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SYSTEMATIC REVIEW

REVISED Is diabetes associated with malaria and malaria severity? A systematic review of observational studies [version 3; peer review: 2 approved]

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Abstract

Background: We conducted a systematic review to study the association between diabetes and malaria as well as malaria severity.
Methods: The search was conducted in Embase, Global Health, MEDLINE, Scopus and Web of Science. Titles and abstracts were screened, full-text studied and information extracted for qualitative synthesis. Risk of bias was assessed with ROBINS-I criteria. The exposure was diabetes and the outcome malaria or malaria severity.
Results: Of 1992 results, three studies were included (n=7,226). Two studies found strong associations: people with diabetes had higher odds of malaria (adjusted odds ratio (aOR): 1.46 (95% CI: 1.06-2.03)) and severe malaria (aOR: 2.98 (95% CI: 1.25-7.09)). One study did not find conclusive evidence: aOR for severe malaria was 0.95 (95% CI: 0.71-1.28). Risk of bias was high in all the studies.
Conclusions: Although the available evidence on the association between diabetes and malaria is limited, the results may suggest there is a non-trivial positive relationship between these conditions.

Keywords

malaria, diabetes, multi-morbidity, co-morbidity, syndemics, Peru

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Author roles: Carrillo-Larco RM: Conceptualization, Investigation, Writing – Original Draft Preparation, Writing – Review & Editing; **Altez-Fernandez C**: Investigation, Writing – Review & Editing; **Ugarte-Gil C**: Conceptualization, Writing – Review & Editing

How to cite this article: Carrillo-Larco RM, Altez-Fernandez C and Ugarte-Gil C. **Is diabetes associated with malaria and malaria severity? A systematic review of observational studies [version 3; peer review: 2 approved]** Wellcome Open Research 2019, **4**:136 (https://doi.org/10.12688/wellcomeopenres.15467.3)

First published: 19 Sep 2019, **4**:136 (https://doi.org/10.12688/wellcomeopenres.15467.1)

REVISED **Amendments from Version 2**

One reviewer suggested that we make a clarification regarding the study selection. We have modified the corresponding lines to better reflect our methodology. We then modified the limitations section accordingly.

Any further responses from the reviewers can be found at the end of the article

Introduction

In a global context where non-communicable diseases lead the ranking of mortality and disease burden, malaria is a tropical disease still accountable for thousands of years of life lost and years lived with disability disproportionally affecting low- and middle-income countries (LMICs)[1,2]. The current multi-morbidity and syndemics paradigm calls to study diseases as clusters rather than isolate entities[3,4], and new links between diseases could signal innovative prevention paths, e.g., adequate control of socio-demographic determinants for both conditions. Moreover, this knowledge could also provide relevant evidence on treatment and management, e.g., medications and their interactions for subjects with both illnesses. Therefore, looking at unknown associations between non-communicable diseases and malaria seems relevant, particularly for diseases for which incidence has swiftly risen in the last decades such as diabetes[5–7]. Even though there is evidence about the increasing co-morbidity between diabetes and infectious diseases[7,8], the concept that diabetes could be a "risk factor" for malaria is relatively new[7,9]. Although relevant, available evidence is still sparse, including letters, brief reviews and animal models[10–12]. To the best of our knowledge, no systematic review has yet summarised the evidence on the association between diabetes and malaria. In so doing, the magnitude of this association could be explored, and research gaps identified. Consequently, we aimed to conduct a systematic review of observational studies addressing the association between diabetes and malaria as well as the association between diabetes and malaria severity.

Methods
Study design
This is a systematic review of the literature following the PRISMA guidelines[13] *Extended data* (p. 2); the checklist is available on Figshare[14]. This work was registered at PROPSERO (ID CRD42018105771).

Search strategy
The search was conducted in Ovid, including Embase, Global Health and MEDLINE, as well as in Scopus and Web of Science; for specific terms used in these search engines please refer to *Extended data* (pp. 4–7). The search was conducted from inception to July 31st 2018, and no language restrictions were set. However, the search in Ovid was restricted to human subjects; the search in Scopus was restricted to articles and medicine as subject area; and the search in Web of Science was restricted to articles.

Selection criteria
We sought studies that included humans subjects, had a comparator group (e.g., healthy individuals or subjects without

diabetes), and the outcome was malaria diagnosis or severity. In detail, studies were selected if they included human subjects regardless of where they had been enrolled, i.e., these could have been population-based/community studies or hospital-based samples; no age restrictions were set. The study followed an observational design, e.g., cross-sectional, case-control or cohort study. Case reports and non-comparative studies were excluded. The exposure variable was diabetes defined as either a laboratory test (e.g., fasting plasma glucose ≥126 mg/dL), self-reported diagnosis or currently receiving medication for diabetes; these variables could have been actively collected or retrieved from medical records. The exposure of interest could have been any kind of diabetes (e.g., type 1 or type 2). The outcome was either malaria diagnosis or malaria severity regardless of the species as defined in each original report; for example, cases could should have had laboratory confirmation (e.g., blood smears, rapid diagnostic tests or polymerase chain reactions (PCR)) or based on clinical or discharge records.

Data collection
Using the Rayyan online tool[15], two reviewers (RMC-L and CA-F) independently screened titles and abstracts retrieved from the search strategy (agreement 0.99 and Kappa 0.99, *Extended data (p. 8)*). The full text of the studies that both reviewers agreed met selection criteria were sought; in addition, studies on which both reviewers had a discrepant opinion were also retrieved in full text. These full texts were studied by two reviewers (RMC-L and CA-F) independently to select those for final inclusion. The authors agreed on items that needed to be extracted from each study and RMC-L sought these pieces of information; all the authors reviewed the extraction process.

