., 2006). Another reason for exclusion was the focus on maternal exposure and subsequent risk for childhood brain tumours, as opposed to personal use and risk in adulthood (Rollison et al., 2006). Thus, a systematic review on personal hair dye use and the risk of adulthood glioma and meningioma, specifically, does not exist within the medical literature.

1. Research Question and Objectives

Components of the intended research question can be constructed within a PICO framework.

- **Population:** Adults (≥ 18 years old, males and females)

- **Intervention/Exposure:** Personal hair dye use (ever, permanent, semi-permanent, temporary)
- **Comparator:** N/A
- **Outcomes:** Glioma sub-types (astrocytoma, glioblastoma, oligoastrocytoma, oligodendroglioma, ependymoma) and meningioma
- **Study Designs:** Case-control and cohort studies.

Research Question: Based on available case-control and cohort studies, is personal hair dye use (permanent, semi-permanent, and temporary) associated with adult onset of glioma sub-types (astrocytoma, glioblastoma, oligoastrocytoma, oligodendroglioma, ependymoma) and/or meningioma?

Objectives:

- To identify relevant observational studies (case-control and cohort) focusing on the effects of personal hair dye use and the onset of glioma and/or meningioma in an attempt to provide an overall conclusion regarding this association.
- If permissible (at least three separate study estimates), to conduct a meta-analysis on relevant studies (with data pertaining to Never vs. Ever, Never vs. Permanent, Never, vs. Semi-Permanent and Never vs. Temporary).
- To provide a current-up to date, high methodological quality systematic review and meta-analysis on the association between personal hair dye use and glioma/meningioma, as dictated by AMSTAR criteria, to be used by health policy makers and relevant stakeholders.

2. Methods

2.1. Literature Search Strategy

With the guidance of a health information specialist at the University of Ottawa, search strategies were developed and tailored for the following bibliographic databases: PubMed, Medline, Embase, CINAHL, TOXLINE and PsycINFO (see **Appendix**). AARP Ageline was excluded as they were deemed irrelevant based on the searches conducted in Phase 1. Grey Literature sources, such as ProQuest Dissertation and Thesis Database, as well as Google and Google Scholar were searched. “Other sources” of literature were also considered. Bibliographies of included studies were searched, studies included in previous reviews were considered and hand-searching of disease-specific journals, such as Cancer Causes and Control and the International Journal of Cancer was completed as well.

All search strategies generally followed the same template. The following concept groups: Disease terms, risk terms, smoking terms, and a filter for identifying observational studies were all combined with the Boolean operator AND. Search terms within each concept group were combined the Boolean operator OR. Searches were conducted to include all published relevant articles up to January 25, 2013

2.2. A Priori Selection Criteria

Studies were included if they had satisfied all of the following inclusion criteria:

- Studies have to focus on the onset on at least one of the following brain tumours: glioma, astrocytoma, oligodendroglioma, oligoastrocytoma, ependymoma, glioblastoma, meningioma
- Studies have to focus on personal hair dye use as exposure and must provide risk estimates with 95% confidence intervals.
- Personal hair dye use has to be the main exposure variable, and cannot be combined with another exposure variable as part of an interaction term.
- Studies have to be of either case-control or cohort study design.
- Studies have to be published in English or French.
- Full-text of studies needs to be retrievable.

Studies were excluded if they had satisfied at least one of the following exclusion criteria:

- Studies which focus on childhood primary brain tumours.

2.3. Study Selection Method

After the removal of duplicates, identified studies were subjected to two levels of screening (title/abstract and full text) using the same screening questions for each level within Distiller SR (Evidence Partners, Ottawa, Canada) (**See Appendix**). A method known as “liberal accelerated” screening was used whereby only one reviewer’s input is needed to advance an article to the next level; however decisions from two reviewers are needed to exclude an article. The first reviewer (PQ) screens 100% of the articles, and the second reviewer (MH) duplicate screens the excluded articles identified by the first reviewer. Any conflicts will be resolved by consensus and a kappa statistic will be determined for the strength of agreement for excluded studies between the two reviewers.

