Association between Plasmodium falciparum malaria and the mental disorders in children between five and 19 years in sub-Saharan Africa: a systematic review

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Executive summary

Background

Mental disorders, also called psychiatric disorders, refer to unconventional or anomalous behavioral patterns, feelings, thoughts, perceptions and beliefs that cause distress or disability, and which are not developmentally or socially acceptable. Plasmodium falciparum (P. falciparum) malaria is the most common parasitic infection of the central nervous system and sub-Saharan Africa has the highest burden of this disease. Children living in this region of the world bear the brunt of P. falciparum malaria and neurological complications commonly associated with it.

Objectives

The objective of this review was to synthesize the best available evidence on the association of P. falciparum malaria and the short-term and long-term mental disorders of children.

Inclusion criteria

Types of participants

Study participants aged five to 19 years who were residing in sub-Saharan Africa.

Types of intervention(s)/phenomena of interest

This review considered studies that examined the association between P. falciparum malaria (cerebral malaria, repetitive uncomplicated malaria or asymptomatic malaria) as exposure and a range of mental disorders as an outcome.

Types of studies

This review considered epidemiological study designs including randomized controlled trials, non-randomized controlled trials, quasi-experimental trials, prospective and retrospective cohort studies, case control studies and analytical cross-sectional studies.

Types of outcomes

This review considered studies that included (but were not limited to) the following mental disorder outcome measures: cognitive deficits and impairments, acquired language disorder, school performance and psychomotor skills. There are many tests to measure these outcomes. Cognitive deficits and impairments are commonly measured with the Mini-Cog Test, language disorders with the Language Delays Assessment Test and psychomotor skills are measured with the Two-point Threshold Test (distance perception) and the Color Timing Test that measures mental speed. School performance is not commonly measured with norm-referenced standardized tests due to the large disparities in achievement between schools. This outcome measure is often picked from class assessment and examination records of the students, relative to their classmates.

Search strategy

A three-step search strategy was utilized in this review. Relevant studies published in the English language from 1980 to 2012, when the association between malaria and mental disorders was highlighted, were considered for inclusion in this review. Unpublished data was also searched for within the same period. The databases searched included PubMed, CINAHL, PsycARTICLES, PsycBITES, PsycINFO, Social Science Citation Index, ProQuest Dissertations and Theses (PQDT)/Digital dissertations, ProQuest Social Services abstracts, ProQuest Sociological abstracts, World Bank, British Library for Development Studies, SCOPUS and Mednar.

Methodological quality

Quantitative papers selected for retrieval were assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute (i.e. JBI-MAStARI). Any disagreements that arose between the reviewers were resolved through discussion.

Data collection

Data were extracted from quantitative papers included in the review using the standardized data extraction tool from JBI-MAStARI. The data extracted included specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives.

Data synthesis

Meta-analysis was not done because the nature of the results from included studies did not make it statistically prudent to pool the results.

Results

A total of eight studies which met the inclusion criteria for this review were identified. Four (50%) studies were conducted in Kenya, three (37.5%) from Uganda and one (12.5%) from Senegal. The results of the review suggested that P. falciparum malaria was associated with mental disorders.

Conclusions

The review suggested that P. falciparum malaria is associated with mental disorders. However, there should be collaboration between investigators in this area so that multi-center trials can be conducted to ascertain the effects of P. falciparum malaria on more focused mental disorder outcomes.

Recommendation for practice

The results from the present review suggest that P. falciparum malaria is associated with mental disorders. Health professionals should therefore be aware of the vulnerability of survivors of malaria to mental disorders and make referrals to mental health professionals when they suspect any mental disorders during the management of malaria cases. However, the scope of the study did not cover temporality to show that P. falciparum malaria led to mental disorders.

Recommendations for research

The current review has shown that there is paucity of studies which focus on common endpoints, methodologies and analysis. There is therefore the need for researchers to collaborate and conduct a multicenter trial in this area.

Keywords

mental disorders, malaria, sub-Saharan Africa, P. falciparum, children

Introduction

Background

Mental disorders, also called psychiatric disorders, refer to unconventional or anomalous behavioral patterns, feelings, thoughts, perceptions and beliefs that cause distress or disability, and which are not developmentally or socially acceptable.

Mental disorders can affect people of all ages and cultures, even though there are some that exclusively affect children, men, women or the elderly.

These disorders are routinely treated with psychotropic medications or with psychotherapy, depending on whether they have an organic or psychosocial etiology. The current practice however incorporates both psychotropic medication and psychotherapy, as the two are not mutually exclusive.

P. falciparum is the commonest cause of malaria in humans and appears to have a propensity for the central nervous system.[4] Understandably, it is the most common parasitic infection of the central nervous system. Every year, over two billion people are infected globally, and over a million children, mostly less than five years die.[1,2]Children living in sub-Saharan Africa bear the brunt of the disease and its common neurological complications, since over 85% of global malaria cases occur in this region of the world.[1,2] In terms of geographical context, sub-Saharan Africa consists of 47 countries which lie south of the Sahara desert, with countries like Mauritania, Mali, Niger, Chad and Sudan serving as the northern boundaries of the sub-region.[2,3]

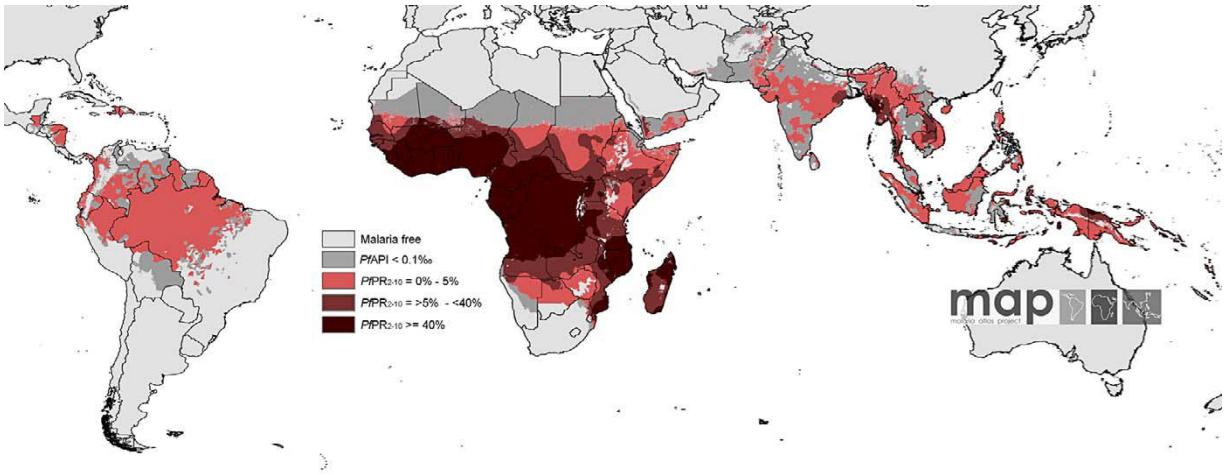

Figure 1: The spatial sistribution of P. falciparum malaria P. falciparum parasite rates

Light red = Low risk

Medium red = Intermediate risk

Dark red = High risk

Nearly a century ago, Anderson provided detailed accounts of the links between P. falciparum malaria and two mental disorders: psychosis and neurosis.[3] From the 1980s, the association between malaria and mental health took center-stage, and many studies corroborated Anderson's findings, and linked malaria with many mental and neurological disorders, such as neurotic behavior, psychosis, impaired executive functioning and epilepsy.[6,7,8] These diverse deficits can only occur in different brain areas, and not in any specific part of the brain. The earlier hypothesis that P. falciparum malaria affects only a specific brain location seems unlikely, given the wide variety of neuropsychological outcomes that are exhibited after infection.[8] These studies have indicated that P. falciparum seems to affect the brain globally, not in a localized fashion.