Risk of bias was assessed using the ROBINS-I criteria[16]; nevertheless, the "Bias due to deviations from intended interventions" criterion was not considered because it did not apply to the studies herein included. RMC-L conducted the risk of bias assessment and all the authors reviewed the results.

The results are presented as a qualitative synthesis. No meta-analysis was planned because very few studies were expected, with high variability among them. Therefore, summary estimates (e.g., odds ratio) are summarized and presented as they were reported by each original study.

Results
Search strategy
The search strategy retrieved 2108 results, 1992 were screened and 10 selected for in-depth scrutiny; finally, three studies were included for qualitative synthesis. Figure 1 depicts the number of studies at each stage of the screening process.

Study characteristics
Table 1 shows the overall characteristics of the selected studies. Of the three studies, two were conducted in high-income countries: USA[17] and Sweden[18]; whereas one was in Africa (Ghana)[19]. All of them were published in the last 8 years and followed a retrospective design. There was heterogeneity in diabetes definition, including blood tests (e.g., fasting glucose) and history based on clinical records.
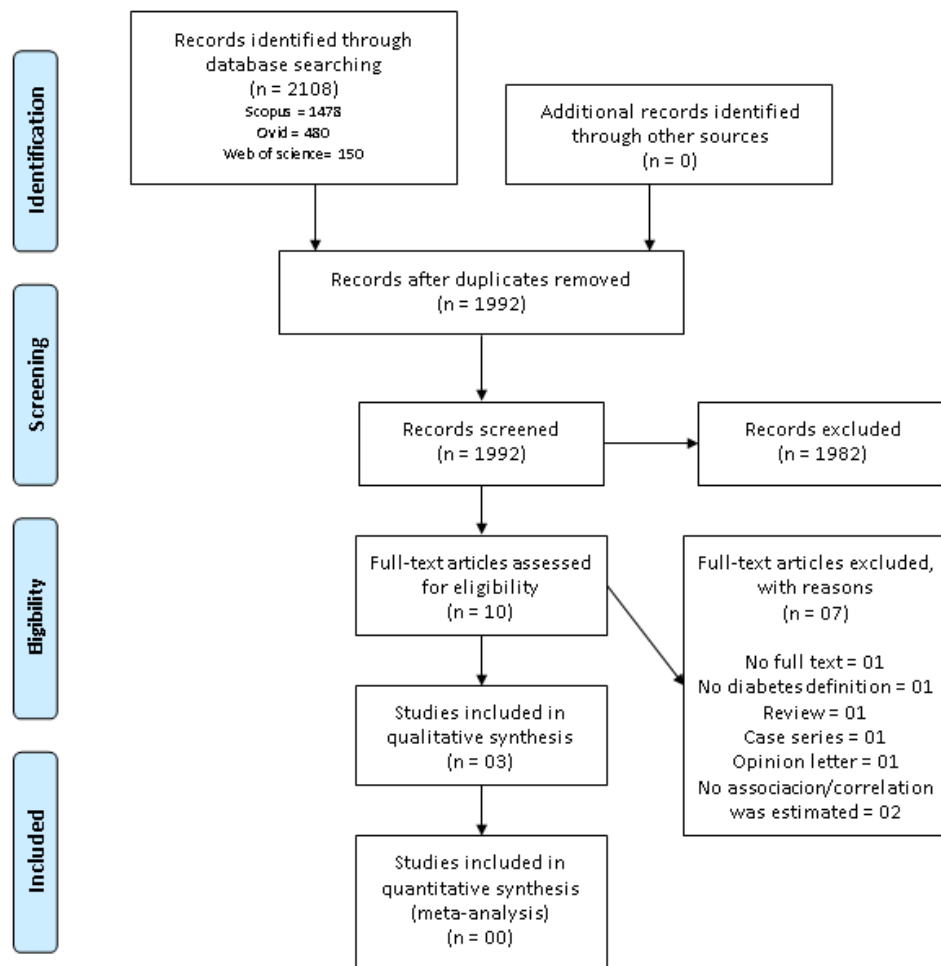
Figure 1. Flow chart of the study selection process.

Diabetes and malaria susceptibility

One of the three selected reports showed a strong positive association between diabetes and malaria susceptibility. People with type 2 diabetes had higher odds of malaria: adjusted odds ratios (aOR) = 1.46; 95% CI: 1.06-2.03 (Table 1)[19].

Diabetes and malaria severity

Of the three selected reports, one provided strong evidence that people with diabetes (including type 1 and 2) had higher odds of severe malaria, aOR = 2.98; 95% CI: 1.25-7.09[18]. One study did not find a strong association, reporting that type 2 diabetes and severe malaria had an aOR = 0.95; 95% CI: 0.71-1.28 (Table 1)[17].

Risk of bias

The risk of bias assessment showed that the three retrieved studies had critical risk of bias. They all had low bias in classification of the intervention, and they presented poor information to assess bias due to missing data. Conversely, the report by Wyss and colleagues was deemed as low risk of bias in the participant selection domain[18]. Table 2 summarizes all criteria for risk of bias assessment, and specific items within each criterion are shown in *Extended data* (pp. 9–11)[14].

Discussion

Summary of evidence

There were three reports addressing the association between diabetes and malaria, one studied malaria diagnosis[19] whereas two malaria severity or complications[17,18]. There was a strong positive association between diabetes and malaria diagnosis[19], and only one study found compelling evidence of an association between diabetes and malaria severity[18]. Across these three studies, overall risk of bias was high.

