Project Title

An assessment of whether the retinal vasculature and the presence of retinal vessel damage can offer a prognostic indicator of cerebrovascular events such as strokes when examined using digital retinal photography: a literature review.

This project report has been submitted to the University of Warwick in partial fulfilment of the requirements for the award of the degree of MSc Health Sciences

Student Number: 1256697

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Abstract

Cerebrovascular events such as strokes present a considerable burden of mortality and morbidity. Risk factors for stroke are well established but current risk stratification methods are less than optimal.

Microvascular damage is involved in stroke aetiology and one may consider that these signs may be visible in the cerebral vasculature prior to occurrence. Imaging the cerebral vasculature can be costly, invasive and impractical and, with the physiology of the brain and the retina being very similar, retinal imaging may provide a more appropriate means of identifying at risk individuals.

This project applied a systematic search to existing literature to determine if a link could be shown between retinal microvascular abnormalities and increased stroke incidence. Eight papers were identified as suitable for inclusion in the final analysis. These papers variously examined the relationship that retinopathy, retinal arterial emboli, and vessel calibre had on stroke incidence.

Overall a positive link between each microvascular abnormality and stroke was demonstrated, with the strongest relationship seen in those individuals with retinopathy. There was a general lack of research on UK populations which raises some questions over how applicable the results would be in a UK setting, and it is important to note that the low incidence of stroke places limitations on the precision of risk estimates.

Each paper's findings supported those of the others which would lend credence to the theory that a link between retinal microvascular abnormalities and stroke incidence is present. This should be used to develop new methods of risk stratification. Further research on UK populations using large study groups and long periods of follow up should be undertaken to better understand how these findings would apply in the UK.

Chapter 1 – Introduction

Cerebrovascular events such as strokes are serious and can have devastating consequences, often occurring suddenly and without warning in otherwise apparently healthy individuals. They occur as a result of vascular dysfunction when vessels carrying oxygenated blood to the brain become blocked, starving areas of the brain of oxygen (ischaemic stroke); or when vessels in the brain rupture, damaging areas of cerebral tissue (haemorrhagic stroke).

Stroke is the second leading cause of death worldwide (World Health Organisation, 2009) and is a major cause of associated morbidity and disability in survivors (Wang et al., 2013). Around 152,000 strokes occur each year in the UK, with around a third resulting in death (Townsend et al., 2012), and with more than half of survivors left dependant on others for day to day activities (Adamson et al., 2004).

With cerebral vascular dysfunction being involved in stroke aetiology, it could be considered that the prognostic indicators of such events could be visible in other parts of the body prior to occurrence. The retina in particular is physiologically similar very similar to the brain (Wong, 2004) and intuitively one may consider that the retina could offer insight into cerebral vascular dysfunction allowing earlier prediction of strokes. With such a burden of mortality and morbidity it is important that those at risk are identified early so that they can be treated. Earlier treatment and intervention of at risk individuals has the potential to reduce the risk of cardiovascular events occurring.

This paper will aim to identify whether there is a link between visibly detectable vascular dysfunction in the retina and an increased incidence of stroke through a systematic review of the existing literature.

Chapter 2 – Background

Strokes remain a major cause of morbidity and mortality and many risk factors are well established. Boysen et al. (1988), Sacco et al. (1997) and the NHS website (accessed 29.03.2015) all identify age, gender, ethnicity, socio economic deprivation, smoking habits, hypertension, diabetes, high cholesterol, being overweight and lack of exercise as risk factors for stroke.

Hypertension is perhaps the biggest modifiable risk factor for stroke (Johansson, 1999), with many estimates suggesting stroke risk to be higher by a factor of four in those individuals considered to be hypertensive (Sacco et al., 1997). It has been established that tackling hypertension and its multifactorial causes can lead to a significant reduction in stroke incidence, as well as in stroke mortality (MacMahon & Rogers, 1994; Burt et al., 1995), and it is important to target interventions at those individuals identified as at risk of stroke. Such interventions can involve lifestyle changes such as increased exercise, stopping smoking and changes to diet, as well as pharmacological therapy. Age and ethnicity are unmodifiable risk factors for stroke, with the likelihood increasing with age and in black and minority ethnic groups, and one may assume with an increasingly ageing population in the UK that the incidence of stroke may be on the rise.

Despite the fact that risk factors are well established it is not possible to definitively predict which individuals will suffer a stroke. Examination of the microvasculature of the brain may provide a better indicator but this would be both invasive and harmful to the patient or, in the case of magnetic resonance imaging (MRI), impractical and expensive.

In the UK and internationally the rate at which modifiable risk factors are controlled remains low (Kearney et al., 2004; Cruz-Flores et al., 2011), and this poor control is associated with inadequate risk factor detection and management (Marshall et al., 2013). With a large cohort of patients

potentially at risk of stroke but not identified as such, it is important to look at other methods of identification.

With the retina and the brain being physiologically similar it may be possible to examine the retina to identify the early signs of vascular dysfunction which may offer a prognostic indicator for the likelihood of stroke. Examination of the retinal vasculature is relatively simple and non-invasive and is in use on a large scale in England with a well-established national screening programme for the detection of diabetic retinopathy.

Diabetic retinopathy occurs due to the chronic hyperglycemia characteristic of diabetes mellitus. This has a deleterious effect on the vasculature and can cause vascular dysfunction. When vascular dysfunction occurs the tight junctions between the cells which make up the blood vessel walls become more permeable and vessels can leak, leading to ischaemia and oedema. Hypoxia is the end result of such vascular dysfunction and hypoxic tissues will begin to produce vascular endothelial growth factor (VEGF). Whilst VEGF is a catalyst for angiogenesis, it also significantly increases vascular permeability making the blood vessels prone to leakage This process can lead to kidney damage (diabetic nephropathy), nerve damage (diabetic neuropathy) and damage to the retina (diabetic retinopathy), as well as increasing the risk of heart attacks and strokes.

Screening for diabetic retinopathy involves eligible patients being called for screening on an annual basis. Examination of the retina takes place using digital retinal photography through a dilated pupil and two 45 degree fields of each eye are captured. These are then assessed for the features of retinopathy by suitably qualified personnel. Such features include micronaneurysms, retinal haemorrhages, venous beading, intra-retinal microvascular abnormalities, neovascular growth, and pre-retinal and vitreous haemorrhages.

Retinal photography is a proven way of imaging the retina to detect vascular disease. Historically, the 'gold standard' for imaging the retina to detect diabetic retinopathy and maculopathy was seven-field stereo photography. Scanlon et al. (2003) found seven-field stereo to have a sensitivity of 96.4% and a specificity of 82.9% for the detection of diabetic retinopathy and maculopathy when compared to an ophthalmologist's examination using slit-lamp biomicroscopy. Despite its accuracy, seven-field stereo is time consuming to use and involves a considerable time investment in the training of operators and so proved unsuitable for use on a large scale.

Two-field digital retinal photography became the standard method of retinal imaging in organised systematic screening as it has been shown to be both sensitive and specific in detecting diabetic retinopathy and maculopathy when the images produced are examined by trained and accredited graders. It is a means of imaging the retina through a dilated pupil using two, standard, 45 degree fields, one macula-centred and one disc-centred, using a digital camera. It has advantages over seven-field stereo in that it is affordable and easy to use, meaning a lower time-investment in training of operators.

A number of studies have examined the accuracy of two-field digital retinal photography for the detection of retinal disease and have found it to be both sensitive and specific. The results of these studies are shown in Table 1 below.

Table 1: Sensitivity & Specificity of two-field digital retinal photography

Sensitivity	Specificity	Reference Standard	Pop. Size	Author
74%	92%	Ophthalmologist	360	Ku et al. (2013)
82.8%	96%	Ophthalmologist	239	Scanlon et al. (2003)
89%	97%	Ophthalmologist	773	Harding et al. (1995)
90%	87%	Ophthalmologist	584	Sharp et al. (2003)
92%	96%	Ophthalmologist	320	Lopez-Bastida et al. (2007)
93%	87%	Ophthalmologist	586	Olson et al. (2003)
97.1%	95.5%	Ophthalmologist	98	Boucher et al. (2003)

All the studies, bar the Ku et al. paper, show high sensitivity which demonstrates that digital retinal photography provides a reliable method of accurately detecting those individuals with retinopathy features present. Specificity in all studies is also very high which makes for a low rate of false positive results when digital retinal photography is used as a test.

The lower sensitivity quoted by the Ku paper may be due to the fact that the study participants were exclusively aboriginal Australians who, as well as not being representative of a UK population, often have poorer pupil dilation which can impact on image quality and make assessment more difficult. The majority of the studies in table one include use standardized methods of image capture for each group, as well as for assessing retinopathy levels, meaning that the findings could be interpreted as generally reliable and applicable to the wider population in the main. However, all studies have small numbers of participants which should be remembered when the results are being considered as the sample size may not be sufficiently large enough to demonstrate a statistically significant effect.

In addition to the detection of diabetic retinopathy, screening also allows for the opportunistic identification of non-diabetes related conditions such as hypertension and arterial emboli. With the

ability to detect retinal vascular dysfunction and features such as arterial emboli so well established, it may be possible to identify patients at risk of stroke through imaging the retina. Such identification would enable earlier intervention and management which could in turn reduce the risk of such events occurring, reduce the burden of disease and lead to improved outcomes for patients.

This project has the following aims and objectives:

2.1 Aim

The aim of this paper is to undertake a review of the literature in order to determine if the presence of certain observable signs in the retinal vasculature can offer insight into whether the patient is at increased risk of suffering a major cerebrovascular event such as a stroke.

2.2 Objectives

1. To systematically examine the existing literature and critically appraise the results.
2. To conduct an analysis of whether the evidence suggests a positive link between retinal vascular changes and increased incidence of cerebrovascular events.
3. To explore the possible reasons behind any link.
4. To make recommendations for future practice based on the results.

Chapter 3: Methodology

3.1 Background - The Literature Review

This study aims to build on existing knowledge in order to determine if increased risk of serious cerebrovascular events can be predicted from the appearance of the retinal vasculature. Project constraints precluded the possibility of conducting any original primary research and, as a systematic examination of the existing literature can provide a sound base upon which further research can be founded (Oliver, 2012; Cooper 1998), it was felt that a literature review was the most appropriate method of answering the research question.