Cerebral malaria and mental disorders

Cerebral malaria complications have been shown to be caused by the sequestration of infected erythrocytes within cerebral blood vessels. This seems to be an essential component of the pathogenesis, even though other factors such as convulsions, acidosis or hypoglycemia can cause cognitive deficits and impair consciousness.[9] Cerebral malaria has been regarded as the most severe neurological complication of P. falciparum malaria, and it is relatively common in children living in sub-Saharan Africa.[2,5,10] It has become increasingly recognized that cerebral malaria may cause persistent neurological and cognitive deficits that span a wide range of cognitive functions long after the infection has been successfully treated with antimalarial drugs, even in asymptomatic individuals.[9] It is estimated that between 10%-28% of children who survive an episode of cerebral malaria develop neurological and psychiatric sequelae.[10]

Acute psychiatric complications that have been described in cerebral malaria include schizophrenic and manic syndromes, typical and atypical depression, anxiety attacks, acute confusional states, possession or trance-like states, delirium, amnesia, irritability, violence, impaired memory, and acute personality changes.[11] In addition to acute conditions, studies have also reported persistent deficiencies including attentional memory, learning and language impairments, visuospatial and motor deficits, and psychiatric disorders.[8, 9, 10] In another study that focused on mental disorders in cerebral malaria, Thiam and his colleagues listed mental confusion, delirium, visual hallucinations and motor agitation as some of the mental disorders diagnosed among in-patients of a psychiatric facility in Senegal.[12] Cerebral malaria can disrupt neuropsychological integration during critical developmental periods, impacting negatively on global neurological integrity, attentional vigilance, perceptual acuity, and subsequent development of visual-spatial processing and memory that is foundational to global cognitive ability.

Dugbartey and his colleagues conducted several studies about the neuropsychology of cerebral malaria in Ghana generally, and also about simple reaction time and cognitive information processing efficiency and somatosensory discrimination deficits after cerebral malaria in Ghanaian children.[1,2,14,15] They found significantly lower differences in reaction time, and information processing in children with repetitive uncomplicated malaria as against those episodes.

Other forms of severe malaria and mental disorders

Complicated malaria with multiple convulsions has also been found to lead to persistent neuropsychiatric impairments and deficits among children. For example, Carter and colleagues found neurocognitive impairments associated with severe P. falciparum malaria in Kenyan children who survived severe malaria.[8] This study also found evidence of acquired childhood language disorder, persistent neurocognitive deficits and developmental impairments among child survivors of severe malaria.

Uncomplicated malaria and mental disorders

Some studies have shown mental disorders are not only associated with cerebral and severe malaria, but also appear to occur in patients who have suffered repetitive uncomplicated malarial infections. The impairment of fine motor skills which affect psychomotor coordination in later life has also been found as sequelae in asymptomatic P. falciparum infection.[8,10]

Carter and colleagues indicated that in addition to being the cause of death of one million children every year, repetitive uncomplicated P. falciparum malaria in children is now known to leave survivors with multiple cognitive, motor and many other mental disorders. This is a matter of great concern, given the endemic nature of malaria in sub-Saharan Africa and the fact that the children who survive the episodes live with persistent negative sequelae.[8]

A study examining the mental health effects of uncomplicated malaria showed that children who had non-severe malarial infection still performed significantly poorer in scholastic tasks two weeks post-acute infection compared to controls.[12] Further findings have also pointed to the possibility that repeated non-severe malaria attacks have a significant negative effect on cognitive performance, manifesting as impairment in school performance.[12,13] These studies controlled for the effect of absence from school, so that the students used for the study had a non-significant difference in the number of days spent at school. Taken together, the deficits suffered by children who survived severe malaria, cerebral malaria, repetitive uncomplicated malaria and asymptomatic malaria included deficits in attention, memory, visuo-spatial skills, language, memory and general school performance. [12,13] Other studies have associated malaria with schizophrenic and manic syndromes, typical and atypical depression, anxiety attacks, mental confusion, amnesia, irritability, violence and acute personality changes.[7] Other negative sequelae that have followed episodes of malaria include visual hallucinations, motor agitation and an effect on the executive functions of the victims.[7,8]

Different studies have examined the mental health sequelae of P. falciparum malaria in a wide range of age groups of children, many of them in narrow age bands. For this review therefore, it was deemed necessary to extend the age band from five to 19 years so as to capture as many studies as possible. The broad age-band for this review is also aimed at looking at studies which looked at late-teen malaria survivors, so as to ascertain how far the deficits can persist in childhood. The review focused on sub-Saharan Africa as P. falciparum malaria is highly endemic in this region as compared to other regions of the world.[17] To summarize, the studies have indicated, among others, that cerebral malaria makes sufferers vulnerable to depression, memory loss, personality change, violence, post-traumatic stress and disorder. Severe malaria exposes victims to psychotic disorders, depressive disorders, memory impairment, irritability and violence, while repetitive uncomplicated malaria makes sufferers vulnerable to impairment in school performance, psychomotor problems, and impairment of fine motor skills.

Potential outcome for research and policy

Even though there are efforts aimed at preventive strategies, most government policies on malaria in sub-Saharan Africa are focused on early treatment and the prevention of mortality due to malarial episodes. This systematic review was therefore conducted to draw together the studies that have documented the negative and persistent mental disorders of survivors of P. falciparum malaria, with the overall aim of shaping policy towards malaria preventive strategies since the negative impacts of malaria have been shown to go far beyond successful treatment.

A preliminary search of Joanna Briggs Institute Library of Systematic Reviews, Cochrane Library, PubMed and CINAHL has revealed no existing systematic review on the topic of interest.

Objectives

The objective of this review was to identify and synthesize the best available evidence on the association of P. falciparum malaria and the short-term and long-term mental disorders of children and teenagers aged between five years and 19 years in sub-Saharan Africa.

More specifically, the objectives were to identify the effects of malaria episodes on children's memory, attention, general school performance, schizophrenic and manic syndromes, typical and atypical depression, anxiety attacks, mental confusion, amnesia, irritability, violence and acute personality changes.

In addition, this review also considered studies that looked at other negative sequelae such as visual hallucinations, motor agitation and those that reported negative effects on the executive functions of the victims in sub-Saharan Africa.

Inclusion criteria

Types of participants

This review considered studies that included children and teenagers aged between five and 19 years, who resided in sub-Saharan Africa. Children below five years of age are prone to active bouts of P. falciparum malaria as compared to older children,[18] hence the lower age limit of five years to capture persons not prone to active bouts of malaria disease. The other reason for not including children who were younger than five years was the fact that standardized tools for the assessment of the cognitive, language and other developmental processes in this category of younger children are very scarce, and in most cases have very low validity. The upper age limit of the group was 19 years, as the scope of this review was to include children and teenagers.