Limitations

The study designs followed by the reviewed studies were case-control[19] and retrospective analyses[17,18]. Although these methodologies provide relevant evidence and have several strengths, regarding the topic at hand the evidence they offer still needs further verification with stronger observational approaches.

Table 1. Characteristic of the studies included in the systematic review and reported measures of association.

Study	Country	Design	Setting	Study population	Sample size	% diabetes/ % malaria	Exposure	Outcome	Main result
Malaria Susceptibility									
Danquah I, et al.[19] (2010)	Ghana	Case-control study	Health centre	Men and women aged ≥18 years	1,466	46% / by PCR 14.1% had Plasmodium spp. infection (91.8% P. falciparum)	Type 2 diabetes: treatment or fasting plasma glucose ≥7 mmol/L	Malaria: PCR was used to identify Plasmodium infection and species	Type 2 diabetes was associated with higher odds of Plasmodium falciparum infection: aOR = 1.46 (95% CI: 1.06-2.03)
Malaria Severity									
Wyss K, et al.[18] (2017)	Sweden	Retrospective observational study	National surveillance data (Public Health Agency)	All adults (≥18 years) with Plasmodium falciparum microbiologically confirmed	937 individuals with P. falciparum, of which 9.8% were severe	In severe cases 9.8% had diabetes	Diabetes: as per the ICD-10 codes registered, including type 1, type 2 and unspecified	Severe malaria: 2012 WHO criteria (modified by the authors)	Regardless of hyperparasitemia, diabetes was associated with higher odds of severe malaria: aOR = 2.98 (95% CI: 1.25-7.09)
Khuu D, et al.[17] (2018)	USA	Retrospective observational study	Based on hospital records from State Inpatient Database	Men and women whose discharge records had malaria (ICD-9 codes) as the primary or secondary diagnoses	4,823 severe malaria hospitalizations	Among severe malaria inpatients, 10.4% type 2 diabetes	Based on the hospital records; no further details	Severe malaria: CDC criteria (modified by the authors). Malaria complications: where the discharge record noted malaria plus one or more complications (e.g., neurological symptoms)	Type 2 diabetes was not associated with severe malaria or malaria plus complications: aOR = 0.95 (95% CI: 0.71-1.28) [severe malaria]; aOR = 1.06 (95% CI: 0.60-1.88) [malaria with ARDS]; aOR = 0.93 (95% CI: 0.55-1.57) [cerebral malaria]; aOR = 1.16 (95% CI: 0.75-1.80) [malaria with severe anaemia]; aOR = 1.20 (95% CI: 0.82-1.74) [malaria with renal failure]; aOR = 0.83 (95% CI: 0.36-1.92) [malaria with jaundice]

Table 2. Risk of bias assessment.

Variable	Study		
	Danquah I, *et al.*[19]	Wyss K, *et al.*[18]	Khuu D, *et al.*[17]
Bias due to confounding	Serious risk of bias	Serious risk of bias	Serious risk of bias
Bias in selection of participants into the study	Critical risk of bias	Low risk of bias	Critical risk of bias
Bias in classification of interventions	Low risk of bias	Low risk of bias	Low risk of bias
Bias due to missing data	No information	No information	No information
Bias in measurement of outcomes	Moderate risk of bias	Moderate risk of bias	Moderate risk of bias
Bias in selection of the reported result	Moderate risk of bias	Moderate risk of bias	Moderate risk of bias
Judgement	**Critical risk of bias**	**Critical risk of bias**	**Critical risk of bias**

These could include prospective cohorts or thoroughly conceived analysis following a casual-inference methodology. On the other hand, we acknowledge that the reviewed studies ascertained both the exposure and outcome following valid methodologies, which in turn suggests that addressing the association of interest is feasible and supports our call for further studies in this field.

Differences in malaria severity definition could limit our conclusions too. One report ascertained malaria severity with laboratory tests[18], and the other extracted the information from hospital discharge records[17]. The second report was included in the review because hospital records are most likely to be based on laboratory tests, even though this was not disclosed in the publication. The different methodologies these studies followed could explain why the former report showed a strong association whereas the latter failed to show compelling evidence, even though they both had a similar proportion of people with diabetes among severe malaria cases[17,18].

This review has some strengths and limitations. First, we searched five international search engines, which allowed us to cover thousands of published materials. Therefore, our results show what there is available at a global scale and thus signal a dearth of strong evidence on the association between diabetes and malaria. Second, there are several tools to assess risk of bias. The one we followed, ROBINS-I, is a domain-based approach which seems to be a better approach in comparison to tools without domains; nevertheless, it has also been suggested that ROBINS-I labels more studies as of high risk of bias[20]. Regardless of the assessed domains and other properties of the ROBINS-I, the study design (e.g., case-control) followed by the reviewed reports already suggest high risk of bias. This is not a critique on the available evidence, but rather a call to build on the available literature and conduct more comprehensive research. Third, we defined malaria and malaria severity as in the original publications. Differences in malaria definitions could explain some results as discussed above[17,18]. Nonetheless, two of the three selected reports confirmed their cases with laboratory methods while one used discharge records. The positive and strong association these two publications found[18,19], supports the potential association between diabetes and malaria, while also signalling the dearth of evidence on this subject.

Implications for research

This systematic review found three studies following a case-control[19] and retrospective analysis approach[17,18]. Although they did a great effort to ascertain the exposure and outcome with precision, e.g., using biomarkers for diabetes or PCR for malaria, they lacked generalizability because their study populations were based on (small) patients samples instead of general population samples. The selected reports also followed the most suitable research design given their locations; for example, a case-control study was feasible for Danquah and colleagues in Ghana where malaria is prevalent[19], though it would be challenging for other researchers in USA and Sweden where retrospective analysis based on clinical records is much efficient[17,18]. All these studies have provided relevant evidence and have sparked interest in this novel yet relevant study field: diabetes and malaria.

