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ORIGINAL RESEARCH ARTICLE

Heart failure associated with imported malaria: a nationwide Danish cohort study

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Abstract

Aims Despite adequate treatment, recent studies have hypothesized that malaria may affect long-term cardiovascular function. We aimed to investigate the long-term risk of cardiovascular events and death in individuals with a history of imported malaria in Denmark.

Methods Using nationwide Danish registries, we followed individuals with a history of malaria for the risk of incident heart failure (HF), myocardial infarction (MI), cardiovascular death and all-cause death (1 January 1994 to 1 January 2017). The population was age- and sex-matched with individuals without a history of malaria from the Danish population (ratio 1:9). We excluded patients with known HF and ischaemic heart disease at inclusion.

Results We identified 3912 cases with a history of malaria (mean age 33 ± 17 years, 57% male, 41% *Plasmodium falciparum* infections). The median follow-up was 9.8 years (interquartile range 3.9–16.4 years). Event rates per 1000 person-years for individuals with a history vs. no history of malaria were HF: 1.84 vs. 1.32; MI: 1.28 vs. 1.30; cardiovascular death: 1.40 vs. 1.77; and all-cause death: 5.04 vs. 5.28. In Cox proportional hazards models adjusted for cardiovascular risk factors, concomitant pharmacotherapy, region of origin, household income and educational level, malaria was associated with HF (HR: 1.59 [1.21–2.09], $P = 0.001$), but not MI (HR: 1.00 [0.72–1.39], $P = 1.00$), cardiovascular death (HR: 1.00 [0.74–1.35], $P = 0.98$) or all-cause death (HR 1.11 [0.94–1.30], $P = 0.21$). Specifically, *P. falciparum* infection was associated with increased risk of HF (HR: 1.64 [1.14–2.36], $P = 0.008$).

Conclusion Individuals with a history of imported malaria, specifically *P. falciparum*, may have an increased risk of incident HF.

Keywords Malaria; Heart failure; Prognosis; Infectious diseases; Epidemiology

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Introduction

Despite recent progress in reducing the burden of malaria globally, malaria remains one of the leading causes of morbidity and mortality in the world, with an estimated 220 million cases and 405 000 deaths reported each year.[1] Specifically, malaria is widespread in low- and middle-income countries, the same regions where three-fourths of all cardiovascular deaths occur.[2,3] Although malaria is most common in subtropical and tropical regions, it may also be found in temperate regions because of globalization and worldwide travelling, leading to importation.[4] Several

observational studies have reported links between infectious diseases and cardiovascular conditions, but so far, only a few small-scale clinical studies have investigated the relationship between malaria and cardiovascular health.[5–7] It is known that severe malaria can affect the cardiac conduction system[8] and may cause myocardial infarction (MI).[9] A link to impairment of cardiac function has also been suggested: One study found that travellers with imported malaria infections more frequently had impaired cardiac output compared with healthy controls,[10] and a case report described how malaria was responsible for heart failure (HF).[11] Although cardiac symptoms in the acute setting of malaria have been described to some extent, no information is available regarding potential long-term cardiovascular impact.

Recently, two studies proposed that malaria might cause chronic endothelial inflammation and contribute to increased risk of hypertension,[12,13] two conditions that are related to HF. Despite this hypothetical link between malaria and HF, only sparse clinical information is available, and no studies have examined cardiovascular prognosis in individuals following a malaria infection. Based on this, we aimed to investigate if individuals with a history of malaria have an increased risk of cardiovascular morbidity and mortality by conducting a Danish nationwide register-based cohort study. Based on the prior studies linking malaria to endothelial dysfunction and hypertension, we hypothesized that malaria causes increased long-term risk of cardiovascular events, and specifically of incident HF.

Methods

Data sources

In Denmark, all individuals have a unique personal civil registration number that is assigned at birth or immigration. This registration number allows linkage of health and administrative data for each individual.[14] In this study, we obtained encrypted and anonymized data from four different registers: The National Patient Registry, the Danish National Population Registry, the Danish National Prescription Registry and the Danish National Causes of Death Registry. In addition, we used data from the World Health Organization (WHO).[15] Additional information, definitions and overview of applied registers are available in the Supporting Information, section 'Data sources'.