Phenomenon of interest/exposure

This review considered studies that examined the association between P. falciparum malaria (cerebral malaria, repetitive uncomplicated malaria or asymptomatic malaria) as exposure and mental disorders as outcome.

Types of studies

The review considered epidemiological study designs including randomized controlled trials, non-randomized controlled trials, quasi-experimental trials, prospective and retrospective cohort studies, case-control studies and analytical cross-sectional studies.

Types of outcomes

This review considered studies that included (but were not limited to) the following mental disorder outcome measures: cognitive deficits and impairments, acquired language disorder, school performance and psychomotor skills. Tools used to measure the outcomes can be found in Appendix IV.

Search strategy

The search strategy (Appendix I) was to find both published and unpublished studies. A three-step search strategy was utilized in this review. An initial limited search of MEDLINE and CINAHL was undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe article. A second search using all identified keywords and index terms was then undertaken across all included databases as shown below. Thirdly, the reference list of all identified reports and articles was searched for additional studies.

Studies published in the English language from 1980 to 2012, when the association between malaria and mental health was highlighted, were considered for inclusion in this review.

The database searched for unpublished studies was Networked Digital Library of Theses and Dissertations (ProQuest).

Initial search words included, but not limited to: Africa, sub-Saharan Africa, malaria, mental health, mental disorders, psychosis, neurosis, cognitive deficits, executive functions, psychomotor skills and neurological deficits.

Searched databases

The databases searched were PubMed, CINAHL, PsycARTICLES, PsycBITES, PsycINFO, Social Science Citation Index, ProQuest Dissertations and Theses (PQDT)/Digital dissertations, ProQuest Social Services abstracts, ProQuest Sociological abstracts, World Bank, British Library for Development Studies, SCOPUS and Mednar.

Method of the review

Quantitative papers selected for retrieval were assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments i.e. Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) (Appendix II). Any disagreements that arose between the reviewers were resolved through discussion.

Data collection

Data were extracted from papers included in the review using the standardized data extraction instrument from JBI-MAStARI (Appendix III).The data extracted include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives.

Data synthesis

Meta-analysis was not done because the nature of the results from included studies did not make it statistically prudent to pool the results. Therefore the results were described in a narrative.

Results

Description of studies

The literature search identified a total of 167 potentially relevant papers of which 37 were retrieved for title and abstract screening. Following title and abstract screening, 10 out of 37 studies did not meet the inclusion criteria for the review. The full texts of the remaining 27 papers were retrieved for detailed examination after which eight papers were selected for methodological assessment using JBI-MAStARI. All the eight papers were included in the study after obtaining a score of >5 which was the inclusion criteria (agreed among reviewers) for this study on the JBI-MAStARI instrument (Appendix IV).

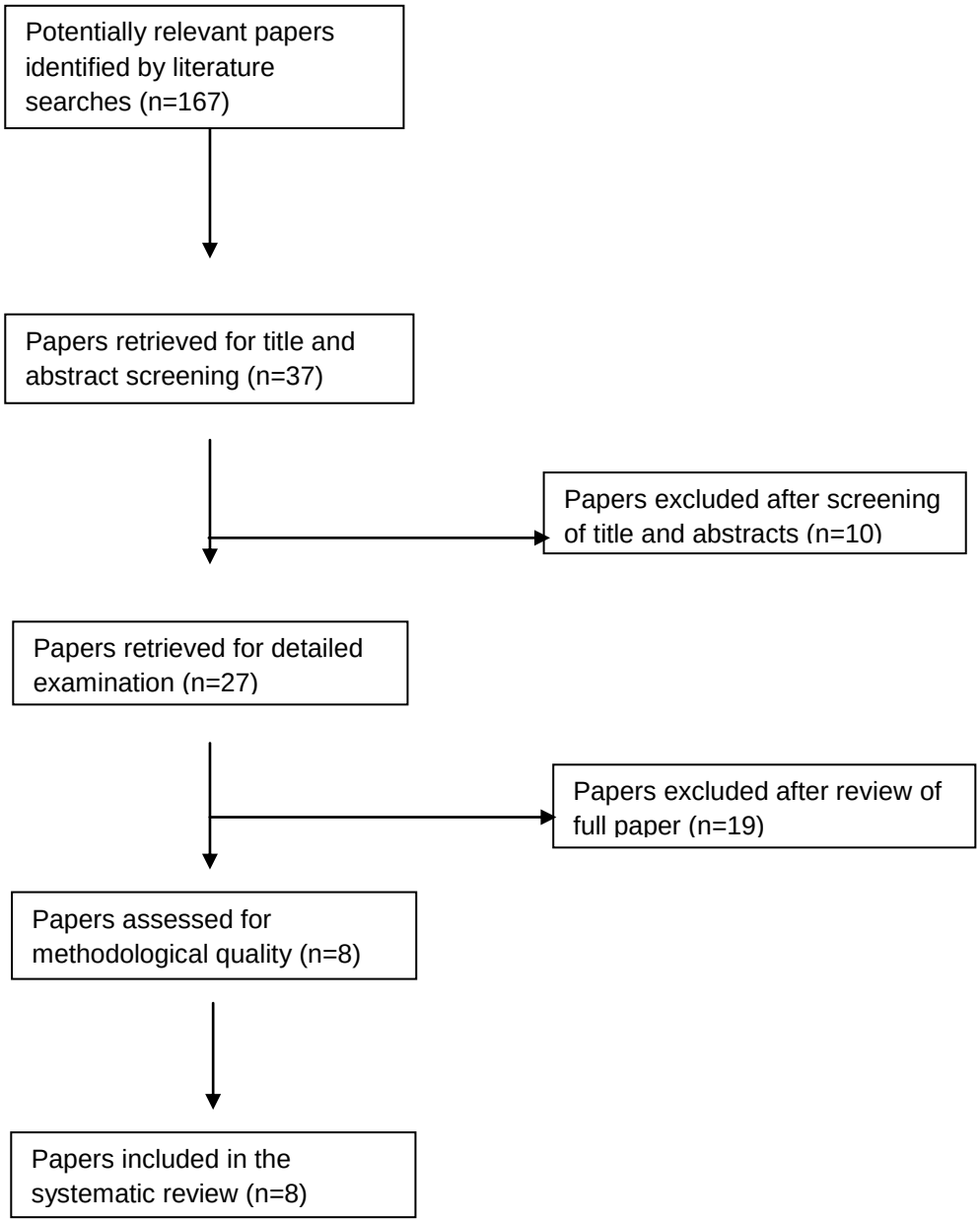

Figure 2: Flowchart detailing identification of included studies

Methodological quality

All the eight included studies (Appendix V) met at least seven of the nine JBI critical appraisal criteria. The eight included studies were therefore of moderate to good quality.

