**A Meta-Analysis of the Impact of Non-Communicable Disease on *Plasmodium Falciparum* Malaria Infection in Hospitalized Adults**

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**Abstract**

While the prevalence of non-communicable disease continues to increase across the globe, little attention has been paid to their effects on the severity of communicable diseases, including malaria. Malaria is one of the more prevalent vector-transmitted communicable diseases, and *Plasmodium falciparum* is the most dangerous malaria parasite, causing the majority of severe and fatal infection. Previous literature reviews have determined those at higher risk for severe malaria are younger, from non-endemic regions, or have improper chemoprophylaxis use, but few studies analyze demographic or chronic health conditions that may impact the severity of malaria infection. The purpose of this meta-analysis was to determine the impact of one or more non-communicable diseases, in particular obesity, diabetes mellitus, and hypertension, on the severity of *Plasmodium falciparum* malaria for hospitalized adults. Odds ratios with 95% confidence intervals were performed using the data from five independent studies as well as a combined sample. Results suggest that obesity, diabetes mellitus, and hypertension each increase the odds of developing severe *Plasmodium falciparum* malaria in hospitalized adults. Obesity increases the odds of developing hyperparasitemia, while diabetes mellitus and hypertension have an insignificant impact on parasitemia level in hospitalized adults. Further research is needed to analyze the impact of chronic diseases for children hospitalized with severe *Plasmodium falciparum*, especially the impact of obesity. Additionally, while this analysis focused on travelers to malaria-endemic regions, the relationship between malaria and non-communicable diseases should be analyzed for people living in malaria-endemic regions. Further studies with a larger sample size of patients with chronic conditions will allow for greater precision in predicting the effects of obesity, diabetes mellitus, and hypertension on the severity of malaria.

**Introduction**

*Communicable and Non-Communicable Disease*

While historically considered two separate categories, non-communicable and communicable diseases interact across the globe. Non-communicable diseases emerge without the aid of a microorganism for transmission and infection. Non-communicable diseases can also be categorized into genetic diseases that people are born with, or as geriatric diseases that affect older individuals from high income or developed countries. The leading causes of death in high income countries are heart disease, Alzheimer’s disease, and stroke, all non-communicable diseases that cannot be spread between individuals.1 Conversely, communicable diseases require a microorganism to infect individuals. Some microorganisms are transmitted directly between individuals, while others require a vector as a vehicle for transmission. Communicable diseases are prevalent across the globe but are more frequent in lower income or developing countries. The leading causes of death in developing countries are neonatal conditions like anemia and respiratory asphyxia, and lower respiratory infections caused by viruses, bacteria, or parasites.1, 2 Non-communicable and communicable diseases are frequently discussed in medicine as separate categories, as if they exist in different spaces and times. Specifically, travel makes it impossible to contain disease in discrete categories in separate regions. For example, over 2 million people travel by air in the United States alone each day, which makes it easier for disease transmission to occur.3 While the patterns of disease vary in different regions of the world, many non-communicable diseases can impact the outcome of communicable disease.

Vector-borne diseases are a common subset of communicable diseases that impact many regions of the world. Biological vectors are animal hosts that harbor and transmit a microorganism to a human through direct contact, thus infecting the individual. The most common vectors are insects (e.g., mosquitoes, ticks, flies), arachnids, and other small arthropods. Vector-borne diseases are particularly present in warmer, tropical climates in the equatorial region of the world. A common vector-borne disease is malaria, that exists in the wide-spread equatorial region of the globe.1 Africa is most burdened by malaria, with more than 95% of all malaria cases in the past year coming from this region.