Baseline data

We collected baseline data for the study cohort on household income, highest educational level and country of origin, defined as country of birth, for all individuals. Country of origin was categorized according to geographical regions. Additional details are provided in the Supporting Information (section 'Baseline data' and *Tables S1*–S3).

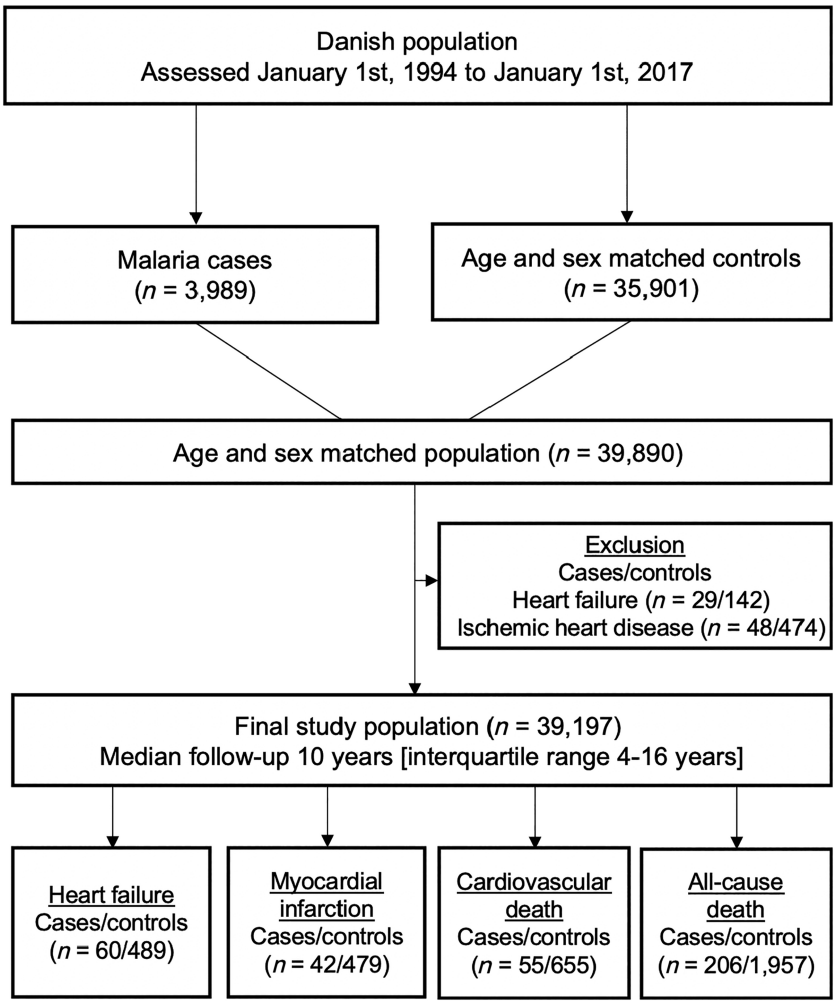
Study subjects

The malaria diagnosis was based on parasitological laboratory confirmation in suspected patients, based on travel history, clinical signs and symptoms. The standard diagnostic test used was malaria microscopy, but with additional diagnostic methods also used, including malaria parasite antigen detection by rapid diagnostic test, assessment of malaria antibody titres by serology and malaria parasite DNA detection by PCR.[16] We retrieved information about in- and outpatient hospital contacts in the Danish National Patient Registry, which includes the entire Danish population, from 1 January 1994 to 1 January 2017. We used the International Classification of Disease 10th revision (ICD-10) diagnosis coding system to identify malaria patients infected with *Plasmodium falciparum* (B50), *Plasmodium vivax* (B51), *Plasmodium malariae* (B52), *Plasmodium ovale* (B53) and non-specified malaria (B54), respectively (total n = 3989). B54 was assigned to cases in which the identification of the malaria species was deemed indeterminate. A subgroup (B549) had no laboratory test performed for malaria. Data on malaria cases (1994–2014) from Danish registries and the WHO[15] are listed in *Table S4*. Persons with $>$30 days between separate diagnoses of malaria were categorized as having $>$1 episode of malaria. We included both primary and secondary diagnosis codes of the individual patient. Study inclusion date was the date of malaria diagnosis, and the same applied to individuals with no history of malaria. For every individual diagnosed with malaria in Danish registries, we identified nine individuals from the general Danish population with no prior record of malaria in the registries (n = 35 901). Individuals with no history of malaria were individually matched by sex and year of birth. Individuals with a history/no history of malaria, who had known HF (n = 29/142) or with ischaemic heart disease (n = 48/474) were excluded, thus yielding a final study population of 39 197 individuals (*Figure 1*).