2.4. Data Extraction Method

Studies which have satisfied the a priori selection criteria will be subjected to the data extraction process. Information on study characteristics, participants, exposures, outcomes and results will be recorded (**see Appendix**). The first reviewer will extract data from all relevant studies, and the second reviewer will duplicate extract a random 25%.

2.5. Study Quality Assessment

As recommended by the Cochrane Collaboration, quality assessment of observational studies will be completed by using the Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Non-Randomised Studies in Meta-Analyses (Reeves et al., 2008; Wells et al., Agency for Healthcare Research and Quality (AHRQ), 2011)(**See Appendix**). NOS was chosen since: it is widely used for quality assessing observational studies, quick to implement, and it has established face and content validity, along with inter-rater reliability (Reeves et al., 2008; Wells et al., Agency for Healthcare Research and Quality (AHRQ), 2011). Methodological issues between cohort and case control studies are evident, and the NOS accounts for such differences by subjecting both types of studies to

different scales. The following components are addressed for both scales: selection (4 stars), comparability (2 stars) and ascertainment of exposure/outcome of interest (3 stars). The maximum score on this scale is nine stars (Wells et al., Castillo et al., 2010).

Although standard scoring thresholds have yet to be determined, many studies have consistently used the threshold of ≥ 5 stars and <5 stars to represent studies of high and low quality (Regwan et al., 2010; Wai et al., 2010; Tilney et al., 2007; Yeung et al., 2011; Lui et al., 2010).

2.6. Statistical Analysis

A quantitative summary were considered for the following analyses: (a) Never vs. Permanent; (b) Never, vs. Semi-Permanent; and (c) Never vs. Temporary. A meta-analysis was attempted if there were greater than three relevant studies per analysis and if heterogeneity tests determined that the pooling of numerous risk estimates was appropriate. Analysis was analyzed by cohort and case-control estimates separately.

Degree of heterogeneity was determined by conducting the following statistical tests, Cochran's Q and I^2 (Ioannidis, 2008). As outlined in the Cochrane Collaboration, I^2 percentages between 0%-40%, 30%-60%, 50%-90%, 75%-100% represents unimportant, moderate, substantial, and considerable heterogeneity, respectively (Higgins & Green, 2008). Due to the low power of the Cochran's Q test to detect true heterogeneity, the threshold for significance was increased to $p=0.1$, meaning any p -value ≤ 0.1 was considered statistically significant for heterogeneity and any p -value >0.1 was considered homogeneous (Higgins & Green, 2008; Higgins et al., 2003).

Random effects models based on the DerSimonian and Laird Method (DLM), a variation of the inverse variance method (Higgins & Green, 2008; Deeks et al) was used to pool estimates together as opposed to using the fixed effects models. Since variability is always present, random effects modeling generates more conservative estimates for determining significance by producing wider confidence intervals, allowing one to be more cautious in their conclusions. The standard errors and the log risk or odds ratios of eligible point estimates were inputted into Review Manager version 5, resulting in pooled adjusted point estimates (Deeks et al.). If sufficient data existed, sub-group analyses based sex and histological sub-type was attempted. Publication bias was assessed for symmetry through inverted funnel plots generated by Review Manager.

2.7. Planned Sensitivity/Subgroup Analyses

It has been decided a priori from previous studies in the field, that if substantial heterogeneity exists and sufficient data is available, sub-group analysis will be attempted. All included studies will be pooled by study design to determine the presence of heterogeneity. Sub-group analyses will then be attempted by pooling studies with similar histological sub-types, disease classification systems (ICD codes, simple histological confirmation) sex, and exposure categories. (Harder et al., 2008; Bondy et al., 2008; Tan et al., 2010; Kan et al., 2008; Egger et al., 2001; Huss et al., 2008; Melnyk & Fineout-Overholt, 2010). By doing so, effect estimates which may differ based on certain characteristics will be identified and interpreted.