Literature reviews aim to apply detailed and focussed search criteria in order to identify, evaluate and summarise the findings of relevant individual studies to provide an overall synthesis (Centre for Reviews and Dissemination, 2009), and to clarify gaps in knowledge that point to further research being needed (Greenhalgh, 2010). Whilst previous research into a subject may have been undertaken, the aim of a systematic literature review is to bring this knowledge together to see if a more definitive link or relationship can be seen, as the synthesised evidence from a number of studies can be seen to be more reliable as evidence than that from a single study alone. A systematic review aims for an objective search of the literature, and aims to apply predetermined inclusion and exclusion criteria before critically appraising what is found to be relevant. Findings are then formulated based on what has been extracted and synthesised from the evidence base (Shea et al., 2007). This project aims to identify existing research that has addressed the link between the appearance of the retinal vasculature and incidence of cerebrovascular events.

By conducting a literature review the reviewer hopes to find all the published data on a single topic, without being biased in any way towards any one aspect of the argument. It is important to fully detail the methods and search terms used, along with an explanation of which papers were included and which were excluded, and why (Goldacre, 2012). This allows them to be reviewed and

replicated by others, and means that the results are reliable, people can depend on them, and they do not mislead (Evans et al., 2006).

3.2 The Search

It was important to develop a strategy for searching so that the widest range of relevant information and research on the subject could be identified. In order to retrieve as much of the relevant research as possible it was important to consider what search terms would be used and which sources of information to search. It was then necessary to consider how the information identified in the searches would be assessed for suitability and how the final results would be critically analysed and appraised.

3.2.1 Databases searched

An abundance of peer reviewed, published literature is available through a number of databases such as PubMed which can be searched electronically. This literature review involved searching a number of the available databases in order to identify, where possible, all the relevant research. As stated by Greenhalgh (2010) and Aveyard (2010), multiple databases need to be searched in order to ensure that no stone is left unturned; PubMed may identify papers which do not appear on Embase and vice versa for example.

Databases were chosen on the basis that they were primarily concerned with medical research as this was most appropriate to the project question. Table 2 shows the databases that were searched for this literature review, and the reasons why they were chosen.

Table 2: List of databases

Database Searched	Reasons
Medline	Largest medical database. Comprehensive list of journals. Indexed using MeSH terms.
PubMed	Although very similar to Medline, may contain non-indexed articles.
Embase	Includes over 3,500 journals. Focussed on research in human medicine and biomedical fields
BioMed Central	Spans broad area.

3.2.2 Search terms

The search terms used needed to be broad enough to identify all the relevant literature but not so broad that analysing the number of results became unmanageable within the project timeframes. In order to do this the project question was analysed and the keywords that captured the essence of the question were identified and synonyms of these keywords were drawn up, as recommended by Aveyard (2010). As the author saw it, the relevant terms within the research question were: stroke; cerebrovascular event; retinal vasculature; retinal vessel damage; digital retinal photography. This led to the final set of search terms shown in Table 3.

Table 3: Search terms used

Stroke	Retinal vessels	Retinal photography
Cerebrovascular event	Retinal artery	Photography
	Retinal diseases	Ophthalmic imaging
	Retinopathy	

Search terms were combined with Boolean operators 'AND and 'OR'. The search identified a large number of papers which were then assessed for inclusion or exclusion in the final results of the review.

3.3 Inclusion and exclusion criteria

By their nature literature searches need to be broad enough to catch all the relevant literature so it stands to reason that they will also pick up plenty of less relevant literature. Because of this the researcher needs to apply inclusion and exclusion criteria in order to ensure that only the relevant papers are included in the final analysis. The criteria applied to inclusion and exclusion is shown in Table 4. The rationale behind each of these criteria is explained below.

Table 4: Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Primary research	Primary research that was unrelated to the study question being answered; systematic reviews; editorial articles; letters.
Study population did not have pre-existing stroke.	Study population had pre-existing stroke.
Population followed up over 4 years or more.	Population followed up for less than four years.
Large study population	Small study population
Published in English	Published in language other than English.
Study in humans	Study in animals
Participants not specifically diabetic	All participants diabetic

3.3.1 Primary Research

The intention of this literature review is to gather the most accurate and relevant evidence possible in order to inform the question being asked. Research that is not relevant will not inform, whilst

letters and editorial comment will provide opinion rather than evidence that can be assessed. Systematic reviews will provide a synthesis of evidence from a number of sources but are not strictly primary research and so were also excluded.

3.3.2 Study population does not have pre-existing stroke

It was expected that, because of the search terms to be used, research would be identified that examines the presence of retinopathy signs in study participants that have already suffered a stroke. Whilst such studies may show evidence of a correlation between the presence of retinopathy signs and existing stroke, they do not offer any insight into the value of retinopathy as a stroke predictor; retinopathy signs in someone with a previous stroke could be interpreted as a possible result of the stroke. The purpose of this paper is to determine whether retinopathy signs in patients who have not suffered a stroke can act as predictors for occurrence of stroke in the future and so studies using participants with existing stroke will be excluded from the final analysis. Studies which use presence or absence or retinopathy signs to determine the study and control groups and stroke incidence as the outcome measure will be included.

3.3.4 Population followed up for a minimum of three years

Whilst cerebrovascular events occur at a specific time and are not ongoing, vascular risk factors may appear many years prior to a stroke, and could even increase the likelihood of a stroke recurring (Frost et al., 2014). Because of this study groups will need to be followed up over several years following baseline assessment in order for there to be sufficient incident stroke cases to assess a relationship to retinal microvascular signs. Studies observing sample groups over shorter periods of time were treated with caution as the time period may not be sufficient to demonstrate a link.

Three years was judged by the author to be a reasonable cut-off point as it allows sufficient time for stroke incidence to manifest whilst not unnecessarily excluding the majority of research.

3.3.5 Large sample size

Strokes are fortunately relatively uncommon amongst the population as a whole. This implies that large cohorts would need to be studied in order to observe a sufficient stroke incidence to reliably determine any effect. Therefore the size of the population studied had a bearing on whether the study was included in the final analysis. Studies with smaller sample sizes are also more prone to finding misleading or inaccurate results. This does not necessarily mean that studies with small sample sizes will be automatically excluded from the final analysis, but it will be important to take this into account when examining the results and using them to inform the argument.

3.3.6 Published in English

As the author can only read in the English language, studies published in languages other than English where a translated version was not available were excluded from the final analysis. Time and financial constraints prevented the author from seeking translation services.

3.3.7 Study population human

The purpose of this project is to see if a link can be demonstrated between retinal vessel disorder and increased stroke risk. If such a link exists it may be possible to make recommendations for earlier identifications of those at risk of stroke in the future so that interventions may be implemented with the aim of reducing mortality and morbidity. Although animals can shows signs of retinopathy and can also suffer strokes, this evidence would not be reliable enough to use to recommend changes to future intervention and care in humans. Because of this, studies involving animals were excluded from the final analysis.

3.3.8 Diabetic study population

As discussed previously, diabetes can lead to microvascular dysfunction and is a risk factor for stroke. Because of this the author reflected that studies that recruited only diabetic populations would see an artificially high stroke incidence when considered against the general population as a

whole and it would be impossible to determine whether any incident strokes were as a result of hypertension, or whether they were as a result of diabetes. In addition it was felt that such studies would see an artificially high level of retinopathy signs when compared to the general population which again could skew the results.

It is also important to be aware that the aim of this project is to identify whether retinopathy signs can be equated with an increased risk of stroke in the general population so that recommendations can be made, if appropriate, for changes to current identification process for at risk individuals as currently identification of these individuals remains poor (Grosso et al., 2005). Individuals with diabetes are slightly better served in this respect since the NHS diabetic eye screening programme already has such protocols in place on a localised level for opportunistic identification of non-diabetes related retinal signs such as arterial emboli.

These factors led to the decision to exclude research that included only diabetic populations. Studies that recruited populations that happened to contain some diabetic individuals were included as they were deemed to be representative of the wider population.

3.4 Limitations of the search

All research methods have their limitations. A literature search aims to identify as much of the existing research related to the project question in as systematic, clearly described and replicable a way as possible, but there will be some problems and weaknesses within the work. Searching databases is not infallible and it is possible that not all the relevant research was identified and some papers may have been indexed under terms that were not searched.

Systematic literature searches produced to the standard of a Cochrane Review would be examined and critiqued prior to publication by a number of independent reviewers. Due to the constraints of

the project the author recognises that this type of peer review was not possible in this case and is a limitation of the project.

It is also important to be aware that there is always the possibility of publication bias misleading the final analysis. The papers included in this project all showed a positive effect and have been published in academic journals but, as Goldacre (2012) points out, studies that show negative results are more likely to go unpublished than those which show positive results. It therefore stands to reason that some studies on this subject could have been conducted which showed no effect and went unpublished. Such a situation can occur for a number of, seemingly entirely legitimate, reasons, such as trials that appear to show no effect being stopped early so as not to 'waste' any more money, or final results not being written up and submitted for publication due to the assumption that a negative result is an uninteresting result, or even journal editors failing to select negative results for publication for the same reason. This is perhaps less common now than it was in the past but it is a factor that should always be considered when appraising the evidence from a literature review.

3.4.1 The Existing Literature Review

The author encountered some problems when a systematic literature review addressing an almost identical topic to this project was identified at a very late stage. This review, by Baker et al. (2008), searched the literature to examine the link between retinal vascular signs and stroke, with a focus on population based studies published up to 2007, and was not identified by the author's own literature search. Discovering this review at such a late stage was frustrating as there was insufficient time within the constraints of the project to alter the focus of the literature search in order to ensure that work was not being duplicated and that the project is not merely rehashing someone else's methods, as recommended by Aveyard (2010). It is also fair to say that there is a lack of generally

accepted guidance on how to successfully integrate the results of an existing systematic review into a new review (Robinson et al., 2014).

Initially the Baker review needed to be subject to a process of critical appraisal in order to assess its quality. This was done using the same process as for the papers included in the final analysis, using a combination of PICO and the CASP tool for appraising systematic reviews (Appendix 2)

It was immediately apparent that the Baker paper was published in 2008 and only included papers published up to 2007. This makes the research eight years old. The search performed for this project was carried out in 2015 and the final analysis includes two papers which would not have been available to the Baker review: Kawasaki et al. (2012) and Cheung et al. (2013). This was reassuring as it meant that this project was not merely identifying and analysing the same research that had been gathered together before, and that new evidence was being identified which adds to the overall picture. Whitlock et al. (2008) suggest that many literature reviews are out of date within three to five years in any case so the author felt confident that this project could continue as originally planned.

The Baker review applies a clearly focussed question and the search strategy identified cohort studies that addressed this question. The quality of the studies identified and the strengths and weakness of each are discussed. Whilst Baker used perhaps a more comprehensive set of search terms than those chosen by the author for this review, it is clear that the search was only performed on the Medline database and there is no mention in the methodology of additional databases being searched. This review searched on four databases and so could be considered more comprehensive in this respect. Because of these reasons, it was felt that this review was not merely covering old ground and that new evidence had been found to inform the question being studied. The implications of discovering the Baker review at such a late stage are dealt with in Chapter 6.