A relevant research approach, as suggested by Broz *et al.*, would be how to improve diabetes control in people with malaria[21]. Because malaria would imply haemolysis, this could impair the accuracy of HbA1c to inform about diabetes control; potential solutions could include daily glucose monitor or fructosamine[22]. We believe that a population-based cohort study that has assessed diabetes would be a key asset in further elucidating the (true) association between diabetes and malaria. We are confident that these studies are available somewhere, with interest in LMICs, and that soon they will produce evidence in order to identify whether addressing diabetes could reduce malaria burden.

Implications for public health and clinical practice

At this this time we believe it is premature to draw any strong conclusions for clinical practice or public health. Nevertheless, we could suggest strengthening malaria prevention strategies for people with diabetes, particularly in highly endemic areas or among travellers to these settings. In accordance to international guidelines suggesting prophylactic treatment for travels to malaria highly-endemic areas[23,24], these recommendations could be stronger for people with diabetes.

Diabetes and malaria: the epidemiological context

Global estimates inform that Africa is the region with the largest number of Malaria cases, where Nigeria, followed by the

Democratic Republic of Congo, accounts for most of these[25]. Although there has been a decrease since 1990, West and Central Africa exhibit the highest malaria death rates, with Mali, Burkina Faso and Niger leading the ranking[26]. On the other hand, epidemiological evidence shows that from 1980 to 2014, diabetes prevalence has doubled in most sub-Saharan nations[5,6]. Regarding the above highlighted countries, diabetes prevalence in Nigeria and the Democratic Republic of Congo has increased by 2- and 2.5-fold, respectively; these estimates for Mali, Burkina Faso and Niger were 2.6-, 2.8- and 2.3-fold[5,6]. These country-level estimates could have several potential implications. First, countries with high malaria prevalence have experienced a dramatic increase in diabetes prevalence. Perhaps, this could imply that the rising diabetes burden makes it difficult to lessen malaria burden despite large efforts on this matter. Second, Burkina Faso, one of the countries with high malaria death rates have also had an utterly increase in diabetes prevalence. This could suggest that the increasing diabetes burden may be leading to more severe cases with fatal outcomes. Third, as diabetes prevalence keeps rising in malaria endemic areas, larger populations could be at high risk of malaria. This could lead to call to strengthen diabetes prevention and early diagnosis programs, not only to stop non-communicable diseases but also because of a potential positive impact on malaria control. These ecological arguments, along with the evidence summarized in this review, suggest of a possible co-morbidity (if not synergism) between diabetes and malaria that deserves further and comprehensive scrutiny.

Diabetes and malaria: pathways

The aim of this review was to synthetize the evidence about diabetes as an associated factor with higher malaria prevalence, incidence or severity. Even though we could not assess diabetes as a 'risk factor' in the strict definition of the term because of the lack of prospective studies, we summarized preliminary evidence that suggest diabetes could be associated with malaria and malaria severity. In addition to this finding, biological pathways have been proposed to explain this association.

Olivier and colleagues summarized key aspects of immune response in malaria, highlighting features of early infection including that phagocytes such as monocytes, macrophages and neutrophils lead the immunological response[27]; this role of monocytes and macrophages during erythrocyte infection has been studied before, particularly in response to *Plasmodium* hemozoin and Glycosylphosphatidylinositol[28–31]. However, macrophage phagocytic activity seems to be reduced in diabetics[32–35], and this is paramount in the association between diabetes and tuberculosis[36]. This impaired immunity, particularly regarding those cells with responsibilities against malaria, could explain the association between diabetes and malaria[11]. These arguments, i.e. impaired immunity, support solid hypotheses to explain higher malaria susceptibility and malaria severity among people with diabetes.

Other possible pathways between diabetes and malaria include hyperinsulinemia, which has been suggested to affect mosquitos

in a way that they have a reduced immune response against *Plasmodium falciparum*[37]. This implies there would be more mosquitos to spread malaria. Although we are unaware of robust evidence to support this potential explanation, Raghunath hypothesised that diabetics who take metformin would attract more mosquitos because this medication increases the concentration of lactic acid in their sweat, a compound that attracts mosquitoes[10]; however, biguanides appear to positively interact with anti-malaria drugs[38]. These additional arguments to support the association between diabetes and malaria render further importance to the study of this co-morbidity; not only because this would enrich science, but because it could also provide innovative prevention or treatment strategies.

Conclusions

Despite conducting a comprehensive systematic review, the results showed there is paucity in the evidence about the association between diabetes and malaria as well as between diabetes and malaria severity. Of the three reviewed studies, one found a strong association between diabetes and malaria diagnosis, and one between diabetes and malaria severity; one study did not find strong evidence of association between diabetes and malaria severity. The three studies had high risk of bias, with one following a case-control design while the other two conducted a retrospective analysis. This limited evidence precludes drawing a strong conclusion on the associations of interest. Although there is evidence signalling biologically plausible pathways between diabetes and malaria as well as malaria severity. It is still premature to make clinical or public health recommendations to address the (possible) synergism between diabetes and malaria. On the other hand, this review signals the dearth of evidence on this association, both in terms of quantity and quality of available research; this calls to further study these associations and others between communicable and non-communicable diseases particularly in places with high or raising burden of both.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Extended data

Figshare: IS DIABETES ASSOCIATED WITH MALARIA AND MALARIA SEVERITY? A SYSTEMATIC REVIEW OF OBSERVATIONAL STUDIES - SUPPLEMENTARY MATERIAL. https://doi.org/10.6084/m9.figshare.9789740.v2[14].