Findings of the review

A total of eight studies were included in the review. Four (50%) studies were conducted in Kenya,[22,23,24,26] three (37.5%) were from Uganda[19,20,25] and one (12.5%) from Senegal.[21] Apart from one study that recruited controls from the hospital all the other studies used community controls. The study populations were almost homogeneous in terms of age as the ages of all the study participants enrolled were between five and 12 years (four [50%] studies enrolled children between five and 12 years, two [25%] between six and nine years, one [12.5%] between eight and nine years and one [12.5%] between 6 and 7 years). The following is the summary of the findings from the included studies. Based on the fact that some of the studies focused on the effects of P. falciperum malaria on cognitive disorders and functioning while others focused on language and speech disorders and delays as main outcomes, the results were categorized into "Effect of P. falciparum malaria on cognitive disorders " and "Effect of P. falciparum malaria on language and speech" .

Effect of P. falciparummalaria on cognitive disorders

A prospective case-control study conducted by Bangirana et al.[19] compared 62 malaria cases (Cerebral malaria [CM]-nine, malaria with seizures [M/S]-34, and malaria with impaired consciousness-19) to 61 community controls. Their cognitive ability (working memory, reasoning, learning, visual spatial skills and attention), behavior (internalizing and externalizing problems) and academic achievement (arithmetic, spelling and reading) were compared three months after enrolment. Children in the malaria group had behavioral deficits when compared to the control group. Whereas there was a significant internalizing behavioral deficit (estimated mean difference = -3.71, 95% CI [-6.34 to -1.08], p = 0.007), the externalizing behavioral deficit was not statistically significant (estimated mean difference = -1.60, 95% CI [-5.29 to -2.09], p = 0.40). In addition, the malaria group had lower scores for working memory, reasoning learning, visual spatial skills and attention but none of them was statistically significant.

Another study by Boivin and colleagues[20]compared children aged five to12 years with cerebral malaria (n=44) and uncomplicated malaria (UM) (n=54) to healthy community controls (n=89). Assessment of cognitive abilities in the areas of working memory, attention and learning were done three months and six months post-discharged. Six months post-discharge cognitive test results showed significant deficits in the areas of working memory (11.9% vs 2.3%, p=0.04) and attention (16.7% vs 2.3%, p=0.005). However, deficits seen in the area of learning were not statistically significant (4.8 vs 1.1, p=0.25). Children with CM were also 3.7 (OR =3.7, 95% CI [1.3–10.7], p = 0.02) times more likely to have cognitive deficits as compared to healthy community children. At six months, there were no statistically significant deficits in all areas when UM children were compared to community controls. Moreover, the UM group was 1.79 (OR=1.79, 95% CI [0.44–7.21], p-value not shown) times more likely to have cognitive deficits as compared to the controls. However no statistically significant effect was seen.

Boivin et al.[21] also carried out a case control study among five to12 year old Senegalese children to compare 29 CM cases recruited from hospital and 29 aged-matched controls with “mild malaria” from the same hospital. Cognitive deficits of CM and control children were assessed on the average of six years post-discharge of cases. The study found out that CM children had lower scores on the global scales (sequential, simultaneous, mental composite and nonverbal composite), sequential processing subtests (hand movements, number recall and word order) and simultaneous processing subtests (gestalt closure, triangles, matrix analogies, spatial memory and photo series). The CM children had significant lower scores on all global scales i.e. sequential (83.7 vs 95.4, p<0.01), simultaneous (72.2 vs 87.6, p<0.05), mental composite (75.0 vs 89.6, p<0.05) and nonverbal composite (77.3 vs 92.4, p<0.05). Also the CM children had significant lower scores on the two of the sequential subtests i.e. hand movements (6.5 vs 8.2, p<0.01) and word order (6.4 vs 9.0, p<0.05). The CM children scored lower on the number recall (9.1 vs 10.6, p-value not shown) subtest but it was not statistically significant (p-values were shown for only statistically significant associations). In addition, spatial memory (5.7 vs 8.2, p<0.05) and photo series (4.3 vs 7.3, p<0.01) were the only two simultaneous processing subtests that the CM children had significant lower scores. The lower scores of the CM children on the gestalt closure (3.3 vs 4.6, p-value not shown), triangles (6.5 vs 9.0, p-value not shown) and matrix analogies (8.5 vs 11.7, p-value not shown) subtests were not statistically significant.

Measures relevant to attention capacity (percentage of omission errors, correct response time latency, correct response time latency variability and D prime) and impulsivity (percentage of commission errors) were also recorded. The CM children had a significantly higher (i.e. worse) mean score on percentage of omission errors (23 vs 11, p<0.05). However, there was no statistically significant difference between the means of the CM children and the control children with regards to the other measures (correct response time latency, correct response time latency variability, D prime and percentage of commission errors).Also, in a retrospective case-control study conducted by Carter and colleagues[23] among six to nine year old Kenyan children, 152 children with CM and 156 with malaria and complicated seizures (M/S) were compared to 179 community controls. The follow-up period for the children was between 20 and 112 months. Increased prevalence of epilepsy was seen among CM (9.2%) and M/S (11.5%) children as compared to community controls (2.2%). The CM (OR=4.4, 95% CI [1.4-3.7], p=0.01) and M/S (OR=6.1, 95% CI [2.0-18.3], p=0.001) groups had increased odds of having epilepsy as compared to the controls.

Deficits in cognition were also found in the areas of attention, working memory and tactile learning in a study conducted by Chandy et al.[25] among five to12 year old Ugandan children. Forty-four CM and 54 UM were compared with 89 community controls in a cohort study with a follow-up period of two years. At two years of follow-up, the cognitive test indicated that there was a statistically significant cognitive deficit among cases in the area of attention as compared to controls (18.4% vs 2.5%, p=0.005). However, the cognitive deficits among cases in the areas of working memory and tactile learning were not statistically significant. The CM group had 3.67 (OR=3.67, 95% CI [1.10-12.13], p=0.03) fold risk of cognitive deficit compared to community controls.

Kihara et al.[26] conducted a retrospective case-control study in Kenya among six to seven year old children to test for cognitive deficits (auditory and visual paradigms). Event related potentials (ERPs) were used to compare novelty processing among 50 children exposed to severe malaria (CM-27,

malaria with seizures-14, malaria with prostration-9) with 77 community controls. The comparison was done by exposing both groups of children to novelty (or unexpected stimuli) and then their response to unexpected stimuli was determined by P3a amplitude which was the highest peak between specific time points (250ms-450ms for Auditory Paradigms and 270ms-450ms for Visual Paradigm). The smaller the P3a amplitude of a child, the lower the child's cognitive ability. It was found out in this study that children exposed to severe malaria had smaller P3a amplitudes to novelty in both auditory [F (3, 119)=4.545, p=0.005] and visual [F (3, 119)=6.708, p<0.001] paradigms compared to unexposed children.

Effect of P. falciparum malaria on language and speech

The following is a summary of results of effect of falciparum malaria on language and speech.

Carter and colleagues[22] conducted a cohort study to assess the speech and language deficits among eight to nine year old Kenyan children after a follow-up of at least two years. Twenty-five children with severe malaria (CM-13 and non-cerebral malaria-12) were compared to 27 community controls. Children with severe malaria were found to have lower scores on each aspect of language assessment. However, statistically significant lower scores were found on the aspects of language comprehension (p =0.02), syntax (p = 0.02), content words (p = 0.02) and function words (p =0.004) components of lexical semantics.