3.5 Ethical Approval

As this paper involves a review of already published literature it was confirmed that ethical approval would not be needed. Literature reviews do not involve any primary, or new, research and will not involve accessing confidential information such as patient records, and as such do not meet the criteria as defined by The University of Warwick for requiring ethics approval.

Chapter 4 –Search Results & Critical Appraisal

4.1 Search results

Altogether the database searches identified eight studies which were deemed suitable for inclusion in the final analysis. A summary of these final papers is shown in Table 5. It is important to note that a number of papers included in this final analysis were part of much larger studies. These larger studies are: the Atherosclerosis Risk in Communities (ARIC) Study; the Singapore Malay Eye Study (SiMES); the Multi Ethnic Study of Atherosclerosis (MESA); the Beaver Dam Eye Study (BDES); the Blue Mountains Eye Study (BMES); and the Cardiovascular Health Study (CHS). These are each summarised below.

4.1.1 The ARIC Study

The ARIC study is sponsored by the US National Heart, Lung, and Blood Institute (NHLBI) and is a prospective epidemiologic study conducted in four U.S. communities. The overall aim of ARIC is to investigate the causes of atherosclerosis and its clinical outcomes so that variations in cardiovascular risk factors, medical care, and disease by race, gender, location, and date can be analysed. To date, the ARIC project has published over 800 articles in peer-reviewed journals (http://www2.cscc.unc.edu/aric/, accessed 20/04/2015).

4.1.2 The SiMES

The SiMES is a survey of Singaporean Malay adults aged 40-79 living in designated study areas to the south and west of Singapore. Almost 6,000 participants were randomly selected from a list provided by the Ministry of Health in Singapore. Participants are subject to a number of tests at baseline including retinal photography. These images are then assessed by a team of image graders in order to build up a databank of retinal images. Participants have been followed up over a number of years (the SiMES is still ongoing) providing researchers with a wealth of data to access when conducting their own studies.

4.1.3 The MESA

The MESA is a medical research study involving more than 6,000 men and women from six communities in the United States. MESA is sponsored by the NHLBI of the US National Institutes of Health. The MESA aims to study the characteristics of subclinical cardiovascular disease and the risk factors that predict progression to clinically overt cardiovascular disease or progression of the subclinical disease. The study population consists of 6,814 asymptomatic men and women aged 45-84 (http://www.mesa-nhlbi.org/aboutMESA.aspx, accessed 11/07/2015).

4.1.4 The BDES

The Beaver Dam Eye Study is funded by the National Eye Institute in the United States. The study's aim is to collect information on the prevalence and incidence of age-related cataract, macular degeneration and retinopathy which began in 1987. Approximately 5000 participants were recruited and given baseline examinations between 1988 and 1990. So far, follow up has taken place at five-, 10-, 15-, and 20-year intervals.

Retinal images were captured for all participants at baseline and a standard scale was developed to describe the severity of these abnormalities. The BDES completed its 20-year follow-up at the end of 2010 (http://www.bdeyestudy.org/, accessed 20/05/2015).

4.1.5 The BMES

The Blue Mountains Eye Study, conducted by the Centre for Vision Research at the University of Sydney, began in 1992 and was a population-based survey intended to provide clinical data on a sample of older Australians living in the Blue Mountains situated to the west of Sydney. This data has been the subject of a number of studies. The original study recruited a sample of 3,654 persons aged 49-97 years (http://www.aihw.gov.au/eye-health-data-sources/#BMES, accessed 20/05/2015).

4.1.6 The CHS

The Cardiovascular Health Study is an observational study of risk factors for cardiovascular disease in adults 65 years or older funded by the US NHLBI. It began in 1989 and continued to 1999. Participants underwent annual clinical examinations such as measurement of blood pressure and cholesterol. Measures such as echocardiography of the heart, carotid ultrasound, and cranial MRI were also undertaken. The main outcome measures were heart disease, angina, heart failure, stroke, transient ischemic attack, and mortality (https://chs-nhlbi.org/, accessed 10/04/2015).

Table 5: List of papers included in final analysis

Authors	Year	Study Title	Participants	Type of study	Journal
Cheung CY Tay WT Ikram MK Ong YT De Silva DA Chow KY Wong TY	2013	Retinal microvascular changes and risk of stroke: the Singapore Malay Eye Study.	3189	Cohort	Stroke
Cooper LS Wong TY Klein R Sharrett AR Bryan RN Hubbard LD Couper DJ Heiss G Sorlie PD	2006	Retinal microvascular abnormalities and MRI-defined subclinical cerebral infarction: the Atherosclerosis Risk in Communities Study.	1,684	Cohort	European Heart Journal
Kawasaki R Xie J Cheung N Lamoureux E Klein R Klein BE Cotch MF Sharrett AR Shea S Wong TY	2012	Retinal microvascular signs and risk of stroke: the Multi-Ethnic Study of Atherosclerosis (MESA).	4,849	Cohort	Stroke

Authors	Year	Study Title	Participants	Type of study	Journal
Klein R Klein BE Moss SE Meuer SM	2003	Retinal emboli and cardiovascular disease: the Beaver Dam Eye Study.	4926	Cohort	Transactions of the American Ophthalmological Society
Mitchell P Wang J Wong T Smith W Klein R Leeder S	2005	Retinal microvascular signs and risk of stroke and stroke mortality	3654	Cohort	Neurology
Wong TY Kamineni A Klein R Sharrett AR Klein BE Siscovick DS Cushman M Duncan BB	2006	Quantitative retinal venular caliber and risk of cardiovascular disease in older persons: the cardiovascular health study.	1992	Cohort	Archives of Internal Medicine
Wong TY Klein R Couper DJ Cooper LS Shahar E Hubbard LD Wofford MR Sharrett AR	2001	Retinal microvascular abnormalities and incident stroke: the Atherosclerosis Risk in Communities Study.	10,358	Cohort	The Lancet

Authors	Year	Study Title	Participants	Type of study	Journal
Wong TY Klein R Sharrett AR Couper DJ Klein BE Liao DP Hubbard LD Mosley TH	2002	Cerebral white matter lesions, retinopathy, and incident clinical stroke. (Uses ARIC Study)	1684	Cohort	Journal of the American Medical Association

4.2 Critical appraisal

Critical appraisal forms an important part of assessing the validity of healthcare research. It is important that the research methodology is scrutinised so that findings and conclusions can definitively be considered evidence (Marchevsky, 2000).

Sackett et al. (1997) recommend using the PICO approach as one of the first steps in critically appraising medical research. PICO is an acronym for population, intervention, control/comparison group, and outcome, and assessing research in this way means that the four main aspects of study will be considered as follows:

1. Is the population studied clearly defined and appropriate to the question being asked?
2. Is the intervention clearly described and measured?
3. Is there a well described control group who were not given the intervention?
4. Is there a defined outcome measure and has this been measured appropriately?

The process of critical appraisal will differ depending on the type of research being examined and although there is no single universally agreed hierarchy of evidence, there is a general agreement on the relative strengths of the different types of research. This hierarchy, as described by Aveyard (2010) is as follows:

1. Systematic reviews and meta-analyses
2. Randomised controlled trials
3. Observational studies (cohort and case control)
4. Surveys
5. Case reports
6. Qualitative studies

7. Expert opinion
8. Anecdotal opinion

All eight studies identified in this review were population-based cohort studies. As outlined by Greenhalgh (2010), cohort studies involve two groups of participants, selected on the basis of the difference in their exposure to a particular agent, who are then followed up over a number of years to assess differences in outcome. In the case of the cohort studies included in this project's final analysis, the two 'exposure' groups are those with retinal microvascular abnormalities at baseline versus those with no abnormalities, and the outcome measure is incident stroke over the follow up period.

To a certain extent it was expected that this project would identify cohort studies due the nature of project's question. In effect, this project is examining whether there is a difference in stroke incidence in two groups: those with retinal microvascular abnormalities and those without. Because individuals will either have abnormalities or not, it would not have been possible for an RCT to have been conducted to answer the question; the cohort group and the control group are not allocated at random and arise naturally in the population (Aveyard, 2010). In theory, both groups should be a similar as possible in all important aspects except for the exposure being measured, but this is rarely the case, making selection bias inherent in cohort studies (Grimes and Schulz, 2002).

Due in part to these constraints, cohort studies rank lower than systematic reviews and randomised controlled trials in the hierarchy of evidence, and it is important to consider that the limitations of a cohort study mean that correlation can be shown but one should exercise a degree of caution when definitively attributing causation.

In the context of PICO, a strong cohort study on the subject being studied for this project would include:

P: A large, diverse population.

I: A clear method of identifying those with retinal microvascular abnormalities and those without.

C: A control group without microvascular abnormalities well matched to the group with abnormalities.

O: Definitively confirmed incident stroke as the outcome measure.

Cohort studies have some weaknesses because, although they are similar to randomised controlled trials (RCTs) in that they both assess the impact of an intervention (or equivalent) on two different groups, an RCT aims to have as little heterogeneity between the two groups as possible by randomising selection, something that is effectively impossible in a cohort study. Few, if any, cohort studies succeed in matching demographics such as age, gender profiles, socio economic status and pre-existing morbidities between the two groups (Greenhalgh, 2010; Rochon et al., 2005), and all these factors need taking into account when critically appraising the literature.

In the case of this project, once the inclusion and exclusion criteria were applied to the results of the literature search, the final papers selected for inclusion were subject to critical appraisal in order to determine what weight they add to the argument. With a number of papers to critically appraise it is important to ensure that this is done in a systematic manner so the use of a critical appraisal tool is important. The Critical Appraisal Skills Programme (CASP) has developed a number of tools for making sense of evidence, available on the CASP website (www.casp-uk.net).

All the CASP tools are designed to be used when reading research and include tools for systematic reviews, randomised controlled trials, cohort studies, case control studies, economic evaluations, diagnostic studies, and qualitative studies, and as such are the most appropriate for use with the research identified by the literature review.

In addition to the CASP tools Rochon et al. (2005) outlined a number of factors to consider when assessing cohort studies. In summary these are:

1. What comparison is being made?
2. Does the comparison make clinical sense?
3. What are the potential selection biases?

PICO and the checklist outlined by Rochon et al. will be used in combination with the CASP tool for cohort studies to critically appraise the papers included in the final analysis. An example of the CASP tool used can be found in Appendix 1. A summary of the critical appraisal of each paper can be found in Table 6.