*Malaria*

Malaria kills an average of 600,000 people globally each year, and it has one of the highest prevalence of all communicable diseases at nearly 241 million clinical cases worldwide in 2020.4, 5 *Plasmodium falciparum* is one of four mosquito-transmitted parasites that infects humans with malaria.6 *Plasmodium falciparum* causes over 90% of all malaria deaths and often results in progression to severe malaria compared to the other *Plasmodium* species.7 *Plasmodium falciparum* occupies most regions of the globe, while the other *Plasmodium* species reside in more specific niches, resulting in less impact on humans. Infections from *Plasmodium falciparum* are more likely to progress to severe or fatal forms. The *Anopheles* mosquito transmits the malaria-causing parasites, and there are roughly 430 mosquito species in the *Anopheles* genus. Approximately 30-40 of these species are capable of transmitting malaria.8 When an individual is bitten by a female Anopheles mosquito, the parasites are transmitted into the bloodstream as sporozoites, the small spore-like life stage of *Plasmodium sp*.9 The sporozoites multiply and mature in the human liver, then travel via vesicles through the bloodstream. The parasites invade the erythrocytes and digest the components resulting in reduced erythrocyte number and function. The destruction of erythrocytes results in several adverse reactions and symptoms of malaria infections.

The symptoms of malaria vary widely among individuals and can range from mild to severe. Many mild symptoms are flu-like and not necessarily indicative of malaria. The most common clinical manifestation is fever, which is typically one of the first symptoms to arise following the incubation period.10 Other possible symptoms can include nausea, headache, chills, muscle ache, and fatigue. Moderate or uncomplicated malaria will consist only of these mild symptoms, and the disease will not progress any further.

Severe malaria results in organ failure or other complications that do not resolve on their own. Symptoms include impaired consciousness, pulmonary edema, convulsions, shock, abnormal bleeding, and acidosis. *Plasmodium falciparum* malaria has far more severe complications than *Plasmodium vivax* or *Plasmodium ovale*, other common forms of malaria. Oftentimes, if treatment is not initiated, an infected patient can progress to severe malaria quickly when infected with *Plasmodium falciparum*. The most severe form of malaria is cerebral malaria, where infection leads to neurological complications resulting in long term cognitive impairments or death.11 While cerebral malaria has a high mortality rate, it is rare, especially in adults, and it will not be considered separately from other severe symptoms.12 The standard laboratory index for severe malaria is hyperparasitemia. Hyperparasitemia occurs when 5% or more of total erythrocytes are infected by malaria parasites.13 Hyperparasitemia is not required for severe malaria infections, as severe clinical manifestations can present with parasitemia levels less than 5%. Severe malaria can be labeled as hyperparasitemia (>5%), severe clinical manifestations, or a combination of both.

There are several factors that can impact the progression of complications from malaria by either increasing or decreasing their risk of severity. Heterozygous Sickle Cell Anemia is a widely known protective factor against malaria that prompts the immune system to clear the sickle-shaped parasite-infected erythrocytes.14 While this genetic disease decreases risk of severe infection of malaria, many diseases can increase the chances of developing serious and life-threatening symptoms after infection.

Few studies have identified the possible impact of non-communicable diseases on the severity of *Plasmodium falciparum* infection.15, 16, 17 In particular, three chronic diseases obesity, diabetes mellitus, and hypertension are increasing in prevalence worldwide and have the potential to influence the severity of malaria infection. The purpose of this study is to identify the possible impact of these diseases on the severity of *Plasmodium falciparum* malaria in hospitalized adults.

*Non-Communicable Diseases*

*Obesity*

The obesity epidemic is a great public health concern, impacting millions of people around the globe with increasing prevalence each year. The World Health Organization defines obesity as “abnormal or excessive fat accumulation that presents a risk to health.”18 Body mass index (BMI) is one of the several ways to determine a person’s adipose accumulation, and it will be used to determine the measure of obesity in this report. The BMI calculation is weight in kilograms divided by height in meters squared.19 Obesity was declared an epidemic in the 1980s, marking it as a major public health concern, and the global obesity rates continue to rise. According to data from the World Health Organization, 39% of adults had a BMI above 25, and 13% of adults were categorized as obese in the world in 2016.20 There are several behavioral, environmental, and genetic factors that affect a person’s disposition for obesity. Regardless of how obesity is acquired, there are many characteristic components to a high BMI.