Carter et al.[24] also conducted a retrospective case-control study to assess language impairment among three groups of Kenyan children six to nine years old. Children with CM (n=152) and C/S (n=156) were compared to 179 community controls in a follow-up period of 20 to 112 months. Language performance was measured using a battery of tests. The major components of speech and language including cognitive performance, neurological/motor skills, behavior, hearing and vision were tested. The study found out that 18 (11.8%) of the CM group, 14 (9%) of the M/S group, and four (2.2%) of the control group had language impairment. CM children (OR= 3.68, 95% CI [1.09 - 12.4], p=0.04) were more likely to have impairment-level scores compared to the control children. The M/S group (OR=3.12, 95% CI [0.9–10.8], p=0.07) had higher odds of impairment-levels as compared to the unexposed group. However, this was not statistically significant.

Discussion

The aim of this review was to explore the association of P. falciparum malaria on mental disorders among children and teenagers between five and 19 years of age. However, the studies that met the inclusion criteria had persons aged between five and 12 years. The results of the review showed that P. falciparum malaria is associated with mental disorders both in the short and long term.

Eight studies were selected for appraisal using the JBI standardized critical appraisal instrument. The eight studies were selected because they met the criteria of having a total score of >5 on the appraisal instrument (as was agreed among the team of reviewers prior to beginning the review). All the eight studies extracted for the review indicated that P. falciparum malaria was associated with mental disorders. Reviewing the methodology of the studies, most of the outcomes on cognition used a common battery of tests. Of the six studies that tested outcomes on cognitive disorders, four[19,20,21,25] of them used K-ABC and TOVA to assess working memory and attention deficits respectively. Two[23,26] of them however used EEP to assess epilepsy and ERPs for auditory and visual paradigms assessment. Moreover, three[19,20,25] of the four studies that used K-ABC and TOVA for cognitive

assessments used community controls. The four studies that used common battery of tests, assessed for cognitive abilities for at least three and at most 112 months post-discharged. Although the studies did not use the same statistical methods in their analyses, covariates were adjusted for and there were some significant associations of P. falciparum malaria with cognitive deficits for both the short and long term follow-up periods. The results of the four studies suggest that P. falciparum malaria is associated with both the short and long term mental disorders. However this finding needs to be interpreted with caution, because there was slight variability in the determination of end points, definition of cases and statistical analysis. Furthermore, the differences in mental disorder outcomes and choice of statistical method (i.e. whereas some studies were estimating odds ratios, others were estimating mean difference) made meta-analysis impossible. Performing meta-analyses would have given this review enough statistical power because some of the studies had small sample sizes. Moreover, two[23, 26] of the studies used a battery of tests and methodologies that were quite different from the other four. Despite using different batteries and methodologies, the results of the two studies indicated an association of P. falciparum malaria with mental disorders. Also, since some of the studies[23,24,26] were cross-sectional, it would be difficult to conclude that P. falciparum malaria leads to mental health disorders. However, the scope of this study was association and not causality.

The findings of this review are consistent with a review conducted by Kihara et al. (2006) among children and adult populations in Africa, Asia and North America where the follow-up period was at least six months. It was found out that malaria affects neuro-cognitive function in both the short and long term. Although, this review used: 1) only a sub-Saharan population; 2) a greater number of end points (outcomes); and only children between the ages five to12, the results were still consistent with the review conducted by Kihara et al. (2006).

The results of two studies[22,24] conducted by Carter and his colleagues showed that P. falciparum malaria is associated with speech and language impairments. The two studies used the same instrument to test for speech and language disorders. However, one estimated[24] odds ratios and the other[23] estimated mean difference making meta-analysis difficult.

Limitation

The review searched for literature in only English language and it is possible that results of primary studies in other languages relevant to this review were excluded.

Conclusion

The review indicates that P. falciparum malaria is associated with mental disorders. However, mental disorder outcomes are numerous and make the scope of the endpoints very broad. Moreover, studies conducted on mental disorders and P. falciparum malaria do not follow any particular set standards, leading to difficulties in the conduct of meta-analysis. There should be collaboration between investigators in this area so that multi-center trials can be conducted to ascertain the effect of P. falciparum malaria on a more focused set of mental disorder outcomes. Notwithstanding the widespread outcomes and variation in methodologies, this review has shown that P. falciparum malaria is associated with mental disorders in sub-Saharan Africa. Therefore health facilities in sub-Saharan Africa need to form strong ties with mental health facilities/institutions for prompt referral of such cases.

Implications for practice

The results from the present review suggest that P. falciparum malaria is associated with mental disorders and this has important implications for practice. Health professionals should therefore be aware of the vulnerability of survivors of malaria to mental disorders and they should make appropriate referrals to mental health professionals when they suspect of any mental disorders during the management of malaria cases. However, the scope of the study did not cover temporality to show that P. falciparum malaria led to mental disorders.

Implications for research

The current review has shown that there is paucity of studies that focus on common endpoints, methodologies and analysis. There is therefore the need for researchers to collaborate and conduct a multicenter trial in this area.

Conflict of Interest

The authors of this review have no individual or joint conflict of interest.

Acknowledgements

The reviewers wish to acknowledge the JBI Affiliate Center at the Kintampo Health Research Center for their initial comprehensive training of the first three authors, and for their continued motivation.

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24. Carter JA, Lees JA, Gona JK. Severe falciparum malaria and acquired childhood language disorder. *Developmental Medicine & Child Neurology* 2006; 48: 51–57.

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Appendix I: Search strategy

PubMed(28)

CINAHL (5)

1. Malaria and mental health
2. Malaria and psychosis
3. Malaria and neurosis
4. Malaria and cognitive deficits
5. Malaria and executive functions
6. Malaria and psychomotor skills
7. Malaria and neurological deficits
8. Malaria and school performance
9. Malaria and acquired language disorder

PsycARTICLES (0)

PsycBITE (0)

PsycINFO (18)

ProQuest Dissertations and Theses (PQDT)/ Digital dissertations (0)

Web of Science= Social Science Citation Index + science citation index expanded + arts and humanities citation index (44)

ProQuest Social Services abstracts (0)

ProQuest Sociological abstracts (0)

World Bank (0)

British Library for Development Studies (0)

SCOPUS (42)

Mednar (15)

1. Malaria and mental health
2. Malaria and psychosis
3. Malaria and neurosis
4. Malaria and cognitive deficits
5. Malaria and executive functions
6. Malaria and psychomotor skills
7. Malaria and neurological deficits
8. Malaria and school performance
9. Malaria and acquired language disorder
10. Malaria and neuropsychology

11. Malaria and cognitive performance
12. Malaria and speech disorders
13. Malaria and epilepsy
14. Malaria and cognition disorders
15. Malaria and mental disorders
16. Malaria and cerebral complications

Appendix II: Appraisal instruments

MAStARI appraisal Instrument

JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Was the assignment to treatment groups truly random?	☐	☐	☐	☐
2. Were participants blinded to treatment allocation?	☐	☐	☐	☐
3. Was allocation to treatment groups concealed from the allocator?	☐	☐	☐	☐
4. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
5. Were those assessing outcomes blind to the treatment allocation?	☐	☐	☐	☐
6. Were the control and treatment groups comparable at entry?	☐	☐	☐	☐
7. Were groups treated identically other than for the named interventions	☐	☐	☐	☐
8. Were outcomes measured in the same way for all groups?	☐	☐	☐	☐
9. Were outcomes measured in a reliable way?	☐	☐	☐	☐
10. Was appropriate statistical analysis used?	☐	☐	☐	☐
	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