4.2.1 The final papers

Overall, eight papers were identified as suitable for inclusion in the final analysis. A critical analysis and appraisal of their strengths, weaknesses, and what weight of evidence they provide is discussed below.

4.2.1.1 Cheung et al. (2012)

This paper had a clearly stated aim to examine the relationship between retinal microvascular measures and incident stroke in an Asian Malay population. The process for identifying the study population was well described and selection was randomised through the use of computer

generated lists. Over three thousand participants were included with a wide age range and all underwent standardised test procedures. Identification of incident stroke benefitted from being linked to the Singapore National Registry of Diseases Office, which requires the electronic recording of such cases by law. Assessors of this data were blinded through the anonymising of patient details minimising possible bias.

Weaknesses include the very specific population studied. All participants are of Asian Malay ethnicity and were solely recruited from South Western Singapore which raises questions over how reliably the results could be applied to multi-ethnic populations in England.

4.2.1.2 Cooper et al. (2006)

This paper's strengths lie in the authors' clearly stated aim to examine the association between retinal microvascular abnormalities and MRI-defined cerebral infarcts; the multi-ethnic cohort; standardised test procedures for identifying retinal vascular features; and the use of MRI to define cerebral infarcts rather than relying on medical records and/or self-reporting of stroke outcomes. MRI is likely to be a more accurate method of identifying and classify stroke.

Although a multi-ethnic cohort is included, the main weakness of this study is that, as in the Cheung et al paper, participants are from two south eastern US communities so one cannot automatically assume that the results would be applicable to an English cohort. Selection bias is also noted as excluded participants were more likely to be older and to have a higher prevalence of cardiovascular risk factors.

4.2.1.3 Kawasaki et al. (2012)

This is a well-structured study involving almost five-thousand participants with the clearly stated aim of examining the relationship of retinal signs with incident stroke in a multi-ethnic cohort. The

ethnicity of the cohort is well described with White, African-American, Hispanic and Asian ethnicities proportionally represented. Test procedures were standardised for all participants, with vessel calibre being measured using a semi-automated computer programme following a detailed protocol. As in the previous study, this was conducted in the United States with an American study population, raising questions over how the results could be reasonably applied to a UK population. With such a low number of incident strokes in the study population limitations are placed on the precision of the risk estimates, although Kawasaki recognises this in the analysis. The fact that confounding effects from factors such as long term hypertension cannot be ruled out is also discussed.

4.2.1.4 Klein et al. (2003)

Klein's cohort study, using the BDES, is well described and has a follow up period of up to ten years from baseline. The study population is approaching 5,000 in number and has a fairly equal gender mix. Procedures for identifying retinal features were standardised for all participants and characteristics masked to the image graders. Procedures for identifying stroke mortality were also standardised but were limited to stroke being recorded as cause of death on the death certificate. Although Klein's intention was to examine the relationship between retinal emboli and cardiovascular mortality, this does mean that stroke incidence may have been underestimated as those individuals who had strokes and survived would not have been counted in this outcome category.

There are some limitations to the study. Klein recognises that emboli can be of short duration and so not be present upon assessment which may lead to an underestimation of their prevalence.

4.2.1.5 Mitchell et al. (2005)

Mitchell's cohort study uses the BMES population and has clearly stated aims. Standardised methods are used for identifying and classifying retinopathy, although it is noted that these are

somewhat complex. As in other papers analysed in this project, Mitchell recognises that the relatively low incidence of stroke limits the precision of risk estimates. It is also important to consider the effect of hypertension and diabetes on the association between retinopathy and stroke risk. Mitchell controls for this but explains that it is not possible to be sure that these confounding factors have been completely adjusted for.

Outcome measures are reliant on self-reporting of stroke, although these reports are validated. Stroke deaths are identified by checking national registry and identifying those cases where stroke is listed as cause of death. However, autopsies are not routinely performed on the general population in Australia which may lead to inaccuracies as there is no means of validating cause of death, and Mitchell recognises this limitation.

4.2.1.6 Wong et al. (2001)

Wong's prospective, population-based cohort study is well structured and, with over 10,000 participants, examines a large, multi-ethnic sample recruited from the community. Stroke cases were validated by a physician and retinal assessments involved standardised and detailed procedures for all participants.

As in the Kawasaki study, the number of incident stroke cases in the Wong paper is very low, despite the large sample size, which limits the precision of the risk outcomes. Wong also notes that hypertension is likely to be a strong confounding factor which should be taken into account when considering the results, despite efforts to control for this.

4.2.1.7 Wong et al. (2002)

The second paper by Wong is well described but uses a smaller study population. Graders of retinal photographs were blinded to the participant characteristics, minimising the possibility of bias.

Methods of stroke identification are well described, with cases classified by an independent physician and a computer algorithm, with a second physician providing arbitration on disagreements. The low numbers of incident stroke cases may impact on the precision of risk estimates and this is recognised by Wong in the study. The possible confounding effect of hypertension on the results is also noted.

4.2.1.8 Wong et al. (2006)

Wong's prospective cohort study addresses a clearly focussed question and is well structured. The methods are well described and means of identifying stroke outcome and vessel calibre are standardised. This study includes participants recruited from four different communities but the sample size is one of the smaller ones out of all the research identified by this review. Wong also identifies an important limitation of the study. Retinal photography was performed 10 years after the participants, who were in an older age group, were recruited into the study which may give rise to bias. Many participants had ungradeable images due to the higher prevalence of media opacities, and it is possible that those with larger vessel calibre suffered a higher mortality rate prior to photography and so were excluded from the study, which may underestimate the risk.

Table 6: Summary of Critical Appraisal Using CASP Tool for Cohort Studies

CASP Question	Cheung et al. (2013)	Cooper et al. (2006)	Kawasaki et al. (2012)	Klein et al. (2003)	Mitchell et al. (2005)	Wong et al. (2001)	Wong et al. (2002)	Wong et al. (2006)
Does it address a focussed issue?	Yes. Clearly defined pop. Well defined outcomes.	Yes. Population well defined. Clearly defined risk factors. Outcomes well described. Clear that study aims to detect a relationship between retinal signs & cerebral infarcts.	Yes. Clearly defined pop. Well defined outcomes.	Yes. Population clearly defined. Relationship between retinal emboli and stroke incidence well described.	Yes Population clearly described. Aims objectives stated, It is clear that the study aims to address the link between retinal microvascular signs and stroke mortality.	Part of ARIC study. Intention to examine relationship between retinal microvascular abnormalities and incident stroke clearly stated. Population well defined and described.	Yes. Clearly states a defined population and the desire to examine a link between white matter lesions & retinopathy and incident stroke.	Yes. Clearly states the intention is to address the link between retinal vein calibre and stroke incidence in older people.
Was cohort recruited in an acceptable way?	Yes. Random sampling of data registry.	Yes	Yes. Skewed slightly towards non-Hispanic whites .	Yes. Not random.	Specific communities. Representative of the older urban Australian population.	Population recruited using probability samples	Yes	Yes. Standardised sampling method used.
Was exposure measured accurately?	Yes. Semi-automated method for measuring vessel calibre. Standardised protocol for classifying retinopathy	Yes. Standardised test procedures. Images graded by trained personnel using standard criteria. Validated by independent assessment.	Yes. ETDRS classification for retinopathy used (objective measure).	Yes. Images assessed by trained graders. Arbitration on borderline cases by single individual. Standardised procedure for all cases.	Yes Standardised assessment methods of identifying retinopathy. Used 35mm negative and a viewer – this may not be as effective as using digital images and digital enhancement.	Standardised procedure for assessing retinal abnormalities. Trained graders used, blinded to identity of participants.	Yes. Standardised test procedures. Images graded by trained personnel using standard criteria. Validated by independent assessment	Yes. Vessel calibre assessed by two trained graders. Standardised procedures for all images. Graders blinded to subject characteristics.

CASP Question	Cheung et al. (2013)	Cooper et al. (2006)	Kawasaki et al. (2012)	Klein et al. (2003)	Mitchell et al. (2005)	Wong et al. (2001)	Wong et al. (2002)	Wong et al. (2006)
Was outcome accurately measured?	Yes. Standardised and objective method of measuring. Reliant on accuracy of National Registry of Diseases Register	Yes. Standardised method. MRI defined cerebral infarct more reliable than medical records & self-reporting.	Yes. Measured as objectively as possible. Some reliance on self-reporting but militated against by further physician assessment. Assessors blinded.	Yes. Reliant on self-reporting of stroke or cause of death on death certificate.	To an extent. Reliant on self-reporting of stroke and on death certificate listing stroke. Autopsies not routinely performed on general pop so no means of validating cause of death.	Standardised methods. Relies on checking hospital records and death certifications. May not identify all incident stroke cases.	Yes. Standardised method. Arbitration on disagreements. Reliance on accuracy of records. Possibility of records being missed or incorrect.	Yes. Standardised procedures. Use of MRI to clinically define incident stroke.
Have confounding factors been identified?	Yes Adjustments made for a variety of confounders such as age, gender, blood pressure, cholesterol etc.	Yes Adjustments made in final analysis for a number of stroke risk factors - age, gender, race, blood pressure, diabetes.	Yes. Cardiovascular risk factors adjusted for in final analysis.	Yes Hypertension, age and sex controlled for in final analysis.	Yes Results adjusted for hypertension & diabetes although it is recognised that these may not have been completely controlled for.	Yes. Blood pressure, smoking, diabetes, and other established stroke risk factors identified and controlled for.	Yes Results control for age, sex, race, and vascular risk factors.	Yes Results control for controlling for age, sex, race, blood pressure, diabetes,, cigarette smoking, pack-years of smoking, and cholesterol levels.
Was follow up complete and long enough?	Followed up over 3-5 years	Yes. Followed up from 1987-1995.	Yes. Followed up over 6 years. Not a lot of detail around persons lost to follow up	Yes. 10 year follow up. Details given of those participants that dropped out.	Yes Followed up over 7 years.	Yes. Followed up for average of 3 years.	Follow up for mean of over 4 years.	Yes. Followed up over 5 years – meets inclusion specifications for this project and allows sufficient time for stroke to manifest.
What are the results?	Overall 3 fold increase in stroke incidence in those with retinopathy. AR not reported.	Overall 4 fold increase in MRI defined cerebral infarct in those patients with retinopathy.	Overall 3 fold increase in stroke incidence in those with retinopathy. AR not reported.	Presence of emboli indicates 2.4 fold increase in stroke incidence.	1.7-fold increase in stroke incidence in those participants with retinopathy at baseline.	Risk of stroke increased by factor of 2.58 in those individuals with any retinopathy at baseline.	4.9 fold increase in stroke incidence in those with retinopathy compared to those without.	2.2 fold increase in stroke incidence over follow up period in those with larger retinal vein calibre.