Reporting guidelines

Figshare: PRISMA checklist for 'Is diabetes associated with malaria and malaria severity? A systematic review of observational studies'. https://doi.org/10.6084/m9.figshare.9789740.v1[14].

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Open Peer Review

Current Peer Review Status: ✔ ✔

Version 3

Reviewer Report 13 January 2020

https://doi.org/10.21956/wellcomeopenres.17124.r37372

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Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 2

Reviewer Report 02 December 2019

https://doi.org/10.21956/wellcomeopenres.17091.r37148

? **Katja Wyss**

Division of Infectious Diseases, Department of Medicine Solna, Karolinska Institute, Stockholm, Sweden

I think the authors adequately have addressed my questions and revised the manuscript accordingly except for one aspect: Concerning the definition of malaria, the authors state that "because the work by Khuu and colleagues[1] was based on hospital discharge records from a high-income country, we strongly believe these cases were based on laboratory tests hence the inclusion on the review. In fact, because they based the cases selection on ICD codes, these should have been based on laboratory tests to confirm the diagnostics." I do not object to the inclusion of the study by Khuu et al, however I strongly advocate the authors to correct the selection criteria in the method section. A malaria ICD code cannot be assumed to be the same as microbiological confirmed malaria, discharge records usually include several

discharge diagnosis and these constitute the basis for financial compensation in many high-income countries, thus could also include for example previous malaria in the medical history of the patient or an investigation for suspected malaria. Khuu et al have also discussed this in the limitation section of their paper. Also of importance; if the authors have excluded any studies using malaria ICD codes instead of microbiological confirmed malaria it would not be correct to revise the selection criteria but instead specify that an exception was done for the study by Khuu et al.

References

1. Khuu D, Eberhard M, Bristow B, Javanbakht M, Ash L, Shafir S, Sorvillo F: Risk factors for severe malaria among hospitalized patients in the United States, 2000–2014. *Infection, Disease & Health*. 2018; **23** (2): 93-106 Publisher Full Text

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology of imported malaria and risk factors for severe malaria

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 02 Dec 2019

Rodrigo Carrillo-Larco, School of Public Health, Imperial College London, London, UK

We have modified the selection criteria section as well as the limitations of the study. The new lines read, respectively:

The outcome was either malaria diagnosis or malaria severity regardless of the species as defined in each original report; for example, cases could have had laboratory confirmation (e.g., blood smears, rapid diagnostic tests or polymerase chain reactions (PCR)) or based on clinical or discharge records.

Third, we defined malaria and malaria severity as in the original publications. Differences in malaria definitions could explain some results as discussed above [17, 18]. Nonetheless, two of the three selected reports confirmed their cases with laboratory methods while one used discharge records. The positive and strong association these two publications found, [18, 19] supports the potential association between diabetes and malaria, while also signalling the dearth of evidence on this subject.

Competing Interests: No competing interests were disclosed.

Reviewer Report 26 November 2019

https://doi.org/10.21956/wellcomeopenres.17091.r37149

✓   **Raghunath Pendru** iD

Faculty of Medicine, Department of Microbiology, Texila American University, Georgetown, Guyana

The authors have revised the manuscript according to reviewers' suggestion. The revised manuscript is significantly improved and I feel that this manuscript is suitable for indexing in the current form.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: My research interest is in the field of microbial pathogenesis and molecular genetics of bacterial pathogens especially enteric pathogens. Currently in Guyana, I am interested in studying the incidence of various infections in patients with type 1 and type 2 diabetes with special reference to respiratory infections and candidiasis.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 18 November 2019

?   **Raghunath Pendru** iD

Faculty of Medicine, Department of Microbiology, Texila American University, Georgetown, Guyana

This study is a systematic review to find an association between diabetes and Malaria. Study is highly relevant because diabetes patients are susceptible to various infections because of dysregulation of immune response. Authors have finally selected only three articles addressing the association between diabetes and malaria. One of those articles focused on malaria diagnosis and two others studied malaria severity or complications. Only one study found compelling evidence of an association between diabetes and malaria severity. Authors need to clarify why they have finally selected only three studies for qualitative synthesis from 1992 studies. Ten articles that were selected for in-depth scrutiny should be considered for synthesizing the data. I recommend that they should also include those seven full-text articles for analysis and submit the results as supplementary materials.

Though it is a systemic review, after analysis of the selected articles, authors should be able to form good hypotheses to explain the reasons for high susceptibility of diabetics to malaria infection. They should also be able to explain the reasons for high severity and complications of malaria in diabetics. This study is well designed and deserves indexing after incorporating results from more studies.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: My research interest is in the field of microbial pathogenesis and molecular genetics of bacterial pathogens especially enteric pathogens. Currently in Guyana, I am interested in studying the incidence of various infections in patients with type 1 and type 2 diabetes with special reference to respiratory infections and candidiasis.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 19 Nov 2019
Rodrigo Carrillo-Larco, School of Public Health, Imperial College London, London, UK

Q1: Authors need to clarify why they have finally selected only three studies for qualitative synthesis from 1992 studies. Ten articles that were selected for in-depth scrutiny should be considered for synthesizing the data. I recommend that they should also include those seven full-text articles for analysis and submit the results as supplementary materials.