3. Presentation of Findings

Again, MOOSE guidelines will be used for reporting SRs and MAs (Stoup et al., 2000). The process of identifying, including and excluding relevant articles will be documented through the

PRISMA flow diagram (Moher et al., 2009). Evidence tables derived from data extraction and subsequent qualitative summaries will be presented. If a MA is attempted, a forest plot with the pooled estimate and corresponding 95% confidence intervals, along with statistical values for heterogeneity (Cochrane's Q and I^2) will be provided. An inverted funnel plot will also be provided to address publication bias.

13.16. Appendix P

Phase 2- Personal Hair Dye- Search Strategies for Bibliographic Databases and Grey Literature Sources

Template source (for “syntax guide” and “overview” boxes):

Kaunelis, D. and Farrah, K. “Lecture: Introduction to Literature Searching.” Canadian Agency for Drugs and Technologies in Health (CADTH). University of Ottawa. 12 May 2011.

OVERVIEW OF SEARCH STRATEGIES

Databases (bibliographic):	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations EMBASE PUBMED PsycINFO CINAHL
Grey Literature:	ProQuest (Dissertations and Theses) GoogleScholar Google
Hand-Searching Journals:	Cancer Causes & Control (CCC) International Journal of Cancer
Study Types:	Cohort studies and Case-Control studies (filters in place)

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

OVERVIEW

Databases (bibliographic):	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
Years Covered:	1946- December 31, 2011
Date of Search:	January 28, 2013
Filter:	SIGN (Scottish Intercollegiate Guidelines Network)
	Sources: http://www.sign.ac.uk/methodology/filters.html#obs

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.
/	Searches the search term as a subject heading
.sh	Searches the search term as a subject heading
exp	Explodes a subject heading
adj	Search retrieves records containing search terms which are next to each other.
\$	Truncation (wildcard). Search retrieves all suffix variations of the search term.
.ti	Searches for the search term in the title.
.ab	Searches for the search term in the title.
.fs	Floating Subheadings. Used to help refine the meaning of a subject heading.
.pt	Publication type.
	Sources: Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations Database

Field Guide (2008, January 9). Ovid MEDLINE ® Database Guide. Retrieved from:
<http://www.ovid.com/site/products/ovidguide/medline.htm#advanced>.

Line #	Strategy
1	exp Brain Neoplasms/
2	(primary adj brain adj tumo\$.ab,ti.
3	(brain adj cancer).ab,ti.
4	glioma/ or astrocytoma/ or glioblastoma/ or ependymoma/ or glioma, subependymal/ or oligodendroglioma/
5	meningioma/
6	(oligoastrocytoma\$ or glioma\$ or meningioma\$ or astrocytoma\$).ab,ti. or ependymoma\$.ab,ti. or glioblastoma\$.ab,ti. or astrocytoma\$.ab,ti
7	oligodendroglioma\$.ab,ti.
8	or/1-7
9	exp Risk/
10	etiology.fs.
11	Odds Ratio/
12	prevention& control.fs.
13	or/9-12
14	Hair dyes/
15	Hair dye\$.ab,ti.
16	Personal hair dye\$.ab,ti.
17	Or/14-16
18	8 and 13 and 17
19	limit 18 to humans
20	epidemiologic Studies/
21	exp Case-Control Studies/
22	exp Cohort Studies/
23	case control.tw.
24	(cohort adj (study or studies)).tw.
25	cohort analy\$.tw.
26	(follow up adj (study or studies)).tw.
27	(observational adj (study or studies)).tw.
28	longitudinal.tw.
29	retrospective.tw.
30	or/20-29
31	19 and 30

Embase

OVERVIEW

Databases (bibliographic):	Embase
Years Covered:	1980- December 31, 2011
Date of Search:	January 28, 2013
Filter:	SIGN (Scottish Intercollegiate Guidelines Network)
	Source: http://www.sign.ac.uk/methodology/filters.html#obs

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.
/	Searches the search term as a subject heading
.sh	Searches the search term as a subject heading
exp	Explodes a subject heading
adj	Search retrieves records containing search terms which are next to each other.
adj#	Search retrieves records where the first search term is within <i>n</i> number of words to the second search term.
\$	Truncation (wildcard). Search retrieves all suffix variations of the search term.
.ti	Searches for the search term in the title.
.ab	Searches for the search term in the title.
.fs	Floating Subheadings. Used to help refine the meaning of a subject heading.
.pt	Publication type.
	Sources: Embase Classic + Embase Database
	Database Guide (2007, August 21). EMBASE: Excerpta Medica Database Guide. Retrieved from: http://www.ovid.com/site/products/ovidguide/embase.htm