JBI Critical Appraisal Checklist for Comparable Cohort/ Case Control

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Is sample representative of patients in the population as a whole?	☐	☐	☐	☐
2. Are the patients at a similar point in the course of their condition/illness?	☐	☐	☐	☐
3. Has bias been minimised in relation to selection of cases and of controls?	☐	☐	☐	☐
4. Are confounding factors identified and strategies to deal with them stated?	☐	☐	☐	☐
5. Are outcomes assessed using objective criteria?	☐	☐	☐	☐
6. Was follow up carried out over a sufficient time period?	☐	☐	☐	☐
7. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

JBI Critical Appraisal Checklist for Descriptive / Case Series

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Was study based on a random or pseudo-random sample?	☐	☐	☐	☐
2. Were the criteria for inclusion in the sample clearly defined?	☐	☐	☐	☐
3. Were confounding factors identified and strategies to deal with them stated?	☐	☐	☐	☐
4. Were outcomes assessed using objective criteria?	☐	☐	☐	☐
5. If comparisons are being made, was there sufficient descriptions of the groups?	☐	☐	☐	☐
6. Was follow up carried out over a sufficient time period?	☐	☐	☐	☐
7. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

Appendix III: Data extraction instruments

MAStARI data extraction instrument

JBI Data Extraction Form for Experimental / Observational Studies

Reviewer _____ Date _____

Author _____ Year _____

Journal _____ Record Number _____

Study Method

RCT ☐ Quasi-RCT ☐ Longitudinal ☐

Retrospective ☐ Observational ☐ Other ☐

Participants

Setting _____

Population _____

Sample size

Group A _____ Group B _____

Interventions

Intervention A _____

_____

Intervention B _____

_____

Authors Conclusions:

_____

_____

_____

Reviewers Conclusions:

_____

_____

_____

Study results

Dichotomous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Continuous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Appendix IV: Description of included studies

The following are the descriptions of the study methodologies used by the primary studies.

Effect of P. falciparum malaria on cognitive ability

In a prospective study conducted by ***Boivin et al. in 2007***, Ugandan children aged five to 12 years with cerebral malaria (n=44) and uncomplicated malaria (n=54) were compared to healthy community controls (n=89) recruited from neighboring families of the cases. Assessment of cognitive abilities in the areas of working memory, attention and learning were done three months and six months post-discharged. CM children were enrolled based on World Health Organization (WHO) criteria for CM, i.e. coma (Blantyre coma scale ≤2 or Glasgow coma scale ≤8), presence of P. falciparum on blood smears and no other cause for coma. Also, the UM children were selected on the basis of children having symptoms of malaria (fever, chills, vomiting, or headache), P. falciparum on blood smears, and no evidence of malaria complications or other acute illnesses.

This study tested cognitive ability in the area of working memory using the Kaufman assessment battery for children (K-ABC). Moreover, children's attention deficit disorders were assessed by the test of variables of attention (TOVA) which was a computer-administered continuous performance test. The learning deficit was also assessed with the aid of tactual performance test (TPT). In addition, the nutrition status of the children was assessed by comparing estimated weight-for-age values with that in Epi Info software (Epi Info 6; Centers for Disease Control) to obtain a standardized z-scores. The socio-economic status of children was assessed using a scoring instrument with a checklist of material possessions. Finally, home environment was assessed by using an adapted version of the Home Observation for Measurement of the Environment inventory.

In 2008, Chandy et al. conducted a cohort study with similar characteristics as those of Boivin et al. above. Although the same study participants, measuring instruments and methodology were used, the follow-up period for this study was longer (i.e.two years). Both studies used multivariate logistic regression analysis to compare the risk of having cognitive deficits among the two groups. The children's age, gender, nutritional status, levels of education and home environment scores were adjusted for in the analyses.

The prospective case control study also conducted by ***Bangirana et al. in 2011*** compared 62 cases of malaria with neurological involvement (CM-nine, malaria with seizures-34, malaria with impaired consciousness-19) to 61 community controls. Their cognitive ability (working memory, reasoning, learning, visual spatial skills and attention), behavior (internalizing and externalizing problems) and academic achievement (arithmetic, spelling and reading) were compared three months after enrollment. Cases were children aged –five to 12 years presenting with malaria (Presence of P. falciparum on blood smears) and either one or more of the following: 1) convulsive seizures lasting over 15 minutes or repeated seizures observed by the parent or during admission at the hospital, 2) impaired consciousness (Glasgow coma scale score of ≤14), or 3) coma (i.e. un-arousable coma with normal cerebrospinal fluid).

This study tested working memory using the Kaufman assessment battery for children second edition (KABC-II). Moreover, children's attention deficit disorders were assessed by the test of variables of

attention (TOVA) which was a computer-administered continuous performance test. The Child behavior checklist (CBCL)'a paper-pencil child behavioral rating scale, was used to assess the children's behavior (internalizing and externalizing problems). In addition, the basic skills of reading, spelling and arithmetic among the children were measured using the wide range achievement test-third edition (WRAT-3). Finally, the middle childhood home observation for the measurement of the environment (MC-HOME) was used to assess the quality of the home environment. This study used analysis of covariance (ANCOVA) to compare the means of both groups and age, sex, level of education, nutritional status and quality of the home environment were adjusted for.

Boivin et al. in 2002 also carried out a case control study among five to12 year old Senegalese children to compare 29 CM cases recruited from hospital and 29 aged-matched controls with "mild malaria" from the same hospital. Cognitive deficits of CM and control children were assessed on the average of six years post-discharged of cases. The 29 cases were selected based on WHO criteria for CM. Controls were termed "mild malaria" because the parents of the majority of these children reported a history of at least one episode of malaria without prolonged high fever or coma. Cognitive deficits in the areas of attention and memory (sequential and simultaneous) processing were tested using TOVA and K-ABC respectively. ANCOVA was used in the analysis with age and environment (rural vs urban) adjusted for.

Furthermore, in a retrospective case control study conducted by ***Carter and colleagues in 2004*** among six to nine year old Kenyan children, 152 children with CM and 156 with malaria and complicated seizures (M/S) were compared to 179 community controls. Children were considered to have CM if they had a Blantyre coma score of ≤2 for at least four hours, peripheral parasitemia and the exclusion of other causes of encephalopathy. Children were classified as M/S if they had more than two seizures within 24 hours or focal or prolonged >30 minutes but did not develop coma (i.e. able to localize a painful stimulus within one hour of the seizure). Children's epilepsy was tested using electroencephalogram (EEG).

In a follow-up of the above children between 20 and 112 months, the risk of epilepsy between the exposure and unexposed groups was compared using logistic regression. However, it was not explicitly stated that adjustment for covariates was done in the analysis.