Endpoints

We examined the following endpoints: HF, MI, cardiovascular death and all-cause death. From the Danish National Patient Registry, we obtained information on HF (ICD-10 codes I500–I509, I110, I130, I132, I420, I426–I429) and MI (ICD-10 codes I21–I23). Information on causes of death and all-cause death were obtained from the Danish National Causes of Death Registry, where cardiovascular death was coded as ICD-10 codes I00–I99. All individuals

Figure 1 Flowchart of eligible individuals from the Danish population.



were followed from time of inclusion until death, emigration or the end of the follow-up period, which was 1 January 2017. The positive predictive values in Danish registries are 80%–100% for HF and 98%–100% for acute myocardial infarction.[17]

Statistical analysis

Individuals with a history of malaria were matched to individuals with no history of malaria by age and sex at a ratio of 1:9. Individuals with no history of malaria were selected without replacement. Matching was performed using a risk set sampling method (exposure density matching). Baseline characteristics for the age- and sex-matched population after exclusion of HF and ischaemic heart disease are displayed in *Table 1*. Differences between groups for continuous variables were compared using Student's *t*-test or Wilcoxon rank sum test as appropriate. Categorical variables were compared using chi-square test. We used Cox proportional hazards regression models to assess the association between malaria and the risk of endpoint events at follow-up. The date of malaria diagnosis was the start of follow-up. The proportional hazards assumption was tested on the basis of Schoenfeld residuals. Our multivariable Cox proportional hazards models were adjusted for hypertension, diabetes, cerebrovascular disease, chronic kidney disease, rheumatic heart disease, peripheral vascular disease, chronic obstructive pulmonary disease, cardiovascular pharmacotherapy (anti-thrombotic, beta blocker, calcium blocker, anti-arrhythmic, thiazide, renin–angiotensin system inhibitors, diuretics), region of origin, household income and educational level. Pharmacotherapy was adjusted for as individual treatments and were assessed prior to date of inclusion. Region of origin included

Table 1 Baseline characteristics and event rates stratified by history of malaria as derived from Danish registries