The primary outcome of obesity is an increased amount of adipose tissue throughout the body. Obesity negatively affects many bodily systems and functions depending on the distribution of the adipose tissue resulting in an increase in morbidity and mortality.21 One of the primary effects of increased adipose tissue is on the cardiovascular system. Obesity is associated with increased risk for cardiovascular disease, as well as the other diseases associated with increased cardiac risk including hypertension and diabetes mellitus.22 Excessive weight increases both cardiac output and systolic blood pressure, which causes a cascade of physiological responses including activation of the renin-angiotensin-aldosterone system (RAAS).22 Increased adipose tissue also plays a role in innate immune system response to pathogens. Adipose tissue is associated with production of macrophages and inflammatory cytokines like TNFɑ and IL-6, so an increase in adipose results in an increase in inflammation.23 A pro-inflammatory immune response can be beneficial for fighting infections; however, increased inflammation over a long period of time has adverse health effects. Most commonly, chronic inflammation results in body pain, fatigue, mood disorders, and increased susceptibility to infection.24

*Diabetes Mellitus*

Diabetes mellitus is a chronic metabolic disease characterized by elevated blood glucose and increased insulin resistance.30 There are two main types of diabetes mellitus: type 1 typically occurs when the pancreatic 𝛽 cells produce little or no insulin and type 2 diabetes is a result of bodily resistance to insulin. Approximately 422 million people have a form of diabetes mellitus worldwide, with type 2 diabetes impacting people of middle and lower economic status. Symptoms of untreated diabetes mellitus include rapid weight loss, fatigue, and increased susceptibility to infection.31

Type 2 diabetes has been associated with an increased risk of contracting *Plasmodium falciparum* malaria compared to those without diabetes.32 People with diabetes mellitus also present different malaria symptoms than the average infection such as decreased incidence of hypoglycemia and fever, and increased incidence of vomiting.33 Elevated glucose levels in diabetic cases have been attributed to this difference. However, few studies have analyzed the impact of diabetes mellitus on the severity of *Plasmodium falciparum* infection.

*Hypertension*

Hypertension is a non-communicable disease with a high morbidity and mortality that affects nearly a billion people worldwide. Hypertension is a cardiovascular condition in which the force of the blood against the arteries is persistently high, resulting in a systolic blood pressure above 140 mmHg ad diastolic blood pressure above 90 mmHg.25 Globally, 25% of men and 20% of women are affected by high blood pressure, and it is a major cause of premature death. Additionally, there is a disproportionate impact of hypertension for people of middle and lower economic status. Like obesity, there are many environmental and social factors that impact the risk for hypertension in addition to genetic and behavioral influences. Mechanistically, hypertension has many pathways that contribute to the heightened systolic blood pressure. The most common mechanism of hypertension is increased vascular resistance in the peripheral arterioles taking blood away from the heart.26 The walls of these arterioles contain smooth muscle that remain incorrectly contracted or thickened, contributing to the increased resistance. The endocrine system is thought to also play a role in this resistance through the renin-angiotensin system.26 Renin release from the kidney prompts the conversion of angiotensin I to angiotensin II via the angiotensin converting enzyme (ACE). Angiotensin II is a strong vasoconstrictor and can constrict the blood vessels resulting in an increase in blood pressure. Hypertension typically presents no symptoms until it reaches an extreme point. Many people can live with hypertension without realizing its effect on their bodies. The long-term effects of hypertension include serious organ damage to the kidneys, eyes, or brain, but most commonly, it contributes to heart disease, heart attack, or heart failure.27

The impact of hypertension on malaria severity has been analyzed by a few studies, but it is not considered in terms as a primary risk for travelers to malaria endemic areas.28 Some evidence suggests that malarial infection can lead to hypertension in recovered adults.29 The effects of pre-existing hypertension on malaria severity has been examined less.