CASP Question	Cheung et al. (2013)	Cooper et al. (2006)	Kawasaki et al. (2012)	Klein et al. (2003)	Mitchell et al. (2005)	Wong et al. (2001)	Wong et al. (2002)	Wong et al. (2006)
How precise are the results?	Positive effect. Relatively wide CIs.	Positive but wide CIs	Relatively wide CIs.	Positive effect but relatively wide CIs.	Recognised that stroke incidence may limit precision of results.	Positive and relatively accurate) results.	Not very. Positive link noted but CIs very wide.	Fairly precise, narrow CIs.
Do you believe the results?	Yes. Well run study with good methodology. Randomised selection. Standardised procdures. Positive effect stated.	Yes Positive effect noted. Well described pop.	Yes. Well run study with good methodology. Positive effect stated.	Yes. Well described study population. Clear methodology. Standardised procedures.	Yes Fit with other results. Long follow up, reasonable sample size.	Overall, yes. Well described study population. Clear methodology. Standardised procedures	To an extent. Study well run and standardised procedures used. Final results not very precise. Could be due to relatively small population size.	Yes. Population could be larger. Standardised and accurate measuring of retinal markers and incident stroke.
Can results be applied to local population?	Cohort study was appropriate. Asian Malay pop. Not applicable to UK pop.	Cohort study appropriate. US population – possibly not representative of UK pop. More likely to be younger and non-black ethnicity.	Cohort study was appropriate. US pop. Multi-ethnic. Not immediately applicable to UK pop.	Debatable. Almost exclusively white population. US participants. Questionable whether results could be applied to multi-ethnic UK population.	Debatable. Ethnicity profiles in BMES may not match that of UK population. Lifestyle factors likely to be different.	Possibly. US population. Slightly skewed towards women. Average age of 53.6.	US population – possibly not representative of UK pop. More likely to be younger and non-black ethnicity. Shouldn't be discounted but these factors should be considered.	US pop. Slightly more women than men. Overwhelmingly of white ethnicity. Has some applicability to UK populations.
Do results fit with other evidence?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
What are the implications for practice?	Possible indication that retinopathy signs can act as stroke predictor	Possible indication that retinopathy signs can act as stroke predictor	Possible indication that retinopathy signs can act as stroke predictor.	Link between emboli and stroke incidence. Could allow earlier prediction.	Possible indication that retinopathy signs can act as stroke predictor	Possible indication that retinopathy signs can act as stroke predictor	Unclear link between retinopathy and stroke incidence. Could possibly allow earlier prediction.	Unclear link between emboli and stroke incidence. Could possibly allow earlier prediction.

Chapter 5 – Analysis of Results

The eight studies identified by the literature review show links of varying levels between a number of differing retinal features and stroke incidence. In this chapter these findings will be presented and qualitatively analysed in a thematic way with reference to the relevant papers. The various features assessed for a relationship to incident stroke are:

- Retinal vessel calibre
- Arterial emboli
- Retinopathy (including microaneurysms and retinal haemorrhages).

A summary of the risk ratios for each feature can be found in Table 7.

5.1 Themes

5.1.1 Arterial Emboli

Arterial emboli are small deposits that travel down the retinal arteries until such a point that the vessel width becomes sufficiently narrow to prevent further passage. The embolus then becomes lodged and can restrict blood flow to the portion of the vessel downstream which can cause ischaemia and tissue damage. Emboli can be calcific, formed of cholesterol deposits, or made up of blood that has clotted, and can often be seen relatively clearly on retinal images when present.

The paper by Klein et al. (2003) was the only one to investigate a link between arterial emboli and stroke incidence. Using data from the Beaver Dam Eye Study, Klein produced a large, prospective, population-based cohort study which appears to show that there is a link between retinal arterial emboli and risk of stroke. Almost 5000 participants were included who underwent 30 degree stereoscopic retinal photography at baseline. These images were assessed using standardised protocols and the participants were followed up over a ten year period. The results show that that

those with retinal arterial emboli present at baseline suffered 16.8 stroke deaths per 1000 patient-years over the follow up period compared to 3 stroke deaths per 1000 patient-years in those with no emboli present at baseline (P<0.001). When adjusted for systemic factors, those with retinal emboli at baseline showed a relative risk of being 2.4 (CI, 1.16-4.99) times more likely to have stroke listed on their death certificate than those without. The results, along with the large sample size, long period of follow up, positive confidence intervals and standardised test procedures, appear to show a positive correlation between the presence of retinal arterial emboli and a small increased risk of stroke over a ten year period.

Although the Klein paper uses a large sample size it should be noted that participants were recruited exclusively from the town of Beaver Dam in Wisconsin. This is a town of predominantly white ethnicity in the northern United States (stated as 93% white by the 2010 US census – www.quickfacts.census.gov/qfd/states/55/5505900.html, accessed 20.04.2015) and this should be taken into account when considering the general applicability of the results to other populations, particularly those in the United Kingdom, and in areas of mixed ethnicity.

5.1.2 Retinopathy

Retinopathy occurs when the retinal vessels leak blood into the surrounding retinal tissue. This can be due to a number of factors but usually involves increased permeability and a breakdown of the blood-retinal barrier. This often occurs in individuals with diabetes, or as a result of hypertensive damage to the vessel structure. Weakened vessels can form small microaneurysms in the earliest stages of retinopathy, followed by small flame shaped haemorrhages in the upper layers of the retina. If retinopathy continues to progress deeper blot haemorrhages will form in the photoreceptor layer of the retina and these may become more widespread, with ischaemia and neovascularisation occurring in the later stages.

A number of studies investigated the relationship between retinopathy and incident stroke. Kawasaki et al. (2012) and Cheung et al. (2013) both demonstrated a positive link between the presence of retinopathy and an increased incidence of stroke in non-diabetic individuals. Both studies recruited a large number of participants who underwent fundus photography and were then followed up over a number of years. Kawasaki et al. showed that participants with any level of retinopathy at baseline had a relative risk of being 2.96 (95% CI, 1.50-5.84) times more likely to have suffered a stroke during the six-year follow up period than those with none at baseline. Cheung et al.'s findings were similar: study participants with any level of retinopathy at baseline were shown to have a relative risk of being 2.90 (95% CI, 1.61-5.24) times more likely to have suffered a stroke during the follow up period.

Four earlier papers support the results of the Kawasaki and Cheung studies. Cooper et al. (2006), Mitchell et al. (2005), Wong et al. (2001) and Wong et al. (2002) found a positive link between retinopathy and incident stroke. The paper by Cooper showed a relative risk increase of 4.04 (95% CI, 2.21-7.41) in a prospective cohort study of 1,684 participants. Wong et al. (2001), as part of the ARIC study, recruited over 10,000 participants who underwent digital retinal photography at baseline. They were assessed for presence of retinopathy using standardised protocols in much the same way as those participants in the previously discussed papers and followed up for an average of 3.5 years. Once adjusted for a number of factors including age, race, gender, smoking and diabetes status, those with any retinopathy present at baseline had a relative risk of being 2.46 (95% CI, 1.59-4.20) times more likely to have experienced a stroke than those with no retinopathy. These findings were supported by further research by Wong et al. (2002), again as part of the ARIC study. On this occasion, the presence of retinopathy was shown to increase stroke incidence by a factor of 4.9 (95% CI, 2.0-11.9). Mitchell et al. (2005), using data from the BMES, report a similar relationship between retinopathy and stroke events (relative risk increase of 1.7 [95% CI, 1.0-2.8]).

Whilst the strengths and weaknesses of all six studies have been discussed in the previous chapter it is noted that each paper demonstrates similar findings. The three studies are similar in that they both recruited large numbers of participants (4849 for Kawasaki et al., 3280 for Cheung et al., 10,358 for Wong et al.), although the even gender split (52.8% women) of the Kawasaki study is noted, whereas these details are absent from the Cheung et al. and Wong et al. papers. One should also be aware of the fact that the image capture and assessment process was standardised for all patients in each study, and that those reviewing medical records to determine a diagnosis of stroke were blinded to the study data in the Kawasaki paper, minimising the possibility of bias.

The Cheung study, while providing further evidence that there is a link between retinopathy status and stroke risk, aims to study this link in a purely Singapore Malay population. Whilst the results of the study should be included it is important to consider whether they would apply to a multi-ethnic UK population with large numbers of White British participants. The participants in the Kawasaki et al. paper are multi-ethnic so the findings could be given more weight when considering applicability to a UK population.

When considering the results of any of this research it is important to note that, because strokes are relatively rare in the population as a whole, even large study populations see a relatively low incidence of stroke and this places limits on the accuracy of the risk estimates in both papers. This is something to bear in mind when considering how the results of the studies can be applied to current practice, although the fact that the confidence intervals remain within a positive range leads one to be reasonably confident that the link between the presence of retinopathy and stroke risk is indeed there.

5.1.3 Retinal Vessel Calibre

Microvascular disease in cerebral vessels has been linked to an increased incidence of stroke presentations. Microvascular disease affects vessel structure and can cause blood vessels to widen, increasing their calibre.

In 4169 non-diabetic participants Kawasaki et al. (2012) found that those individuals with central retinal venules of over 223 microns in diameter at baseline showed a relative risk of being 2.16 (95% CI, 0.76-6.18) times more likely more likely to suffer a stroke over the follow up period. These findings are supported by Wong et al. (2006) in a study of 1992 participants aged between 69 and 97 in the United States. Wong et al. found that a larger vessel calibre was associated with a relative risk increase of 2.2 (95% CI, 1.1-3.7) of suffering a stroke over the five year follow up period.

Table 7: Relative risk ratio of incident stroke in relation to retinal microvascular abnormality

Study	n	Outcome	Emboli	Retinopathy (95% CI)	Calibre
Cheung et al.	3280	Stroke		2.90 (1.61-5.24)	
Cooper et al.	1684	Cerebral infarct		4.04 (2.21-7.41)	
Kawasaki et al.	4169	Stroke		2.96 (1.50-5.84)	2.16 (0.76-6.18)
Klein et al.	4926	Stroke	2.4 (1.16-4.99)		
Mitchell et al.	3654	Stroke		1.7 (1.00-2.80)	
Wong et al. (2001)	10358	Stroke		2.58 (1.59-4.20)	
Wong et al. (2002)	1684	Stroke		4.90 (2.00-11.90)	
Wong et al. (2006)	1992	Stroke			2.2 (1.1-3.7)

Chapter 6 – Discussion & Recommendations

Overall, with seven studies identified for inclusion in the final analysis, as well as an existing systematic review, it is clear that this is an important subject that has been considered and investigated previously. The evidence from the final papers appears to support a link between visible retinal microvascular disorder, specifically retinopathy, arterial emboli and vessel calibre, and increased stroke incidence.