	No history of malaria (n = 35 285)	History of malaria (n = 3912)	P
Baseline information			
Age, years	33 ± 18	33 ± 17	0.88
Male, *n* (%)	20 256 (57%)	2246 (57%)	0.99
Co-morbidity			
Hypertension, *n* (%)	557 (2%)	56 (1%)	0.48
Diabetes, *n* (%)	461 (1%)	65 (2%)	0.07
Peripheral vascular disease, *n* (%)	155 (<1%)	14 (<1%)	0.56
Cerebrovascular disease, *n* (%)	211 (1%)	24 (1%)	0.91
Chronic kidney disease, *n* (%)	42 (<1%)	5 (<1%)	0.88
Chronic obstructive pulmonary disease, *n* (%)	170 (1%)	17 (<1%)	0.68
History of rheumatic fever, *n* (%)	<3 (<1%)	<3 (<1%)	0.001
Medication			
Anti-thrombotic, *n* (%)	586 (2%)	47 (1%)	0.031
Thiazide, *n* (%)	489 (1%)	41 (1%)	0.08
Beta blocker, *n* (%)	557 (2%)	46 (1%)	0.052
Renin–angiotensin system inhibitor, *n* (%)	1041 (3%)	104 (3%)	0.30
Loop diuretics, *n* (%)	221 (1%)	21 (1%)	0.50
Spironolactone, *n* (%)	47 (<1%)	4 (<1%)	0.61
Anti-anginal, *n* (%)	28 (<1%)	<3 (<1%)	0.96
Lipid lowering, *n* (%)	663 (2%)	68 (2%)	0.54
Anti-arrhythmic, *n* (%)	9 (<1%)	4 (<1%)	0.01
Verapamil, *n* (%)	43 (<1%)	5 (<1%)	0.92
Diuretics, *n* (%)	711 (2%)	63 (2%)	0.08
Region of origin			<0.001
Europe, *n* (%)	32 022 (91%)	2712 (69%)	
Africa, *n* (%)	479 (1%)	884 (23%)	
Asia, *n* (%)	2,276 (7%)	286 (7%)	
North America, *n* (%)	210 (1%)	8 (<1%)	
South America, *n* (%)	92 (<1%)	6 (<1%)	
Australia/Oceania, n(%)	46 (<1%)	5 (<1%)	
Unknown, *n* (%)	160 (1%)	11 (<1%)	
Malaria species			
Plasmodium falciparum, *n* (%)	N/A	1571 (41%)	
Plasmodium vivax, *n* (%)	N/A	476 (12%)	
Plasmodium ovale, *n* (%)	N/A	176 (4%)	
Plasmodium malariae, *n* (%)	N/A	87 (2%)	
Non-specified, *n* (%)	N/A	1602 (41%)	
Household income			<0.001
Low, *n* (%)	11 832 (34%)	1416 (36%)	
Middle, *n* (%)	11 562 (33%)	1,381 (35%)	
High, *n* (%)	11 891 (34%)	1,115 (29%)	
Highest educational level			<0.001
Basic school < 10 years, *n* (%)	8480 (24%)	630 (16%)	
High school, +3 years, *n* (%)	3147 (9%)	609 (15%)	
Vocational education, *n* (%)	9074 (26%)	621 (16%)	
Short/medium higher, +2–4 years, *n* (%)	3976 (11%)	581 (15%)	
Longer higher, +5 years or more, *n* (%)	1353 (4%)	303 (8%)	
Unknown, *n* (%)	9255 (26%)	1168 (30%)	
Event rates per 1000 person-years			
Heart failure	1.32 (1.21, 1.45)	1.84 (1.43, 2.37)	
Myocardial infarction	1.30 (1.19, 1.42)	1.28 (0.95, 1.74)	
Cardiovascular death	1.77 (1.64, 1.91)	1.40 (1.05, 1.87)	
All-cause death	5.28 (5.05, 5.52)	5.04 (4.32, 5.87)	

the different regions as categorized in *Table 1*. Sensitivity analyses were conducted on subgroups of malaria except for *P. malariae* (small sample size). Additionally, we conducted sensitivity analyses where we excluded individuals with a history of non-specified malaria. The association between HF and cardiovascular death was examined in Cox models using HF status as a time-updated covariate. Stratified by exposure, we constructed a cumulated incidence curve for HF. Two-tailed P-values < 0.05 were considered statistically significant. Statistical analyses were performed using statistical software SAS (v. 9.4) and STATA (v. 14.2).

Ethics

Registry studies do not require ethical approval in Denmark. The study was approved by the Danish Data Protection Agency (2007-58-0015, local ref. No.: GEH 2014-017, I-Suite

no.: 02735). The authors had full access to the data and take full responsibility for their integrity. As the data are governed by the Statistics Denmark, it can only be made available if a formal request is filed with the Danish authorities.