Finally, ***Kihara and colleagues in 2010*** conducted a retrospective case control study in Kenya among six to seven year old children to test cognitive deficits (auditory and visual paradigms). Event related potentials (ERPs) were used to compare novelty processing among 50 children exposed to severe malaria (CM-27, malaria with seizures (MS) -14, malaria with prostration (PM)-9) with 77 age-matched community controls. Children were considered as having CM if they had a Blantyre coma score of ≤2 for at least four hours, peripheral parasitemia and the exclusion of other causes of encephalopathy. Children were classified as MS if they had more than two seizures within 24 hours or focal or prolonged >30 minutes but did not develop coma (i.e. able to localize a painful stimulus within one hour of the seizure). In addition, PM cases were defined as peripheral parasitemia, a Blantyre coma score of threeor four and child is unable to sit or walk without support. One way analysis of variance (ANOVA) was used to compare mean scores for cognitive deficits (auditory and visual paradigms)

Effect of falciparum malaria on language and speech

Carter et al. in 2003 carried out a cohort study to assess the speech and language deficits among eight to -nine year old Kenyan children after a follow-up of at least two years. Twenty-five children with severe malaria (CM-13 and non-cerebral malaria-12) were compared to 27 community controls. Children recruited as CM cases were those with a deep level of unconsciousness with inability to localize a painful stimulus (Blantyre coma score of <2 for 4 or more hours); a P. falciparum asexual parasitemia and exclusion of other encephalopathies. Non-cerebral malaria cases were children with prostration, multiple seizures or severe anemia.

All assessments were derived from validated instruments commonly used in the United Kingdom. However, each assessment was adapted according to the culture and experience of children in the area. Assessments were done in the areas of comprehension, syntax, lexical semantics, higher level language abilities, pragmatics and phonology. Multiple regression analysis was used to compare the mean scores between the cases and the control groups after having adjusted for age and sex.

In addition, ***Carter and colleagues in 2006*** also conducted a retrospective case control study to assess speech and language outcome among three groups of Kenyan children between six and nine years old. Children with CM (n=152) and C/S (n=156) were compared to 179 community controls in a follow-up period of 20-112 months.

Children were considered to have CM if they had a Blantyre coma score of ≤2 for at least four hours, peripheral parasitemia and the exclusion of other causes of encephalopathy. The M/S cases were children who had more than two seizures within 24 hours or focal or prolonged >30 minutes but did not develop coma (i.e. able to localize a painful stimulus within one hour of the seizure).

The battery for the speech and language assessment was a standardized UK battery, modified and revised to suit the study population. Assessments were done in the areas of receptive grammar, receptive vocabulary, syntax, lexical semantics, higher level language, pragmatics, phonology and word finding. Speech and language impairment between the exposure and unexposed group were analyzed using logistic regression after having controlled for age, sex, schooling status, nutritional status and socio-economic status.

Appendix V: Appraisal of included studies based on JBI critical appraisal tools

Studies	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Score
Bangirana et al, 2011 [19]	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	7
Boivin et al, 2007 [20]	Yes	Yes	Yes	Yes	Yes	Yes	No	U	Yes	7
Boivin et al, 2002 [21]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	8
Carter et al, 2003 [22]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	8
Carter et al, 2004 [23]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	8
Carter et al, 2006 [24]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	8
Chandy et al, 2008 [25]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	8
Kihara et al, 2010 [26]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	8

Appendix VI: List of excluded studies

Studies excluded after review of abstracts (10)

[27]Al Serouri AW, Grantham-McGregor SM, Greenwood B, Costello A. Impact of asymptomatic malaria parasitaemia on cognitive function and school achievement of schoolchildren in the Yemen Republic. Parasitology.2000; 121(Pt 4): 337-345.

Reason for exclusion: Study was outside sub-Saharan Africa

[28]Bag S, Samal GC, Deep N, Patra UC, Nayak M, Meher LK. Complicated falciparum malaria. Indian Pediatrics.1994; 31: 821-825

Reason for exclusion: Reference

[29]Bangirana P, Musisi S, Boivin MJ, Ehnvall A, John CC, Bergemann TL et al. Cognition, behavior and academic skills after cognitive rehabilitation in Ugandan children surviving severe malaria: a randomised trial. BMC Neurol. 2011; 11: 96.

Reason for exclusion: Interventional study to rehabilitate children with cognitive problems

[30]Bondi FS. The incidence and outcome of neurological abnormalities in childhood cerebral malaria: A long-term follow-up of 62survivors. Transactions of the Royal Society of Tropical Medicine and Hygiene.1992; 86(1): 17-19.

Reason for exclusion: Described the outcomes under consideration

[31]Canfield CJ, Chongsuphajaisiddhi T, Danis M, Gillis CHM, Krogstad DJ, Molyneux ME, Salako LA, Warrell DA, White NJ, Beales PF, Doberstyn EB, Molineaux L, Najera JA, Sheth UK, Spencer HC, Wernsdorfer WH.. Severe and complicated malaria. Transactions of the Royal Society of Tropical Medicine and Hygiene.1990; 84(Suppl. 2): 1-65.

Reason for exclusion:Reference

[32]Fernando D, de Silva D, Wickremasinghe R. Short-term impact of an acute attack of malaria on the cognitive performance of schoolchildren living in a malaria endemic area of Sri Lanka. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2003; 97(2): 633-639. Reason for exclusion: Study was outside sub-Saharan Africa

[33]Fernando D, Wickremasinghe R, Mendis KN, Wickremasinghe AR. Cognitive performance at school entry of children living in malaria-endemic areas of Sri Lanka. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2003; 97(2): 161-165.

Reason for exclusion: Study was outside sub-Saharan Africa

[34]Kihara M, Carter JA, Newton CRJC. The effect of plasmodium falciparum on cognition: a systematic review. Tropical Medicine and International Health.2006; 11(4): 386-397.

Reason for exclusion: Reference

[35]Roman GC, Senanayake N. Neurological manifestations of malaria. ArqNeuro-Psyquiat (Sao Paulo).1992; 50(1): 3-9.

Reason for exclusion: Reference

(36)Vitor-Silva S, Reyes-Lecca RC, Pinheiro TR, Lacerda MV. Malaria is associated with poor school performance in an endemic area of the Brazilian Amazon. Malar J.2009; 8: 230.

Reason for exclusion: Study was outside sub-Saharan Africa

Studies excluded following a review of full papers (19)

(37)Birbeck GL, Molyneux ME, Kaplan PW, Seydel KB, Chimalizeni YF, Kawaza K, Taylor TE. Blantyre Malaria Project Epilepsy Study (BMPES) of neurological outcomes in retinopathy-positive paediatric cerebral malaria survivors: a prospective cohort study. Lancet Neurology.2010; 9(12): 1173-1181.

Reason for exclusion: Study subjects beyond stipulated age limits

(38)Boivin MJ, Gladstone MJ, Vokhiwa M, Birbeck GL, Magen JG, Page C, Semrud-Clikeman M, Kauye F, Taylor TE. Developmental outcomes in Malawian children with retinopathy-positive cerebral malaria.Trop Med Int Health.2011; 16(3): 263-71. doi: 10.1111/j.1365-3156.2010.02704.x. Epub 2010 Dec 8.

Reason for exclusion: Study subjects beyond stipulated age limits

(39)Brewster DR, Kwiatkowski D, White NJ. Neurological sequelae of cerebral malaria in children. The Lancet.1990; 336(8722): 1039-1043.