*Other Studies*

Few studies have examined risk factors for severe malarial infection and death for travelers to malaria endemic regions.28 These studies have identified behavioral factors such as careless chemoprophylaxis use or delay in seeking care. The only demographic information identified to increase risk of severe malaria infection is age or coinfection with another communicable disease. Obesity, diabetes mellitus, and hypertension are all non-communicable diseases that could interact and impact the outcome of infectious diseases, like malaria caused by *Plasmodium falciparum.* It is likely that a subset of the travelers who contract malaria originate from wealthy countries with a higher prevalence of these particular chronic diseases.34

Even fewer studies have researched the direct and indirect impacts of non-communicable diseases on malaria, and contradicting conclusions have been presented. Two studies focused on the impact of obesity on *Plasmodium falciparum* malaria severity in hospitalized adults. The study from the Hospital for Tropical Diseases in Bangkok, Thailand concluded that overweight and obesity are protective factors against severe *Plasmodium falciparum* malaria infection.16 Conversely, the study from the Public Health Agency of Sweden concluded obesity is a risk factor for severe malaria infection in adults.15 This study also concluded that diabetes mellitus is a risk factor for severe malaria infection in adults. Only one study analyzed the effects of hypertension on malaria; a study from the Charité University Hospital in Berlin, Germany identified hypertension as a contributing risk factor to severe *Plasmodium falciparum* malaria.17 Additional studies included demographic information of patients and severity of malaria infection without analyzing the impacts of obesity, diabetes mellitus, or hypertension on the severity of malaria infection.35, 36

Raw data from the selected studies were reanalyzed for each study separately as well as combined in a larger sample to determine the impact of the non-communicable diseases, obesity, diabetes mellitus, and hypertension on the symptoms and parasitemia severity of malaria caused by *Plasmodium falciparum* infection in hospitalized adults. It is expected that chronic non-communicable diseases will increase the severity of *Plasmodium falciparum* malaria infection. Results from this meta-analysis will provide guidance for malaria disease control, including disease prevention and treatment at the individual and institutional levels.

**Methods**

*Literary Search and Inclusion Criteria*

A literature review of the Google Scholar database was performed from August 2021 through February 2022. Keywords used to find relative articles included “obesity and malaria”, “diabetes and malaria”, and “hypertension and malaria” (Figure 1).

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**Figure 1.** Literary search criteria flowchart.

Furthermore, the search was restricted to human peer-reviewed studies available for free through CU Boulder libraries and databases. To be included in analysis, the data from a study met the following criteria: 1) severity of malaria disease was determined by World Health Organization definition; 2) all cases of malaria were caused by *Plasmodium falciparum* malaria; 3) patient BMI must be listed in the standardized categories; 4) obesity, diabetes mellitus, and hypertension criteria were specified in patients with and without the condition in the context of malaria severity. Excluded papers were either not free to access, did not contain raw data, or analyzed data from non-human test subjects.

*Defining BMI*

BMI is the most common measurement used to define nutritional status in adults. This measurement is calculated as weight in kilograms divided by height in meters squared. The results of the calculation are then placed in a category: underweight (<18.5), normal weight (18.5-24.9), overweight (25.0-29.9), or obese (≥30.0).

*Defining Malaria Severity*

Criteria for severe or complicated *Plasmodium falciparum* malaria were defined using the World Health Organization definition (See Table 1).37 Non-severe or uncomplicated malaria was defined using the Center for Disease Control criteria (See Table 1).13 Both clinical manifestations and laboratory indices were used to define the severity of the malaria infection.

**Table 1.** Criteria for Uncomplicated and Severe *Plasmodium falciparum* Malaria Infection According to World Health Organization and Center for Disease Control Definitions.

|  |  |
| --- | --- |
| Uncomplicated Malaria | Severe Malaria |
| Clinical Manifestations | |
| Irregular fever  Fatigue  Chills  Sweats  Headache  Nausea and vomiting  Myalgia, arthralgia  General malaise  Diarrhea | Impaired consciousness (Glasgow Coma Score <11)  Respiratory distress (acidotic breathing)  Multiple convulsions  Prostration  Shock  Pulmonary edema  Abnormal bleeding  Jaundice (plasma bilirubin >50 𝛍M with parasite count >100,000 𝛍l) |
| Laboratory Indices | |
| Mild to moderate anemia (>7.0 g/dl)  Low parasitemia (<5%) | Severe anemia (hemoglobin concentration <7.0 g/dl)   Hypoglycaemia (plasma glucose <2.2 mM)  Acidosis (base deficit of >8 meq/l)  Hyperlactatemia   Renal impairment (Plasma creatinine >265 𝛍M)  Hyperparasitaemia (>5%) |