Retinopathy was the most common factor assessed for a relationship to stroke incidence and the findings also suggest that the presence of retinopathy has a stronger link than emboli or vessel calibre. All six studies that assessed retinopathy showed similar findings, and this supports the theory that there is a link between the presence of retinopathy and increased stroke risk. Retinal vessel calibre shows perhaps the weakest link to stroke risk, although the association is present. Only Klein et al. looked at arterial emboli as a risk factor for stroke, finding a relative risk ratio similar to that of retinopathy.

It is notable that this project identified an existing literature review at a late stage on the very topic the author selected for their own review. As previously discussed, the review by Baker et al. is eight years old and some of the research identified in the author's review was published after this date so it was felt that this project was not necessarily merely replicating previous work. Nevertheless, it is interesting that the Baker review was not identified in the systematic search of the literature performed for this project, and it is important not to ignore this fact as it raises several questions: why was this paper not picked up earlier, were the original search methods robust, and has this project achieved its intention of identifying all the papers relevant to the question?

The fact that the Baker paper was not picked up at an earlier stage means that the original search methodology may not have been as robust as it could have been. As discussed in section 3.4, literature searches have their limitations and it may be that the search terms selected by the author were not diverse enough to identify all the available research, or that not enough databases were searched. On reflection the author could have used a number of search strategies, such as hand searching journals and attempting to identify unpublished research. Although methods such as these may at first appear to be less reliable than using large database searches, Aveyard (2010) recommends using multiple search strategies, and Greenhalgh and Peacock (2005) state that these manual methods may actually be a more efficient way of identifying relevant papers than relying on pre-defined, protocol-driven strategies.

On the other hand it was reassuring to note that all papers published prior to 2007 and included in the final analysis for this project were also identified by the Baker paper. This gave the author some assurance that relevant literature was not being missed in this project.

Overall it would appear that the presence of arterial emboli, retinopathy and vessel calibre can, to a greater or lesser extent, act as a way of identifying those at increased risk of stroke. This should be considered in context however. Hypertension is the number one risk factor for stroke, in the main because the condition has a harmful effect on the microcirculation of the body which can lead to increased susceptibility to haemorrhagic stroke. Hypertension is also a contributory factor in the development of retinopathy and it is important to consider the implications of this when evaluating the evidence identified in the literature review. All the papers included in the final analysis adjusted for this in their results but many recognised that the confounding effect of hypertension on the findings may not have been wholly negated.

Using retinal imaging to categorise stroke risk may have value in that it gives the clinician a tangible and visible 'result' to show the patient. Encouraging lifestyle changes in patients with hypertension can be challenging as the patient, to all intents and purposes, feels 'well' and may not be sufficiently motivated to make the changes required. Blood pressure readings will not always be understood by the patient and they do not physically demonstrate any evidence of harm. On the other hand, patients often show great interest in their own retinal images, and retinopathy in particular can be very noticeable and often dramatic. As such retinal images may provide clinicians with a tool to illustrate to the patient that their blood pressure is causing them noticeable harm, or that they are at increased risk of stroke, and have the potential to be used during consultations with patients identified as at risk. This 'shock value' may prove more effective in engendering behavioural change than advice alone.

Providing such an indication to the patient of increased stroke risk could also have an impact on stroke mortality. If individuals are made aware of their at-risk status and given appropriate advice on the early symptoms of a stroke they will be in a position where, if they experience symptoms such as numbness, mild paralysis, aphasia, or sensory defect, they are more likely to recognise the signs of a potential stroke and may seek treatment more quickly. Retinal imaging also has the potential to identify at risk individuals who exhibit no risk factors for stroke who would normally remain unidentified as at risk.

Often, patients with hypertension will be totally unaware they have elevated blood pressure and will not exhibit any noticeable symptoms. High blood pressure is often diagnosed during routine checks with the GP and many patients will not visit their GP on a regular basis and their hypertension will remain undiagnosed. In such cases it is worth considering the value of the retinal image as a means of identifying patients with poor blood pressure control and increased stroke risk opportunistically. For example, many high street optometrists offer retinal photography as part of the standard annual

NHS sight test and this may offer a means of reaching those undiagnosed hypertensive patients who are unknown to the GP, identifying stroke risk, and providing a route for referral for intervention and treatment. It is also common for the retina to be examined during ophthalmology consultations. Many older patients will have contact with an ophthalmologist for procedures such a cataract extraction or glaucoma treatment and including a routine assessment of the retina as part of these procedures would enable identification of at risk individuals, many of whom may be unaware of their at-risk status.

Such identification and risk stratification strategies would be more effective if supplemented by public health initiatives designed to help support lifestyle changes, both for at-risk patients and to reduce the numbers falling into the at-risk category.

It cannot be ignored that all eight studies included in the final analysis are conducted with non-UK populations. All other factors aside, this makes it extremely difficult to be sure of how applicable the results would be to a UK population. For example, UK populations in general will have a different ethnicity profile to the SiMES study group and they may experience different lifestyle factors to those in the BDES. All these factors will have an effect on hypertension, weight, lifestyle, and smoking habits, which will in turn affect stroke incidence and the prevalence of retinal pathology.

There is a consensus across much of the research that, despite several well established risk factors for stroke, the current processes for risk stratification are not as effective as they could be, and one of the initial thoughts when embarking on this project was the potential for organised, photographic retinal screening of patients for stroke risk if a link between retinal pathology and stroke incidence could be demonstrated. As things stand it is fair to say that the evidence does not support the implementation of a national stroke screening programme. Stroke incidence is relatively rare in the population as a whole and screening becomes less effective when disease incidence is lower. This is

due to the fact that no screening test is 100 percent accurate so the volume of false positives increases dramatically the rarer the condition being screened for. A national screening programme for stroke would result in many referrals for patients not at increased risk of stroke, increasing pressure on secondary care and potentially exposing patients to treatment unnecessarily.

As discussed in previous chapters, and in many of the studies included in the final analysis, the low incidence of stroke limits the prevalence of the risk estimates which in turn makes it difficult to be completely sure of the evidence. Any screening programme must have a very strong evidence base before it can be recommended and the current evidence base for a link between retinal pathology and stroke risk is not strong enough.

It has been discussed that, although eight good quality studies were identified by this review, there was a lack of large, multi-centre studies in UK populations, and this raises questions over the applicability of the findings to the UK. Recommendations for future research would focus on multi-centre, multi-ethnic cohort studies in a large UK study population, with follow up of ten or more years from baseline. This long period of follow up would allow for a larger stroke incidence which may negate some of the problems around the precision of risk estimates identified previously. In future studies it may also be advantageous to differentiate between stoke subtype when recording outcomes, as the majority of the current research does not differentiate between ischaemic and haemorrhagic stroke. Hypertension is associated with haemorrhagic stroke and may lead to poorer outcomes (Wilmott et al., 2004). Intuitively one may consider that retinopathy signs such as haemorrhages and microaneurysms may be higher in those individuals with hypertension and they may in turn have a higher incidence of haemorrhagic rather than ischaemic stroke. In contrast, ischaemic strokes are caused by blockages in cranial arteries and so one may consider that those individuals with arterial emboli present may have a higher rate of ischaemic stroke. Analysing stroke sub-types separately may provide greater insight and increase the precision of risk stratification.

Chapter 7 – Conclusion

Overall, despite the limitations of the research discussed in this project, the evidence suggests a link between retinal microvascular changes and stroke risk. The findings in each of the papers are similar and, on the whole, the research analysed was robust, used large study groups, addressed a clearly focussed question and identified and attempted to control for confounding factors.

This evidence should be used to inform existing stroke risk identification strategies so interventions can be targeted earlier and more effectively. These strategies should be supplemented by public health initiatives aimed at reducing blood pressure and encouraging healthier lifestyles, an approach which has the potential to reduce stroke incidence, along with associated mortality and morbidity.

But, as ever, further research is needed. In this case cohort studies conducted on a large scale with follow up over a decade or more, using a multi-ethnic UK study population looking at outcomes which differentiate between stroke subtypes could potentially provide greater evidence of a link between retinal vascular disorder and stroke incidence. Ideally, such a trial would involve retinal photography at baseline for all participants and then at regular intervals over the course of the trial, with clear methods of identifying incident stroke throughout the study period.

Problems encountered during the literature search may be overcome by repeating the search using a more comprehensive selection of search terms and employing multiple search methods, such as hand searching journals, to supplement the search of the databases.

In conclusion, the evidence supports a link between retinal microvascular abnormalities and stroke risk which should be used to inform stroke risk stratification methods. This relationship should be the subject of further study in a UK population.