Reason for exclusion: Study subjects beyond stipulated age limits

(40)Carter JA, Mung'ala-Odera V, Neville BGR, Murira G, Mturi N, Musumba C, Newton CRJC.. Persistent neurocognitive impairments associated with severe falciparum malaria in Kenyan children. Journal of Neurology, Neurosurgery and Psychiatry.2005; 76(4): 476-481.

Reason for exclusion: Reference

(41)Carter JA, Ross AJ, Neville BGR, Obiero E, Katana K, Mung'ala-Odera V, Lees JA, Newton CRJC.. Developmental impairments following severe falciparum malaria in children. Tropical Medicine and International Health.2005; 10(1): 3-10.

Reason for exclusion: Reference

(42)Fernando SD, Gunawardena DM, Bandara MRSS, De Silva D, Carter R, Mendis KN, Wickremasinghe AR. The impact of repeated malaria attacks on the school performance of children. American Journal of Tropical Medicine and Hygiene. 2003; 69(6): 582-588.

Reason for exclusion: Study was outside sub-Saharan Africa

(43)Holding PA, Stevenson J, Peshu N, Marsh K. Cognitive sequelae of severe malaria with impaired consciousness. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1999; 93(5): 529-534

Reason for exclusion: Study subjects' age limits not clear

(44)Idro R, Carter JA, Fegan G, Neville BGR, Newton CRJC.Risk factors for persisting neurological and cognitive impairments following cerebral malaria. Archives of Disease in Childhood. 2006; 91(2): 142-148.

Reason for exclusion: Outcomes differ from those stated for review

(45)Idro R, Gwer S, Kahindi M, Gatakaa H, Kazungu T, Ndiritu M, Maitland K, Neville BGR, Kager PA, Newton CRJC.. The incidence, aetiology and outcome of acute seizures in children admitted to a rural Kenyan district hospital. BMC Pediatrics. 2008; 8:5

Reason for exclusion: Study subjects beyond stipulated age limits

(46)Idro R, Ndiritu M, Ogutu B, Mithwani S, Maitland K, Berkley J, Crawley J, Fegan G, Bauni E, Peshu N, Marsh K, Neville B, Newton C, Ndiritu M. Burden, features, and outcome of neurological involvement in acute falciparum malaria in Kenyan children. Journal of the American Medical Association. 2007; 297(20): 2232-2240.

Reason for exclusion: Study subjects beyond stipulated age limits

(47)Idro R, Otieno G, White S, Kahindi A, Fegan G, Ogutu B, Mithwani S, Maitland K, Neville BGR, Newton CRJC.. Decorticate, decerebrate and opisthotonic posturing and seizures in Kenyan children with cerebral malaria. Malaria Journal.2005; 4:57

Reason for exclusion: Study subjects beyond stipulated age limits

(48)Kariuki SM, Ikumi M, Ojal J, Sadarangani M, Idro R, Olotu A, Bejon P, Berkley JA, Marsh K, Newton CRJC. Acute seizures attributable to falciparum malaria in an endemic area on the Kenyan coast. Brain.2011; 134(5): 1519-1528.

Reason for exclusion: Study subjects beyond stipulated age limits

(49)Ngoungou EB, Dulac O, Poudiougou B, Druet-Cabanac M, Dicko A, Traore AM, Coulibaly D, Farnarier G, Tuillas M, Keita MM, Kombila M, Doumbo OK, Preux P-M. Epilepsy as a consequence of cerebral malaria in area in which malaria is endemic in Mali, West Africa. Epilepsia. 2006; 47(5): 873-879.

Reason for exclusion: Study subjects beyond stipulated age limits

(50)Ngoungou EB, Koko J, Druet-Cabanac M, Assengone-Zeh-Nguema Y, Launay MN, Engohang E, Moubeka-Mounguengui M, Kouna-Ndouongo P, Loembe P-M, Preux P-M, Kombila M. Cerebral malaria and sequelarepilepsy: first matched case-control study in Gabon. Epilepsia.2006; 47(12): 2147-2153.

Reason for exclusion: Study subjects beyond stipulated age limits

(51)Nguyen TH, Day NP, Ly VC, Waller D, Mai NT, Bethell DB, Tran TH, White NJ. Post-malaria neurological syndrome.Lancet. 1996; 348(9032): 917-921.

Reason for exclusion: Reference

(52)Opoka RO, Bangirana P, Boivin MJ, John CC, Byarugaba J. Seizure activity and neurological sequelae in Ugandan children who have survived an episode of cerebral malaria. Afr Health Sci. 2009; 9(2): 75-81.

Reason for exclusion: Study subjects beyond stipulated age limits

(53)Sowunmi, A. Clinical study of cerebral malaria in African children. Afr J Med Med Sci. 1997; 26(1-2): 9-11.

Reason for exclusion: Only provides a general description of cerebral malaria

(54)Thuilliez J, Sissoko MS, Toure OB, Kamate P, Berthelemy JC, Doumbo OK. Malaria and primary education in Mali: a longitudinal study in the village of Doneguebougou. SocSci Med. 2010; 71(2): 324-34. Epub 2010 Mar 17.

Reason for exclusion: Does not contain mental health outcomes

(55)Thuilliez J. Fever, malaria and primary repetition rates amongst school children in Mali: Combining demographic and health surveys (DHS) with spatial malariological measures. Social Science and Medicine. 2010; 71(2): 314-323.

Reason for exclusion: Article does not have outcomes of interest

Appendix VII: Characteristics of included studies

Study	Methods	Participants	Exposure	Control	Notes
Bangirana et al., 2011 [19]	Prospective case control	Children between the ages of 5 and 12 years	Children plasmodium falciparum malaria	Children without any illness during recruitment	
Boivin et al., 2007 [20]	Prospective study	Children with ages between 5 and 12 years	Children with cerebral malaria (CM) Children with uncomplicated malaria (UM)	Children without CM and UM	The study had two exposure groups
Boivin et al., 2002 [21]	Case control	Children aged 5-12 years	Cerebral malaria patients	children with "mild malaria"	
Carter et al., 2003 [22]	Cohort study	Children aged 8-9 years	Children with Severe malaria (cerebral malaria -13 and non-cerebral malaria -12)	Children without severe malaria	
Carter et al., 2004 [23]	Retrospective case control	Children with ages between 6 and 9 years	Children with cerebral malaria (CM) Children with malaria and complicated seizures (M/S)	Children without CM and M/S	There were two exposure groups in this study
Carter et al., 2006 [24]	Retrospective case control	Children with ages between 6 and 9 years	Children with cerebral malaria (CM) Children with malaria and complicated	Children without CM and M/S	There were two exposure groups in this study

			seizures (C/S)		
Chandy et al., 2008 [25]	Prospective study	Children with ages between 5 and 12 years	Cerebral malaria children (CM) Children with uncomplicated malaria (UM)	Children without CM and UM	There were two exposure groups
Kihara et al., 2010 [26]	Retrospective case control	Children with ages between 6 and 7 years	Children with severe falciparum malaria (Cerebral malaria - 27, peripheral falciparum malaria- 14, Peripheral falciparum malaria - 9)	Children without severe falciparum malaria	