Results

Baseline

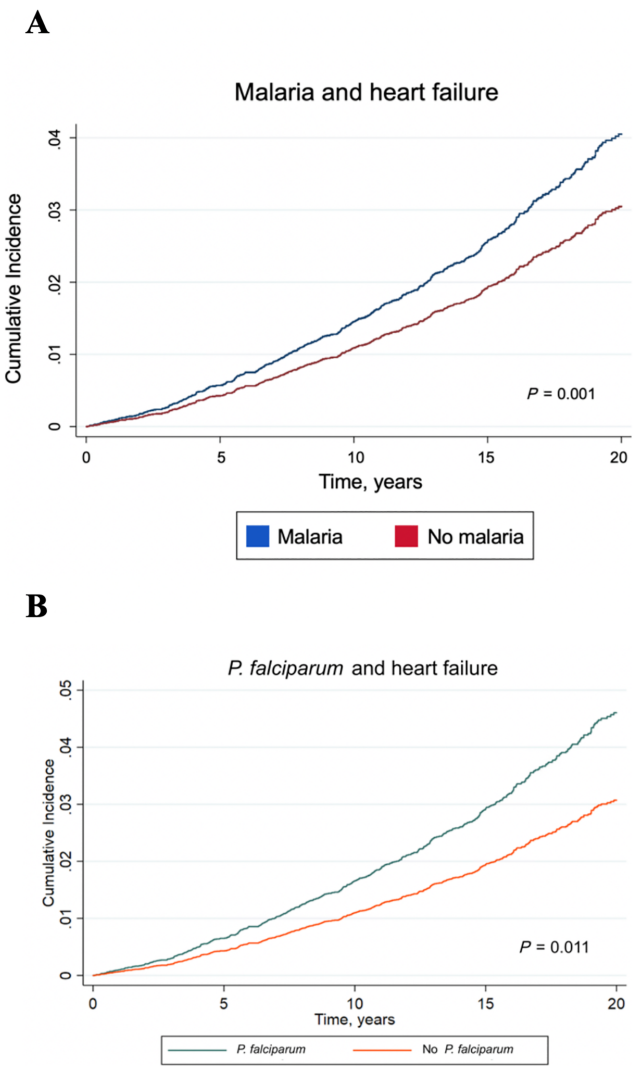
We identified 3912 patients with a history of malaria with a mean age of 33 ± 17 years and 57% males. Baseline characteristics for the study population are displayed in *Table 1*. Median duration of hospitalization following diagnosis of malaria was 2 days (interquartile range [IQR] 0–4 days). Characteristics for patients with non-specified malaria are displayed in *Table S5*. A total of 1571 (41%) individuals had a history of *P. falciparum* malaria infection, and 175 (4%) had experienced more than one episode of malaria. Individuals with a history of malaria used more anti-thrombotic medication and beta blockers. No difference was observed in the prevalence of hypertension. Individuals with a history of malaria were more often of Africa origin compared with individuals with no history of malaria, who mainly were of European origin.

A total of 808 (2%) emigrated from Denmark prior to the end of the study period and were thus only followed until the date of emigration. The median duration of follow-up for HF and MI was 9.9 years (IQR 4.2–16.4 years), and for cardiovascular death, it was 9.8 years (IQR 3.9–16.4 years). Follow-up was 100%. During follow-up of patients with a history of malaria, 60 (2%) developed HF, 42 (1%) had MI, 55 (1%) suffered cardiovascular death, and 206 (5%) died. Among the persons with no history of malaria, 489 (1%) developed HF, 479 (1%) had MI, 655 (2%) suffered cardiovascular death, and 1957 (6%) died (*Figure 1*). Causes of cardiovascular death for persons with a history of malaria were more often hypertensive heart disease (ICD-10: I10-I159) and less frequently coronary artery disease (ICD-10: I20-I289) compared with persons with no history of malaria (*Table S6*).

Risk of cardiovascular events and all-cause death

In univariable survival analyses, individuals with a history of malaria had a significantly increased risk of HF (HR: 1.35 [1.03–1.76], P = 0.031; *Figure 2*) but not of MI (HR: 0.93 [0.67–1.28], P = 0.65), cardiovascular death (HR: 0.80 [0.59–1.08], P = 0.14) or all-cause death (HR: 0.94 [0.80–1.10], P = 0.45). In multivariable models adjusted for cardiovascular risk factors, pharmacotherapy, region of origin, household income and educational level, the association with HF remained significant (HR 1.59 [1.21–2.09], P = 0.001). No associations were found with MI, cardiovascular death or all-cause death (*Figure 3*). When excluding patients with non-specified malaria, the association with HF remained significant (HR: 1.51 [1.07–2.12], P = 0.020). Individuals who developed HF had a significantly increased risk of experiencing cardiovascular death at follow-up (HR: 7.29 [5.99–8.88], $P < 0.001$; *Table S7*).

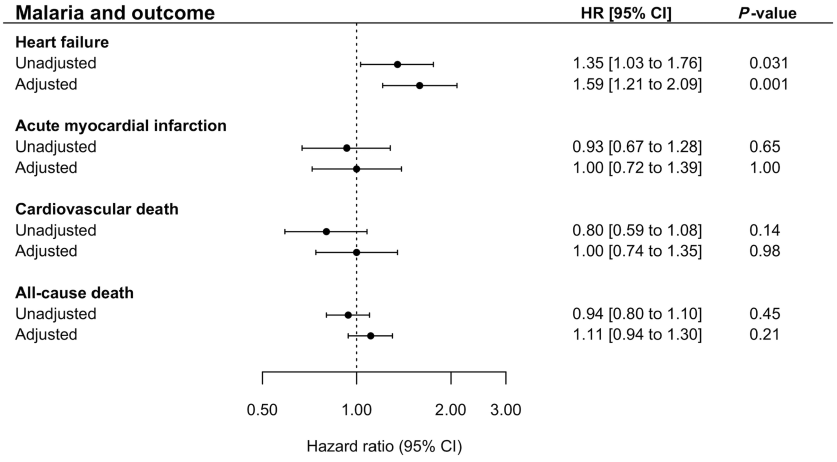
Figure 2 Cumulated incidence of heart failure by (A) malaria exposure and (B) *Plasmodium falciparum*.