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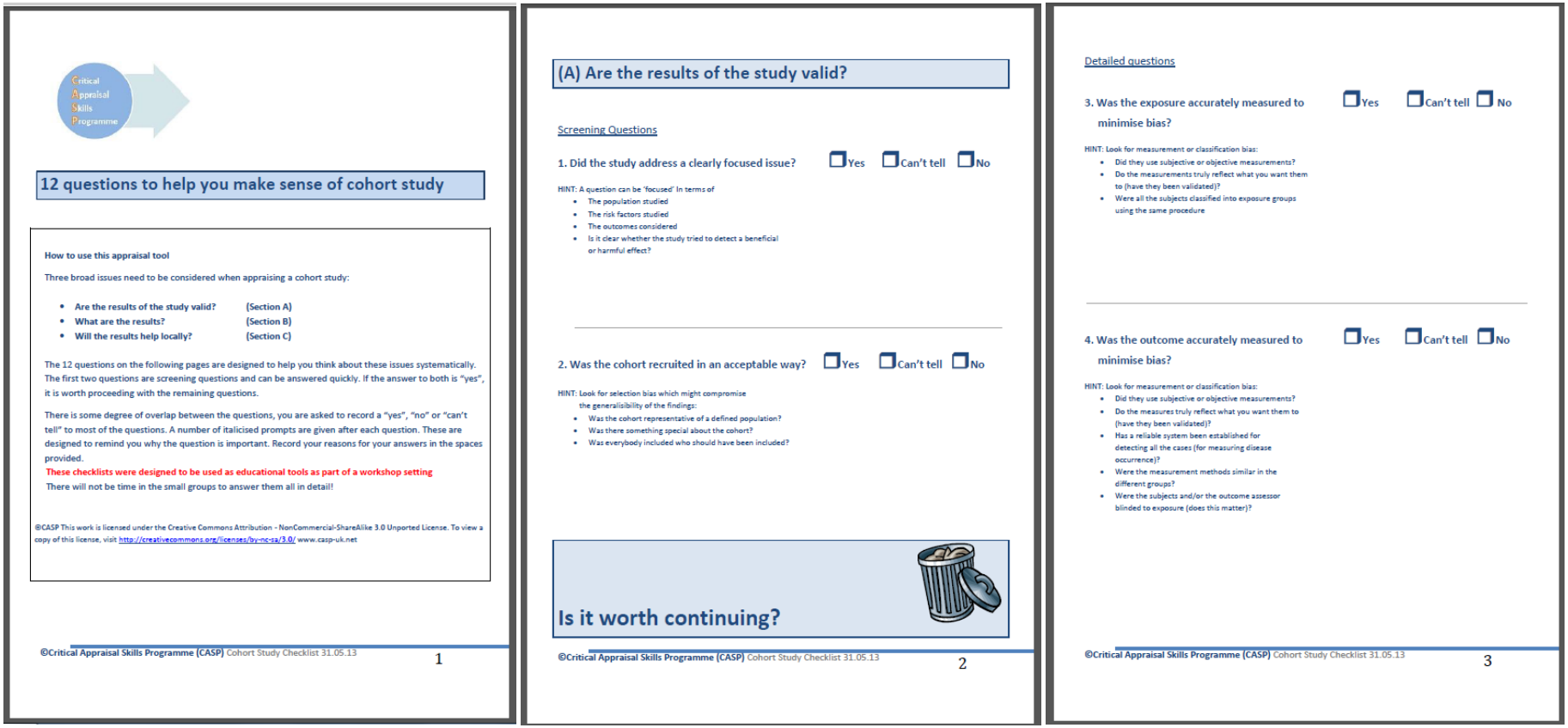
Appendices

Appendix 1 – CASP Tool for appraising cohort studies



Critical Appraisal Skills Programme

12 questions to help you make sense of cohort study

How to use this appraisal tool

Three broad issues need to be considered when appraising a cohort study:

- **Are the results of the study valid?** **(Section A)**
- **What are the results?** **(Section B)**
- **Will the results help locally?** **(Section C)**

The 12 questions on the following pages are designed to help you think about these issues systematically. The first two questions are screening questions and can be answered quickly. If the answer to both is "yes", it is worth proceeding with the remaining questions.

There is some degree of overlap between the questions, you are asked to record a "yes", "no" or "can't tell" to most of the questions. A number of italicised prompts are given after each question. These are designed to remind you why the question is important. Record your reasons for your answers in the spaces provided.

These checklists were designed to be used as educational tools as part of a workshop setting

There will not be time in the small groups to answer them all in detail!

(A) Are the results of the study valid?

Screening Questions

1. Did the study address a clearly focused issue? ❒Yes ❒Can't tell ❒No

HINT: A question can be 'focused' in terms of
- The population studied
- The risk factors studied
- The outcomes considered
- Is it clear whether the study tried to detect a beneficial or harmful effect?

2. Was the cohort recruited in an acceptable way? ❒Yes ❒Can't tell ❒No

HINT: Look for selection bias which might compromise the generalisibility of the findings:
- Was the cohort representative of a defined population?
- Was there something special about the cohort?
- Was everybody included who should have been included?

Is it worth continuing?

Detailed questions

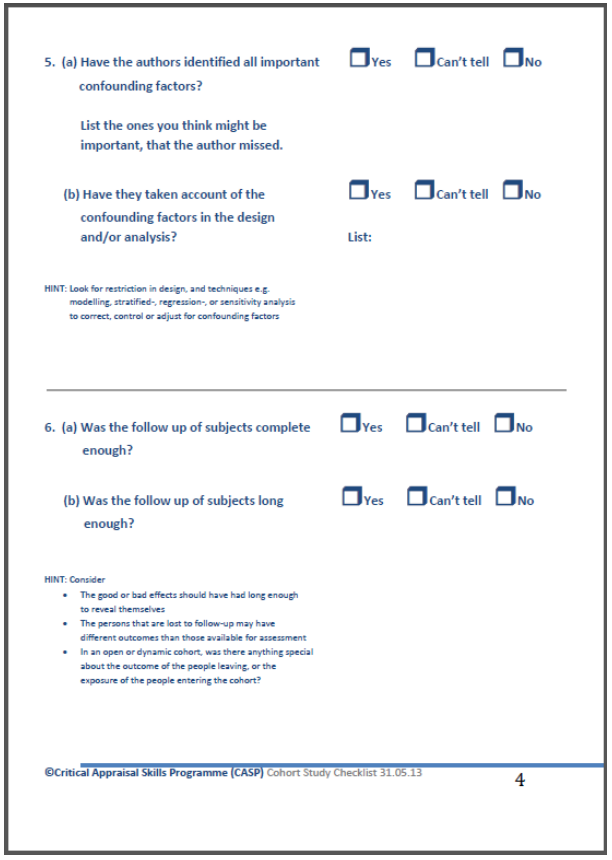
3. Was the exposure accurately measured to minimise bias? ❒Yes ❒Can't tell ❒No

HINT: Look for measurement or classification bias:
- Did they use subjective or objective measurements?
- Do the measurements truly reflect what you want them to (have they been validated)?
- Were all the subjects classified into exposure groups using the same procedure

4. Was the outcome accurately measured to minimise bias? ❒Yes ❒Can't tell ❒No

HINT: Look for measurement or classification bias:
- Did they use subjective or objective measurements?
- Do the measures truly reflect what you want them to (have they been validated)?
- Has a reliable system been established for detecting all the cases (for measuring disease occurrence)?
- Were the measurement methods similar in the different groups?
- Were the subjects and/or the outcome assessor blinded to exposure (does this matter)?

Appendix 1 continued.



5. (a) Have the authors identified all important confounding factors? ❒Yes ❒Can't tell ❒No

List the ones you think might be important, that the author missed.

(b) Have they taken account of the confounding factors in the design and/or analysis? ❒Yes ❒Can't tell ❒No

List:

HINT: Look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

6. (a) Was the follow up of subjects complete enough? ❒Yes ❒Can't tell ❒No

(b) Was the follow up of subjects long enough? ❒Yes ❒Can't tell ❒No

HINT: Consider

- The good or bad effects should have had long enough to reveal themselves
- The persons that are lost to follow-up may have different outcomes than those available for assessment
- In an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort?

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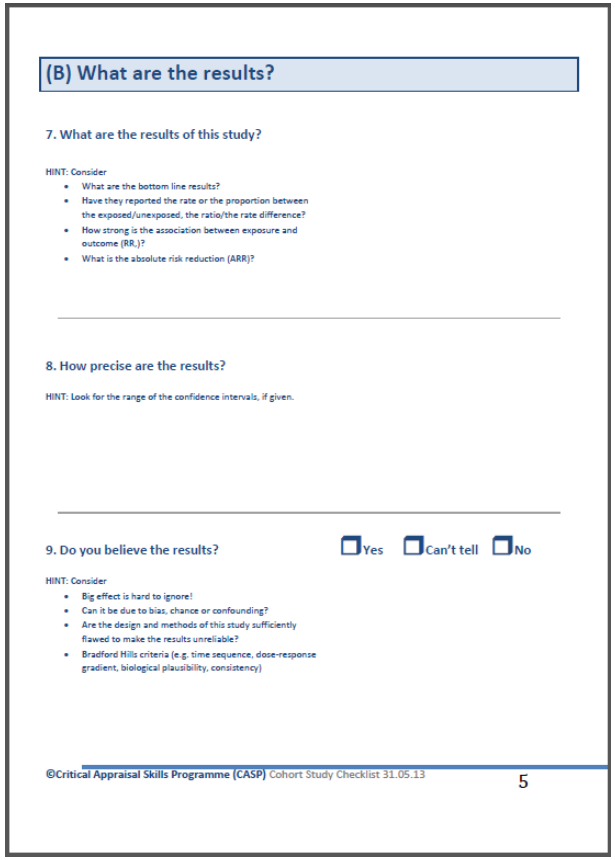

(B) What are the results?

7. What are the results of this study?

HINT: Consider

- What are the bottom line results?
- Have they reported the rate or the proportion between the exposed/unexposed, the ratio/the rate difference?
- How strong is the association between exposure and outcome (RR.)?
- What is the absolute risk reduction (ARR)?

8. How precise are the results?

HINT: Look for the range of the confidence intervals, if given.

9. Do you believe the results? ❒Yes ❒Can't tell ❒No

HINT: Consider

- Big effect is hard to ignore!
- Can it be due to bias, chance or confounding?
- Are the design and methods of this study sufficiently flawed to make the results unreliable?
- Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

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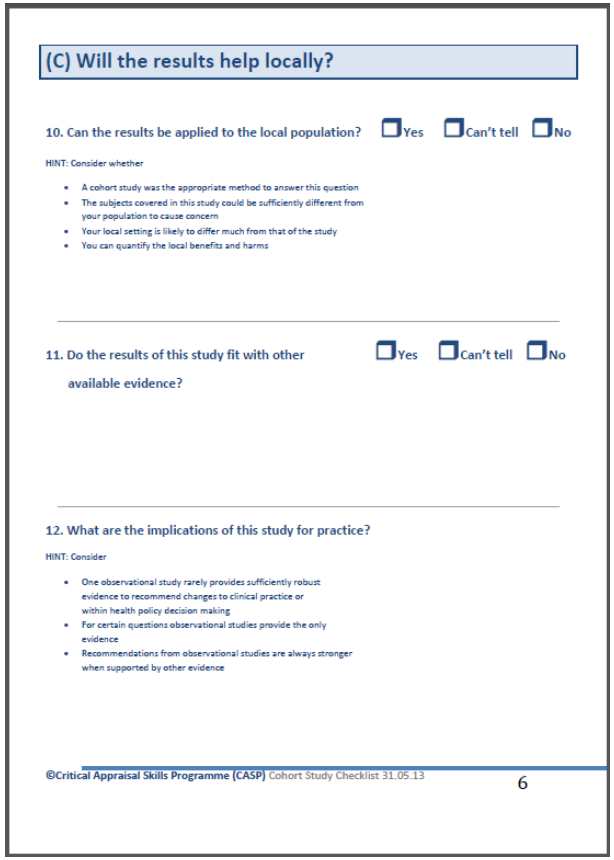

(C) Will the results help locally?