Line #	Strategy
1	brain tumor/ or brain cancer/
2	(primary adj brain adj (tumo\$ or neoplasm\$ or cancer\$)).ti,ab.
3	(brain adj (tumo\$ or neoplasm\$ or cancer\$)).ti,ab.
4	astrocytoma/
5	glioma/ or ependymblastoma/ or ependymoma/ or glioblastoma/ or oligodendroglioma/
6	oligodendroglioma\$.ti,ab.
7	oligoastrocytoma\$.ti,ab.
8	glioma\$.ti,ab.
9	ependymoma\$.ti,ab.
10	glioblastoma\$.ti,ab
11	meningioma\$.ti,ab.
12	meningioma/ or malignant meningioma/
13	or/1-12
14	risk/ or attributable risk/ or high risk behavior/ or high risk population/ or population risk/ or risk assessment/ or risk factor/ or risk reduction/ or "prevention

	and control"/
15	cancer risk/
16	etiology/
17	or/14-16
18	Hair dye/
19	Hair dye\$.ti,ab. or personal hair dye\$.ti,ab.
20	or/18-19
21	13 and 17 and 20
22	limit 21 to humans
23	clinical study/
24	case control study/
25	family study/
26	longitudinal study/
27	retrospective study/
28	prospective study/
29	randomized controlled trials/
30	28 not 29
31	cohort analysis/
32	(cohort adj (study or studies)).tw.
33	(case control adj (study or studies)).tw.
34	(follow up adj (study or studies)).tw.
35	(observational adj (study or studies)).tw.
36	(epidemiologic\$ adj (study or studies)).tw.
37	(cross sectional adj (study or studies)).tw.
38	or/23-27, 30-37
39	22 and 38

PubMed

OVERVIEW

Databases (bibliographic): PubMed
 Years Covered: 1951-December 31, 2011
 Date of Search: January 28, 2013

Filter: n/a

SYNTAX GUIDE

AND Search retrieves records which contain all search terms.
 OR Search retrieves records which contain at least one search term.
 * Truncation (wildcard). Search retrieves all suffix variations of the search term.
 Mesh Medical Subject Heading
 MeSH Terms Medical Subject Heading
 Subheading Medical Subject Heading term
 Title/Abstract Used to further refine a Medical Subject Heading
 Search retrieves records which contain search terms in the title and abstract.
Sources:

PubMed Database

JEFFLINE (Jefferson University). (2010, March). Searching PubMed. Retrieved from:
http://jeffline.jefferson.edu/Ask/Help/Handouts/Searching_PubMed.pdf

((((((((((brain neoplasms[MeSH Terms])) OR (astrocytoma[MeSH Terms])) OR (Glioma[MeSH Terms])) OR (oligodendroglioma[MeSH Terms])) OR (glioblastoma[MeSH Terms])) OR (ependymoma[MeSH Terms])) OR (meningioma[MeSH Terms])) OR (primary brain tumor*[Title/Abstract])) OR (oligoastrocytoma[MeSH Terms])) AND (((((risk[MeSH Terms])) OR (risk factors[MeSH Terms])) OR (odds ratio[MeSH Terms])) OR (causality[MeSH Terms])) OR (prevention and control[MeSH Subheading])) AND (((hair dye[MeSH Terms])) OR (hair dye[Title/Abstract]))

CINAHL

OVERVIEW

Databases (bibliographic):	CINAHL- Cumulative Index to Nursing & Allied Health Literature Database Guide
Years Covered:	1982- December 31, 2011
Date of Search:	January 28, 2013
Filter:	SIGN (Scottish Intercollegiate Guidelines Network) Source: http://www.sign.ac.uk/methodology/filters.html#obs

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.
NOT	Search retrieves records which contains the first search term but not the second.
*	Truncation (wildcard). Search retrieves all suffix variations of the search term.
PT	Publication type.
MH	Exact Subject Heading
TX	All Text

Sources:

CINAHL—Cumulative Index to Nursing & Allied Health Literature Database Guide Database

Database Guide (2007, April 4). CINHAL—Cumulative Index to Nursing & Allied Health Literature Database Guide. Retrieved from:

<http://www.ovid.com/site/products/ovidguide/nursing.htm>.