A1: The three studies finally included in the review were those which met the inclusion criteria detailed in the methodology. Of the ten studies that were selected after the titles/abstract screening, seven were excluded because these did not meet the inclusion criteria. To be consistent with our methodology, and inclusion/exclusion criteria as in any thorough systematic review, we cannot include more results in the review because these do not answer the research question. However, as suggested, we have listed the seven excluded reports in supplementary material (table below).

BORN WC. [Malaria and diabetes mellitus]. Z Tropenmed Parasitol. 1952;3(4):503-7. Undetermined Language. PubMed PMID: 14959277.

Alicke M, Boakye-Appiah JK, Abdul-Jalil I, Henze A, van der Giet M, Schulze MB, Schweigert FJ, Mockenhaupt FP, Bedu-Addo G, Danquah I. Adolescent health in rural Ghana: A cross-sectional study on the co-occurrence of infectious diseases, malnutrition and cardio-metabolic risk factors. PLoS One. 2017;12(7):e0180436. doi: 10.1371/journal.pone.0180436.

Adeleke SI, Asani MO, Belonwu RO, Gwarzo GD, Farouk ZL. Childhood diabetes mellitus in Kano, North West, Nigeria. Niger J Med. 2010;19(2):145-7.

Raghunath P. Impact of type 2 diabetes mellitus on the incidence of malaria. J Infect Public Health. 2017;10(3):357-358.

Ahmed AM, Elawad AM, Saeed OK. Malaria: a question of an etiological role in diabetes mellitus. East Mediterr Health J. 1999;5(4):821-2.

Kalra S, Khandelwal D, Singla R, Aggarwal S, Dutta D. Malaria and diabetes. J Pak Med Assoc. 2017;67(5):810-813.

Mohapatra, Manoj. (2001). Profile of severe falciparum malaria in diabetics. International Journal of Diabetes in Developing Countries. 21.

Q2: Though it is a systemic review, after analysis of the selected articles, authors should be able to form good hypotheses to explain the reasons for high susceptibility of diabetics to malaria infection. They should also be able to explain the reasons for high severity and complications of malaria in diabetics.

A2: We have made it clear what pathophysiological hypothesis could explain the associations of interest (page 10 updated manuscript).

Competing Interests: None.

Reviewer Report 05 November 2019

Katja Wyss

Division of Infectious Diseases, Department of Medicine Solna, Karolinska Institute, Stockholm, Sweden

This systematic review investigated if there is an association between diabetes and malaria as well as diabetes and severity of malaria. The objectives of the review are highly relevant considering the rapid increase in non-communicable diseases like diabetes in countries that at the same time are carrying a heavy malaria burden. However, although a comprehensive literature search was performed, only three studies fulfilled inclusion criteria, and the review has some additional important limitations that need to be addressed.

Abstract/Introduction:
It should be emphasised, as the authors have done in the title but not in the background of neither abstract nor main text, that the aim of the review includes two completely different research questions: 1) If diabetes affects malaria susceptibility and 2) If diabetes affects severity of malaria.
The sentence in the background section of the abstract needs to be rephrased: "We conducted a

systematic review to study the association between diabetes as a risk factor for malaria", change to either *We conducted a systematic review to study the association between diabetes and …* or to *We conducted a systematic review to study if diabetes is a risk factor for…*

Methods:
Selection criteria: Concerning definition of outcome the authors need to specify how severe malaria was defined and revise the definition of malaria cases as laboratory confirmed, see below under results.
Data collection: Suggest that the authors specify in the methods section if screening of articles were done independently by the two reviewers and also include the proportion of agreement between reviewers in the screening process (not only as supplement).

Results:
Ten articles were selected and assessed for eligibility, it would be recommended to add (as supplementary materials) a list of the seven full-text articles that were excluded.

Study characteristics: The authors state that "In all the studies the malaria diagnosis was confirmed with blood tests, including PCR." This is however not correct; the malaria cases in the study by Khuu et al were identified by ICD-9 discharge diagnoses since laboratory results were not included in the NIS (Nationwide Inpatient Sample). This is an important difference and limits the comparison with the study by Wyss et al. In addition, this implies either that the authors need to exclude this study since the case definition does not fit with the one specified under methods, or they need to redo the literature search using a broader definition of malaria, including any additional studies with parasitological un-confirmed cases.

Diabetes and malaria susceptibility: It is important to point out to the readers that the increased risk in this group of diabetics concerned asymptomatic parasitaemia, none of the included subjects presented with fever.

Diabetes and malaria severity: The sentence "Of the selected reports, two provided evidence that people with diabetes had higher odds of severe malaria" should be rephrased. Only one of the papers presented a significantly higher odds of severe malaria for diabetics. However, one could mention that in both studies there was a higher proportion of diabetics among severe cases compared to non-severe. Also, it is important to point out that assessment of severe malaria was based on different methods in the two retrospective studies.

Risk of bias: I do not quite agree concerning the assessment of bias. Could the authors explain why there would be a selection bias in the study by Wyss *et al*. where all malaria cases reported to the national surveillance system were included? In contrast, including only hospital treated malaria patients could result in a selection bias. Also, concerning missing values, there is information about how missing values are handled in relevant tables and discussion for both the study by Khuu *et al*. and Wyss *et al*.