10. Can the results be applied to the local population? ❒Yes ❒Can't tell ❒No

HINT: Consider whether

- A cohort study was the appropriate method to answer this question
- The subjects covered in this study could be sufficiently different from your population to cause concern
- Your local setting is likely to differ much from that of the study
- You can quantify the local benefits and harms

11. Do the results of this study fit with other available evidence? ❒Yes ❒Can't tell ❒No

12. What are the implications of this study for practice?

HINT: Consider

- One observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
- For certain questions observational studies provide the only evidence
- Recommendations from observational studies are always stronger when supported by other evidence

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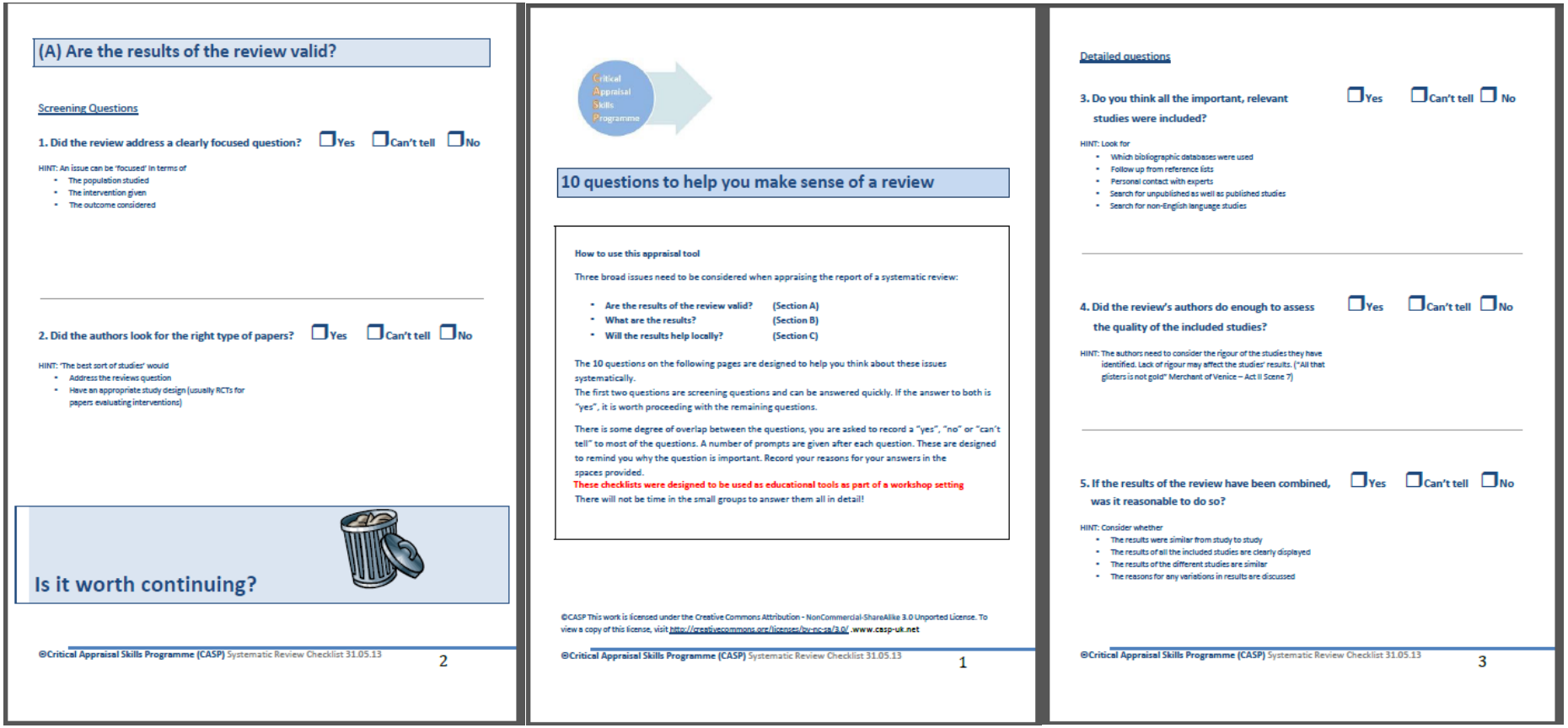
Appendix 2 – CASP tool for appraising reviews



(A) Are the results of the review valid?

Screening Questions

1. Did the review address a clearly focused question? ❒Yes ❒Can't tell ❒No

HINT: An issue can be 'focused' in terms of
- The population studied
- The intervention given
- The outcome considered

2. Did the authors look for the right type of papers? ❒Yes ❒Can't tell ❒No

HINT: 'The best sort of studies' would
- Address the reviews question
- Have an appropriate study design (usually RCTs for papers evaluating interventions)

Is it worth continuing?

Critical Appraisal Skills Programme

10 questions to help you make sense of a review

How to use this appraisal tool

Three broad issues need to be considered when appraising the report of a systematic review:

- **Are the results of the review valid?** (Section A)
- **What are the results?** (Section B)
- **Will the results help locally?** (Section C)

The 10 questions on the following pages are designed to help you think about these issues systematically.
The first two questions are screening questions and can be answered quickly. If the answer to both is "yes", it is worth proceeding with the remaining questions.

There is some degree of overlap between the questions, you are asked to record a "yes", "no" or "can't tell" to most of the questions. A number of prompts are given after each question. These are designed to remind you why the question is important. Record your reasons for your answers in the spaces provided.
These checklists were designed to be used as educational tools as part of a workshop setting
There will not be time in the small groups to answer them all in detail!

Detailed questions

3. Do you think all the important, relevant studies were included? ❒Yes ❒Can't tell ❒No

HINT: Look for
- Which bibliographic databases were used
- Follow up from reference lists
- Personal contact with experts
- Search for unpublished as well as published studies
- Search for non-English language studies

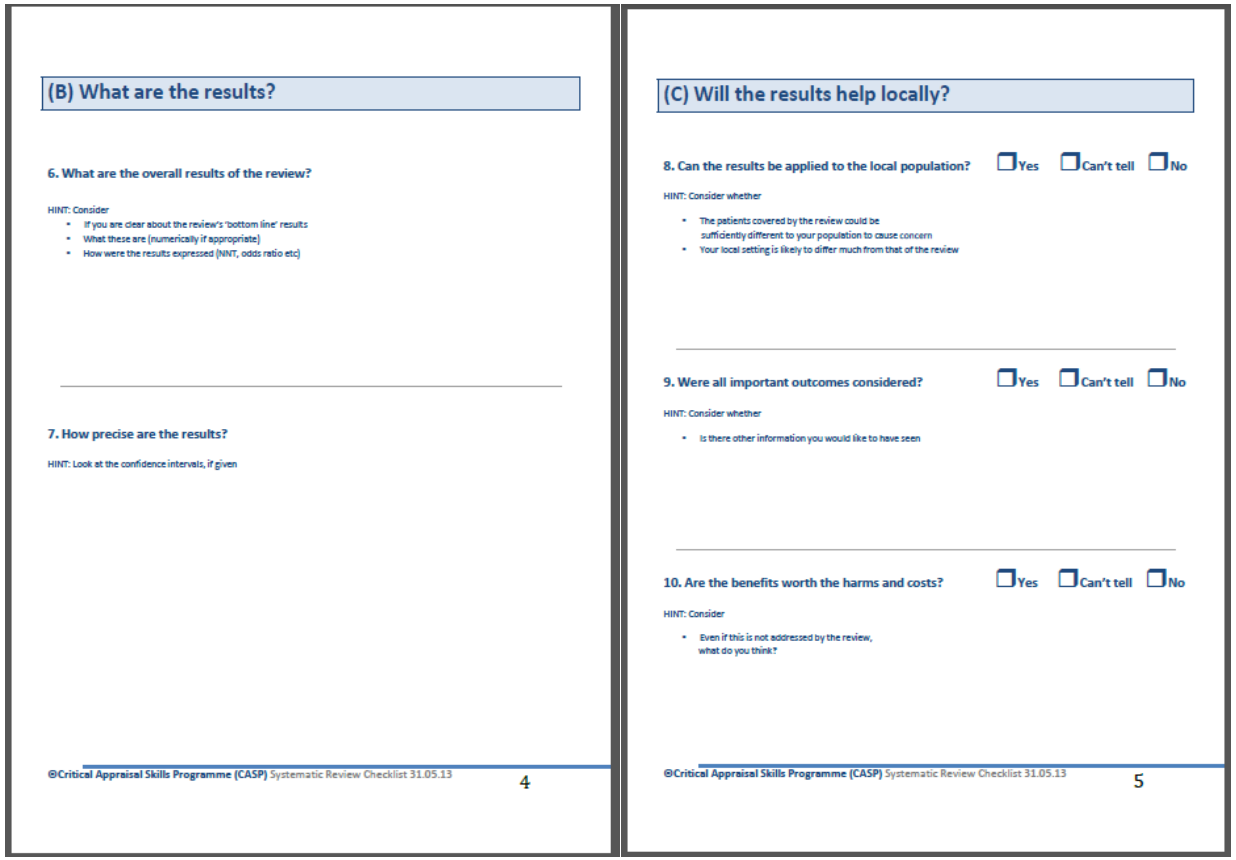
4. Did the review's authors do enough to assess the quality of the included studies? ❒Yes ❒Can't tell ❒No

HINT: The authors need to consider the rigour of the studies they have identified. Lack of rigour may affect the studies' results. ("All that glisters is not gold" Merchant of Venice – Act II Scene 7)

5. If the results of the review have been combined, was it reasonable to do so? ❒Yes ❒Can't tell ❒No

HINT: Consider whether
- The results were similar from study to study
- The results of all the included studies are clearly displayed
- The results of the different studies are similar
- The reasons for any variations in results are discussed

Appendix 2 continued.



(B) What are the results?

6. What are the overall results of the review?

HINT: Consider

- If you are clear about the review's 'bottom line' results
- What these are (numerically if appropriate)
- How were the results expressed (NNT, odds ratio etc)

7. How precise are the results?

HINT: Look at the confidence intervals, if given

(C) Will the results help locally?

8. Can the results be applied to the local population? ❒Yes ❒Can't tell ❒No

HINT: Consider whether

- The patients covered by the review could be sufficiently different to your population to cause concern
- Your local setting is likely to differ much from that of the review

9. Were all important outcomes considered? ❒Yes ❒Can't tell ❒No

HINT: Consider whether

- Is there other information you would like to have seen

10. Are the benefits worth the harms and costs? ❒Yes ❒Can't tell ❒No

HINT: Consider

- Even if this is not addressed by the review, what do you think?