Line #	Strategy
1	(MH "Brain Neoplasms") OR (MH "Glioma") OR (MH "Meningeal Neoplasms") OR (MH "Meningioma")
2	TX "brain cancer" OR TX "brain tumor*" OR TX "primary brain tumor*" OR TX

	"astrocytoma" OR TX "glioblastoma" OR TX "oligodendroglioma" OR TX "oligoastrocytoma" OR TX "ependymoma"
3	(MH "Attributable Risk") OR (MH "Risk Factors") OR TX "etiology" OR TX "causation" OR TX "risk" OR TX "risk factor" OR TX "prevention and control"
4	TX "hair dye*" OR TX "personal hair dye*"
5	S1 or S2
6	S3 and S4 and S5
7	MM "Prospective Studies"
8	MH "Case Control Studies +"
9	MM "Correlational Studies"
10	MM "Noncurrent Prospective Studies"
11	MM "Cross Sectional Studies"
12	TX "cohort study" OR TX "cohort studies"
13	TX "observational study" OR TX "observational studies"
14	S7 or S8 or S9 or S10 or S11 or S12 or S13
15	S6 and S14
16	
17	
18	

PsycINFO

OVERVIEW

Databases (bibliographic):	PsycINFO
Years Covered:	1806- December 31, 2011
Date of Search:	January 28, 2013
Filter:	University of Texas School of Public Health. Search filters for case-control studies, cohort studies, cross-sectional studies, clinical trials. Accessed 26 June 2012. [Ovid] Source: https://sph.uth.tmc.edu/charting/Ovid_PsycINFO_filters.htm

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.
*	Truncation (wildcard). Search retrieves all suffix variations of the search term.
/	Searches the search term as a subject heading
.ab, ti.	Searches for the search term in the abstract and title
.sh	Searches the search term as a subject heading
.id	Searches the search term as a key concept.
Sources:	
	PsycINFO Database

Line #	Strategy
1	brain neoplasms/

2	"primary brain tumo*".ab,ti.
3	brain cancer.ab,ti.
4	"brain tumo*".ab,ti.
5	glioma/
6	astrocytoma.ab,ti.
7	glioblastoma.ab,ti.
8	ependymoma.ab,ti
9	oligodendroglioma.ab,ti.
10	meningioma.ab,ti.
11	oligoastrocytoma.ab,ti.
12	glioma.ab,ti.
13	or/1-12
14	risk factors/ or at risk populations/ or causality/ or predisposition/ or protective factors/ or psychosocial factors/ or risk assessment/ or sociocultural factors/ or "susceptibility (disorders)"/
15	"hair dye*".ab,ti.
16	"personal hair dye*".ab,ti.
17	Or/15-16
18	13 and 14 and 17
19	((case* adj5 control*) or (case adj3 comparison*) or case-comparison or control group*).ti,ab. Not "Literature Review".md.
20	((cohort or longitudinal or prospective or retrospective).ti,ab,id. or longitudinal study.md. or prospective study.md. or retrospective study.md.) not "Literature Review".md.
21	19 or 20
22	18 and 21

PROQUEST Dissertations & Theses (PQDT)

OVERVIEW

Databases (bibliographic): ProQuest Dissertations & Theses
 Years Covered: 1861- December 31, 2011
 Date of Search: June 26, 2012

Filter: No filter

SYNTAX GUIDE

AND Search retrieves records which contain all search terms.
 OR Search retrieves records which contain at least one search term.
 * Truncation (wildcard). Search retrieves all suffix variations of the search term.
 ab Search retrieves records which contain search terms in abstract.