Discussion:
Considering that only three articles were reviewed, it would be appropriate to provide a more thorough analysis concerning the diverging results of the two studies assessing risk factors for severe malaria. Any suggestions to why these studies showed different results? Both reported 10% diabetes among severe cases, however a lower proportion of diabetics among non-severe cases in the study by Wyss *et al*. The authors should consider if the difference could be associated with the selection of malaria cases and definition of severe malaria.
Implications for research: Concerning generalizability, it is important to mention that the studies were done in different types of populations; while the cross-sectional studies were carried out in a non-endemic

setting the case-control study was performed in a malaria endemic area where asymptomatic infections are common and severe manifestations of malaria seldom seen among immunocompetent, non-pregnant adults. Different study designs are required depending on setting and which research question one intends to answer, which also should be pointed out in the discussion. Using a general population sample of diabetics or a population based cohort study as the authors suggested would not be a reasonable approach in a non-endemic setting where the incidence of malaria is extremely low. In an endemic setting the challenge is instead lack of reliable health and recording systems as well as difficulty in the diagnostics of clinical malaria due to both frequent reinfections and asymptomatic parasitaemia.

Epidemiological context: As the authors emphasize, the prevalence of diabetes is increasing in many countries with high malaria transmission. However, I would suggest the authors to be a bit more careful in drawing conclusions concerning malaria mortality based on country estimates of diabetes and malaria prevalence.

Pathways: The possible association of diabetes and risk of malaria infection, and risk of severe disease in an ongoing infection, implies completely different pathobiological mechanisms, which the authors should consider elaborating more on. As an example, there are several studies demonstrating that glucose levels affect parasite growth *in vitro,* which could have implications for malaria severity. Concerning the hypothesis that metformin use could attract mosquitos it would be reasonable to mention that the same drug also has antimalarial effect (Jones *et al* 2002).[1]

Conclusions:
Again, important to clarify that there were two different objectives in this review, and the included studies analysed two distinct outcomes, thus it is not justified to simply conclude that there is an association between diabetes and malaria.

References
1. Jones K, Ward SA: Biguanide-atovaquone synergy against Plasmodium falciparum in vitro.*Antimicrob Agents Chemother*. 2002; **46** (8): 2700-3 PubMed Abstract | Publisher Full Text

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Partly

Is the statistical analysis and its interpretation appropriate?
Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology of imported malaria and risk factors for severe malaria

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 19 Nov 2019

Rodrigo Carrillo-Larco, School of Public Health, Imperial College London, London, UK

<u>**Reviewer #1**</u>

Q1: It should be emphasised, as the authors have done in the title but not in the background of neither abstract nor main text, that the aim of the review includes two completely different research questions: 1) If diabetes affects malaria susceptibility and 2) If diabetes affects severity of malaria. The sentence in the background section of the abstract needs to be rephrased: "We conducted a systematic review to study the association between diabetes as a risk factor for malaria", change to either We conducted a systematic review to study the association between diabetes and … or to We conducted a systematic review to study if diabetes is a risk factor for…

A1: The 'background' section of the abstract, as well as the last sentence of the introduction, have been modified as suggested to reflect that the review focused on both outcomes: malaria and malaria severity.

Q2: Selection criteria: Concerning definition of outcome the authors need to specify how severe malaria was defined and revise the definition of malaria cases as laboratory confirmed, see below under results.

A2: Unlike malaria infection, for which we defined there should have been laboratory confirmation, we did not have a specific definition for malaria severity. We made the first decision to avoid bias or misclassification of malaria cases. However, we strongly believe that severe cases would be treated (and studied) in hospitals or other highly-specialized health facilities. Therefore, they are most likely to rely on laboratory tests to define severity, thus less likely to be subject of bias or misclassification. We have discussed these arguments in the 'limitations' section.

Q3: Data collection: Suggest that the authors specify in the methods section if screening of articles were done independently by the two reviewers and also include the proportion of agreement between reviewers in the screening process (not only as supplement).

A3: We have specified that both review stages (screening and full-text) were conducted by two reviewers independently. Also, as suggested, we have reported the agreement and Kappa metrics. Please refer to 'data collection' section for details.

Q4: Ten articles were selected and assessed for eligibility, it would be recommended to add (as supplementary materials) a list of the seven full-text articles that were excluded.

A4: We have included a list of the seven reports excluded at the second selection stage (full-text). The table below is in the updated supplementary material.

BORN WC. [Malaria and diabetes mellitus]. Z Tropenmed Parasitol. 1952;3(4):503-7. Undetermined Language. PubMed PMID: 14959277.

Alicke M, Boakye-Appiah JK, Abdul-Jalil I, Henze A, van der Giet M, Schulze MB, Schweigert FJ, Mockenhaupt FP, Bedu-Addo G, Danquah I. Adolescent health in rural Ghana: A cross-sectional study on the co-occurrence of infectious diseases, malnutrition and cardio-metabolic risk factors. PLoS One. 2017;12(7):e0180436. doi: 10.1371/journal.pone.0180436.

Adeleke SI, Asani MO, Belonwu RO, Gwarzo GD, Farouk ZL. Childhood diabetes mellitus in Kano, North West, Nigeria. Niger J Med. 2010;19(2):145-7.

Raghunath P. Impact of type 2 diabetes mellitus on the incidence of malaria. J Infect Public Health. 2017;10(3):357-358.

Ahmed AM, Elawad AM, Saeed OK. Malaria: a question of an etiological role in diabetes mellitus. East Mediterr Health J. 1999;5(4):821-2.

Kalra S, Khandelwal D, Singla R, Aggarwal S, Dutta D. Malaria and diabetes. J Pak Med Assoc. 2017;67(5):810-813.

Mohapatra, Manoj. (2001). Profile of severe falciparum malaria in diabetics. International Journal of Diabetes in Developing Countries. 21.