Malaria species

P. falciparum malaria was associated with increased long-term risk of HF, both in unadjusted (HR: 1.59 [1.11–2.27], P = 0.011) and adjusted survival analyses (HR:

Figure 3 Malaria and the risk of heart failure, acute myocardial infarction, cardiovascular death and all-cause death. Unadjusted and adjusted models are presented. Error bars represent 95% confidence intervals. HR indicates hazard ratio.



1.64 [1.14–2.36], *P* = 0.008; *Figure 2B*). By contrast, *P. falciparum* malaria was not a predictor of MI (HR: 1.15 [0.75–1.76], *P* = 0.52), cardiovascular death (HR: 0.97 [0.65–1.45], *P* = 0.90) or all-cause death (HR: 0.93 [0.73–1.17], *P* = 0.53). In adjusted models, individuals with non-specified malaria also had a significantly increased risk of developing HF (HR: 1.56 [1.02–2.41], *P* = 0.042). Other types of malaria (*P. vivax*, *P. ovale*) were not predictors of any of the cardiovascular endpoints or death (*Table 2*).

Discussion

The key finding in this study is that a history of malaria was significantly associated with increased risk of incident HF in a Danish nationwide cohort study of 3912 patients with imported malaria compared with age- and sex-matched individuals without a history of malaria. Specifically, we found that a history of *P. falciparum* was associated with incident HF, whereas no effect was observed for *P. vivax* and *P. ovale*. To our knowledge, this is the first study that has evaluated the long-term risk of cardiovascular events and death in individuals with a history of malaria.

Only few observational and clinical studies have assessed malaria infections and cardiovascular disease, and recently, two reviews suggested that cardiovascular complications may be underreported in the setting of malaria.[18,19] Based on histopathological studies,[20,21] Sprague proposed that the capillary sequestration of infected erythrocytes can cause coronary occlusion and myocardial ischaemia.[22] This complication appeared specifically for *P. falciparum* infection, which is consistent with the fact that only erythrocytes infected with that species display efficient adhesion to endothelial receptors.[23] Autopsy reports in fatal malaria cases have demonstrated how myocardial capillaries have been blocked by parasite-infested red blood cells.[20,24] It has even been argued that the myocardial capillary system might be a favoured site for parasitic sequestration.[25] In line with this, studies of hospitalized malaria patients have reported higher rates of MI[26] and elevated levels of cardiac biomarkers[27,28] compared with controls. In contrast to these findings, we found no significant association with MI at follow-up. A possible reason for this may be that capillary sequestration is relieved following adequate therapy.[5,9] Studies have reported that ischaemic damage acquired during a malaria infection can lead to ischaemic cardiomyopathy and affect left ventricular function.[24,29] Also, myocardial injury may lead to scar formation and left ventricular remodelling and thus increase the risk of developing HF.

Two echocardiographic studies demonstrated how severe malaria may induce decreased contractility of the left ventricle.[5,29] Franzen *et al*.[5] conducted follow-up echocardiograms after 9 months and demonstrated that conventional echocardiographic parameters had returned to normal. However, prognosis was not assessed. Autopsies performed by Spitz *et al*.[25] revealed that a majority of patients exposed to malaria had interstitial myocardial oedema. Another study by Sharma *et al*.[24] found diffuse myocardial fibrosis in a patient with chronic malaria falciparum infection. These findings support the hypothesis that malaria can cause subclinical myocardial damage, leading to decreased cardiac function and eventually HF. Importantly, a majority of the clinical studies only included *P. falciparum* malaria patients, which is the most serious form of malaria, not least due to the capacity of *P.*