Sources:

ProQuest Dissertations & Theses Database

[ab\(brain tumo* OR brain cancer OR brain neoplasm OR glioma OR astrocyoma OR glioblastoma OR ependymoma OR oligodendrogloma OR oligoastrocytoma OR meningioma\) AND ab\(\(risk* OR risk factor OR etiology OR causation OR prevention\)\) AND ab\(\(hair dye\)\)](#)

Cancer Causes & Control (CCC)- Volume 1/1990-Voume 22/2011:

OVERVIEW	
Academic Journal:	Cancer Causes & control (CCC)
Years Covered:	1990-2011
Date of Search:	January 28, 2013
Filter:	n/a

SYNTAX GUIDE	
AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.

“Brain tumor and hair dyes”

“glioma and hair dyes”

“meningioma and hair dyes”

International Journal of Cancer- Volume 1/1966- Volume 129/2011:

OVERVIEW	
Academic Journal:	International Journal of Cancer
Years Covered:	1966-2011
Date of Search:	January 28, 2013
Filter:	n/a

SYNTAX GUIDE	
AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.

“Brain tumor and hair dye (abstract)”
“Glioma and hair dye(abstract)”
“meningioma and hair dye(abstract)”

Google Scholar:

OVERVIEW

Database:	Google Scholar
Years Covered:	?
Date of Search:	January 28, 2013

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.
*	Truncation (wildcard). Search retrieves all suffix variations of the search term.

“Brain tumor and hair dyes”

Google:

OVERVIEW

Database:	Google
Years Covered:	?
Date of Search:	January 28, 2013

SYNTAX GUIDE

AND	Search retrieves records which contain all search terms.
OR	Search retrieves records which contain at least one search term.
*	Truncation (wildcard). Search retrieves all suffix variations of the search term.

“Brain tumor and hair dyes”

13.17. Appendix Q

Phase 2- Personal Hair Dyes: Screening- Level 1: Title and Abstract & Level 2: Full Article

Does the article include ONE or more of the following (focus of onset): GLIOMA,

1. ASTROCYTOMA, OLIGODENDROGLIOMA, OLIGOASTROCYTOMA, EPENDYMOMA, GLIOBLASTOMA, MENINGIOMA]? ***Note*-if the article does not break down primary brain tumours, then exclude.**

Yes

No

Can't Tell

2. Is this article related to hair dye use?

Yes

No

Can't Tell

3. are risk/odds estimates provided with 95% CI?

Yes

No

Can't Tell

4. Does the article consist of childhood primary brain tumours (exclusion criteria) (Ex: childhood medulloblastoma, using the term "pediatric")

Yes

No

Can't Tell

5. Is hair dye use the main exposure variable being analyzed? (ie. if it is analyzed in conjunction with an interaction exposure term, then exclude)

Yes

No

Can't Tell

6. Is the following either a case-control or cohort study?

Yes

No

Can't Tell

7. What type of primary brain tumour?

Glioma

Astrocytoma

Oligodendrogloma

Oligoastrocytoma

Glioblastoma

Ependymoma

Meningioma

Not Applicable

8. Is this article presented in English or French?

Yes

No

Can't Tell

9. Is the full article published before December 31, 2011?

Yes

No

Can't Tell

10. Is the full publication available? *Note- if article is being ordered through RACER, do not complete Level 2 screening until the article is available for review. If article cannot be ordered and is not accessible, complete level 2 screening and select "no" (article will be excluded)

Yes

No

Can't Tell

13.18. Appendix R

Phase 2- Personal Hair Dyes: List of Excluded Studies at Level 2 Screening

1. Is this article related to brain tumours-must include sub-types of interest? (answer: no)

Burch, J. D., Craib, K. J., Choi, B. C., Miller, A. B., Risch, H. A., & Howe, G. R. (1987). An exploratory case-control study of brain tumors in adults. *Journal of the National Cancer Institute*, 78(4), 601-609.

Mendelsohn, J. B., Li, Q. Z., Ji, B. T., Shu, X. O., Yang, G., Li, H. L., ... & Chow, W. H. (2009). Personal use of hair dye and cancer risk in a prospective cohort of Chinese women. *Cancer science*, 100(6), 1088-1091.