Q5: Study characteristics: The authors state that "In all the studies the malaria diagnosis was confirmed with blood tests, including PCR." This is however not correct; the malaria cases in the study by Khuu et al were identified by ICD-9 discharge diagnoses since laboratory results were not included in the NIS (Nationwide Inpatient Sample). This is an important difference and limits the comparison with the study by Wyss et al. In addition, this implies either that the authors need to exclude this study since the case definition does not fit with the one specified under methods, or they need to redo the literature search using a broader definition of malaria, including any additional studies with parasitological un-confirmed cases.

A5: We were aware of the point highlighted by the reviewer, and we agree there may be differences that are now pinpointed in the 'limitations' section. Nevertheless, because the work by Khuu and colleagues was based on hospital discharge records from a high-income country, we strongly believe these cases were based on laboratory tests hence the inclusion on the review. In fact, because they based the cases selection on ICD codes, these should have been based on laboratory tests to confirm the diagnostic.

Q6: Diabetes and malaria severity: The sentence "Of the selected reports, two provided evidence that people with diabetes had higher odds of severe malaria" should be rephrased. Only one of the papers presented a significantly higher odds of severe malaria for diabetics. However, one could mention that in both studies there was a higher proportion of diabetics among severe cases compared to non-severe. Also, it is important to point out that assessment of severe malaria was based on different methods in the two retrospective studies.

A6: We have rephased the corresponding lines in the 'results' section to signal that only one study showed strong association. In addition, as pointed out before (Q5), the 'limitations' section now includes a few lines about the differences in ascertainment methods.

Q7: Risk of bias: I do not quite agree concerning the assessment of bias. Could the authors explain why there would be a selection bias in the study by Wyss et al. where all malaria cases reported to the national surveillance system were included? In contrast, including only hospital treated malaria patients could result in a selection bias. Also, concerning missing values, there is information about how missing values are handled in relevant tables and discussion for both the study by Khuu et al. and Wyss et al.

A7: We considered there was high risk of bias because these were cases reported to the national surveillance system. However, after further consideration and studying, we believe the surveillance system in Sweden should be good enough to register all malaria cases, especially severe cases as studied by Wyss and colleagues. Therefore, we re-classified this study as "low risk of bias" in the "Bias in selection of participants into the study" domain (also updated in supplementary material).

We considered "no information" on bias due to missing data because:
1. Wyss et al conducted multiple imputation for missing values in BMI: "To account for missing BMI, a multiple imputation model with chained equations was performed based on variables related to sever malaria, obesity status, and missing BMI". However, we could not find similar information for diabetes (exposure of interest).

2. Khuu et al reported that multiple imputation was not possible because of limited computational power: "Imputation of missing variables was not feasible due to the large size of the NIS and limited computing power". We still considered this as "no information" because there were no further details about proportion of missing observations.

Q8: Considering that only three articles were reviewed, it would be appropriate to provide a more thorough analysis concerning the diverging results of the two studies assessing risk factors for severe malaria. Any suggestions to why these studies showed different results? Both reported 10% diabetes among severe cases, however a lower proportion of diabetics among non-severe cases in the study by Wyss et al. The authors should consider if the difference could be associated with the selection of malaria cases and definition of severe malaria.

A8: As pinpointed before, we have discussed in the 'limitations' section that a potential driver for the different results between these studies could be the definitions of severe malaria.

Q9: Implications for research: Concerning generalizability, it is important to mention that the studies were done in different types of populations; while the cross-sectional studies were carried out in a non-endemic setting the case-control study was performed in a malaria endemic area where asymptomatic infections are common and severe manifestations of malaria seldom seen among immunocompetent, non-pregnant adults. Different study designs are required depending on setting and which research question one intends to answer, which also should be pointed out in the discussion. Using a general population sample of diabetics or a population-based cohort study as the authors

suggested would not be a reasonable approach in a non-endemic setting where the incidence of malaria is extremely low. In an endemic setting the challenge is instead lack of reliable health and recording systems as well as difficulty in the diagnostics of clinical malaria due to both frequent reinfections and asymptomatic parasitaemia.

A9: As suggested, in the 'implications for research' section we have included a few lines highlighting the differences and strengths of study designs. We agree that a population-based cohort in a non-endemic area would not be reasonable. However, experience has shown us that population-based cohorts in endemic settings where resources are not abundant as in high-income countries, are feasible and provide strong local evidence.

Q10: Epidemiological context: As the authors emphasize, the prevalence of diabetes is increasing in many countries with high malaria transmission. However, I would suggest the authors to be a bit more careful in drawing conclusions concerning malaria mortality based on country estimates of diabetes and malaria prevalence.

A10: We have toned down these lines to be more careful in drawing conclusions concerning malaria mortality based on country estimates.

Q11: Pathways: The possible association of diabetes and risk of malaria infection, and risk of severe disease in an ongoing infection, implies completely different pathobiological mechanisms, which the authors should consider elaborating more on. As an example, there are several studies demonstrating that glucose levels affect parasite growth in vitro, which could have implications for malaria severity. Concerning the hypothesis that metformin use could attract mosquitos it would be reasonable to mention that the same drug also has antimalarial effect (Jones et al 2002).

A11: We would rather not further elaborate on the mechanisms behind the associations of interest. This work intended to give an epidemiological overview, instead of a comprehensive pathophysiological explanation. Concerning the hypothesis that metformin could attract mosquitos, we have now mentioned the antimalarial effects and included the suggested reference.

Q12: Again, important to clarify that there were two different objectives in this review, and the included studies analysed two distinct outcomes, thus it is not justified to simply conclude that there is an association between diabetes and malaria.

A12: As we did in the abstract and introduction, we have also clarified in the conclusion that there were two aims (diabetes-malaria and diabetes-malaria severity).

Competing Interests: None.