Table 2 Species of malaria and risk of cardiovascular events and all-cause death

	Heart failure		Myocardial infarction		Cardiovascular death		All-cause death	
	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
Plasmodium falciparum (*n* = 1571)								
Unadjusted	1.59 (1.11–2.27)	0.011	1.15 (0.75–1.76)	0.52	0.97 (0.65–1.45)	0.90	0.93 (0.73–1.17)	0.53
Adjusted[a]	1.64 (1.14–2.36)	0.008	1.11 (0.72–1.71)	0.62	1.00 (0.67–1.50)	1.00	0.93 (0.74–1.18)	0.58
N (history of malaria/no history)	(32/489)		(24/479)		(26/655)		(91/1957)	
Plasmodium vivax (*n* = 476)								
Unadjusted	0.66 (0.27–1.60)	0.36	0.50 (0.18–1.35)	0.17	0.75 (0.46–1.58)	0.45	0.72 (0.47–1.11)	0.14
Adjusted[a]	0.86 (0.35–2.08)	0.73	0.57 (0.20–1.60)	0.28	1.05 (0.50–2.22)	0.90	0.98 (0.64–1.52)	0.94
N (history of malaria/no history)	(5/489)		(5/479)		(9/655)		(29/1957)	
Plasmodium ovale (*n* = 176)								
Unadjusted	0.53 (0.07–3.77)	0.52	0.24 (0.03–2.06)	0.19	N/A		0.95 (0.45–2.00)	0.90
Adjusted[a]	0.72 (0.10–5.16)	0.75	0.17 (0.02–1.73)	0.13	N/A		1.43 (0.68–3.01)	0.35
N (history of malaria/no history)	(1/489)		(1/479)		(1/655)		(10/1957)	
Non-specified (*n* = 1602)								
Unadjusted	1.48 (0.96–2.27)	0.074	0.63 (0.34–1.20)	0.16	0.56 (0.31–1.01)	0.055	0.91 (0.69–1.19)	0.49
Adjusted[a]	1.56 (1.02–2.41)	0.042	0.60 (0.31–1.16)	0.13	0.58 (0.32–1.05)	0.071	0.96 (0.73–1.25)	0.74
N (history of malaria/no history)	(22/489)		(11/479)		(16/655)		(65/1957)	

[a]Adjusted for hypertension, diabetes, cerebrovascular disease, chronic kidney disease, rheumatic heart disease, peripheral vascular disease, chronic obstructive pulmonary disease, cardiovascular pharmacotherapy (anti-thrombotic, beta blocker, calcium blocker, anti-arrhythmic, thiazide, renin–angiotensin system inhibitors, diuretics), region of origin, household income and educational level.

falciparum-infected erythrocytes to adhere to vascular endothelium.[23] In our sensitivity analyses, we found that only *P. falciparum* malaria was a predictor of HF, supporting the hypothesis that this species is the most likely to cause myocardial damage. A proportion of individuals with a history of malaria in our study were of non-specified type (ICD-10: B54), which could reduce the power and stringency of our analyses. Importantly, when we excluded the group with non-specified malaria, the association with HF remained significant. As well, we observed that this group of patients (ICD-10: B54) also had a significantly increased risk of HF.

Two recent studies have suggested that long-term malaria exposure is linked to cardiovascular conditions, and in particular hypertension.[12,13] Etyang *et al*.[12] propose three situations where malaria can lead to hypertension and affect cardiac health: (i) hypertensive disorders in pregnancy, (ii) stunting and malnutrition in childhood and (iii) elevated levels of angiopoietin-2. All these have been associated with cardiovascular disease independent of malaria. Opposed to this, Gallego-Delgado *et al*. suggest that individuals living in malaria risk regions more often suffer from increased blood pressure caused by higher levels of angiotensinogen-2 (Ang-2).[30] Experimental studies have indicated that Ang-2 protects against cerebral malaria, which is considered one of the most lethal complications to malaria.[1] Because of this beneficial role of elevated levels of Ang-2, the authors propose that evolutionary selective forces could have made hypertension more widespread in malaria regions. Considering that arterial hypertension is one of the strongest risk factors for almost all kinds of acquired cardiovascular diseases, including HF,[31] it may potentially be a part of the mechanism leading to increased risk of HF in patients exposed to malaria. However, in the present study, we observed no significant difference in the prevalence of hypertension between individuals with a history/no history of malaria.

Global significance

A potential link between malaria and increased risk of HF is of global scientific interest and may aid in understanding the increasing burden of cardiovascular disease in low- and middle-income countries. Most medical strategies focus on eliminating the malaria parasite in affected individuals; yet, none have assessed the long-term effects of malaria exposure. The present results bring novel attention to a potentially overlooked complication to malaria and warrant future prospective and larger studies to confirm the results. If present, a causal relationship between malaria and cardiovascular disease would have global impact and could potentially lead to a paradigm shift on how to treat and control cardiovascular disease in malaria risk regions.

Strengths and limitations

The observational nature of this study is the main limitation and does not allow us to conclude on the causality of our findings. Residual confounding may affect our results due to lack of patient characteristics in nationwide registries (e.g. treatment for malaria, left ventricular ejection fraction, blood pressure, body mass index and tobacco). Low sensitivity for the HF diagnosis could influence the results, and there could be observational bias due to patients with malaria more frequently followed and controlled for their malaria, and therefore, HF would be more often diagnosed. Compared with other register-based studies, our study was based on a relatively small sample of patients, and the small number of outcomes represents a limitation. Danish registries reported a higher total number of malaria cases and a lower number of *P. falciparum* compared with data from the WHO (*Table S4*). Data from the WHO were incomplete (no data available from 2014 and onwards), and it did not contain information for each species of *Plasmodium*. Individuals with no history of malaria were matched by sex and age, but otherwise unselected with regard to cardiovascular risk factors and region of origin. We sought to account for this in our multivariable models. Despite that many diagnoses have been validated in Danish registers with excellent predictive value, to our knowledge, malaria has never been validated that way. However, in the Danish healthcare system, it is mandatory to report all diagnoses of malaria to the National Malaria Reference Laboratory. Unfortunately, we had no information on the use of hydroxychloroquine, an antimalarial drug, which may cause cardiomyopathy,[32] nor was information available on symptoms or paraclinical tests related to severity of malaria. Our results should, therefore, be interpreted with caution, as they are exploratory and hypothesis-generating in nature.

Conclusions

In a study of Danish nationwide registries, individuals with a history of malaria had a significantly increased long-term risk of developing HF but not MI, cardiovascular or all-cause death. Specifically, a history of *P. falciparum* was associated with HF. Additional and larger cohort studies of malaria patients in other populations and healthcare systems are required to confirm these findings.

Conflict of interest

Dr Shah reports other from Novartis, personal fees from Philips Ultrasound and personal fees from Bellerophon. Dr Torp-Pedersen reports grants from Bayer and Novo Nordisk. Dr Køber reports personal fees from Novartis and AstraZeneca as speaker at symposium. Dr Solomon reports grants from Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, BMS, Celladon, Cytokinetics, Eidos, Gilead, GSK, Ionis, Lone Star Heart, Mesoblast, MyoKardia, NIH/NHLBI, Novartis, Sanofi Pasteur and Theracos and personal fees from Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, BMS, Cardior, Corvia, Cytokinetics, Daiichi-Sankyo, Gilead, GSK, Ironwood, Merck, Myokardia, Novartis, Roche, Takeda, Theracos, Quantum Genetics, Cardurion, AoBiome, Janssen, Cardiac Dimensions and Tenaya. Dr Biering-Sørensen reports other from Amgen, other from Sanofi Pasteur, other from Amgen, other from Novartis and other from Sanofi Pasteur. PB, GHM, DM, BC, OMS, LSV, JUS, LH, MS and GHG report no conflicts of interest.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Countries and categorization according to geographical regions.
Table S2. Anatomical Therapeutic Chemical (ATC) Classification system applied for use of medication.
Table S3. Definitions of comorbidities based on the International Classification of Diseases 8th and 10th revision (ICD-8/ICD-10) codes and Anatomical Therapeutic Chemical (ATC) Classification codes.
Table S4. Reported malaria cases 1994–2014 from Danish registries and the World Health Organization database.
Table S5. Baseline characteristics for patients with non-specified malaria compared to other malaria cases (*P. falciparum, ovale, vivax, malariae*).
Table S6. Relative distributions of causes of cardiovascular death by ICD-10 codes.
Table S7. Time-dependent Cox proportional hazards models examining the risk of cardiovascular death in patients who developed heart failure. Stratified by individuals with a history and no history of malaria.

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