The typical course of malaria symptoms begins with a fever 10-15 days after the infected mosquito bite, and uncomplicated malaria can also include symptoms of headache, chills, and other nonspecific flu-like symptoms. Malaria can progress to severe infection if untreated, leading to organ failure or death in 24 hours.38

*Selected Study Characteristics*

Five studies were selected for analysis. Each study provided different demographic information on patients, resulting in different combinations for analysis. Table 2 indicates which studies included demographic information for obesity, diabetes mellitus, and hypertension, and the sample size for each. Sample size for zero chronic diseases, one chronic disease, and two chronic diseases were also listed for the studies that included the information. Other relevant demographic information such as age, sex, and location of hospital were included. Many of the patients analyzed in this study were hospitalized for malaria infection after returning from malaria endemic areas on trips or vacations. Patient origin, i.e., whether a person lives in a malaria endemic region or a non-endemic region, influences the frequency of clinical manifestations. Patients from regions with endemic malaria are often semi-immune and often have reduced symptoms and symptom severity.39

**Table 2.** Characteristics of studies analyzed.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Hospital Location** | **Age Distribution** | **Sex Distribution (M/F)** | **Sample Size for Obesity Analysis** | **Sample Size for Diabetes Mellitus Analysis** | **Sample Size for Hypertension Analysis** |
| Wyss, K., et. al., (2017) | Public Health Agency of Sweden | 18-60+ | 623/314 | 570 | 937 | 937 |
| Wilairatana, P., et. al., (2019) | Bangkok Hospital for Tropical Diseases | 18+ | 433/143 | 576 | - | - |
| Hoffmeister, B., Valdez, A., (2019) | Charité University Hospital, Berlin Germany | 18+ | 368/168 | 536 | 536 | 536 |
| Tangpukdee, N., et. al., (2007) | Bangkok Hospital for Tropical Diseases | 15+ | 469/131 | 600 | - | - |
| Sharaf-el-Deen, S., et. al., (2021) | Abbassia Fever Hospital, Cairo, Egypt | 17+ | 82/22 | 104 | 104 | - |

*Data Analysis*

A meta-analysis of five previous studies was performed using the raw BMI, hypertension, diabetes mellitus, and malaria severity data from each study (Table 2). An odds ratio (OR) with 95% confidence interval (CI) was performed to compare the odds of severe malaria infection for the chronic condition groups compared to the groups without chronic conditions (Appendix 1). Odds ratio compares the relative odds of occurrence of the outcome of interest when exposed to the variable of interest and was calculated with the following equation: *OR = (AD)/(BC)*.40 The calculations were performed in Microsoft Excel using contingency tables to set up the data (Table 3).

**Table 3.** Contingency table set up for performing odds ratios. A is the number of cases with severe malaria and the condition present. B is the number of cases with uncomplicated malaria and the condition present. C is the number of cases with severe malaria and the condition absent. D is the number of cases with uncomplicated malaria and the condition absent.

|  |  |  |
| --- | --- | --- |
|  | Severe Malaria | Uncomplicated Malaria |
| Condition Present | A | B |
| Condition Absent | C | D |

An odds ratio above 1.0 means the variable of interest increases the odds of the outcome, while an odds ratio below 1.0 means the variable of interest decreases the odds of the outcome. If the odds ratio equals 1.0, the variable of interest has no impact on the outcome.

The 95% confidence interval contains the lower and upper limits of the range that contains the true mean of the values with 95% confidence and was calculated with the following equations:

*95% CI Lower Limit = EXP(lnOR-1.96\*SQRT(1/a+1/B+1/C+1/D))*

*95% CI Upper Limit = EXP(lnOR+1.96\*SQRT(1/a+1/B+1/C+1/D))*

The 95% CI range indicates the precision of the odds ratio: a large range is less precise, while a small range is more precise.

The calculated odds ratios were converted to percentages to compare the odds of severe infection with the chronic condition to the absence of the chronic condition using the following equation:

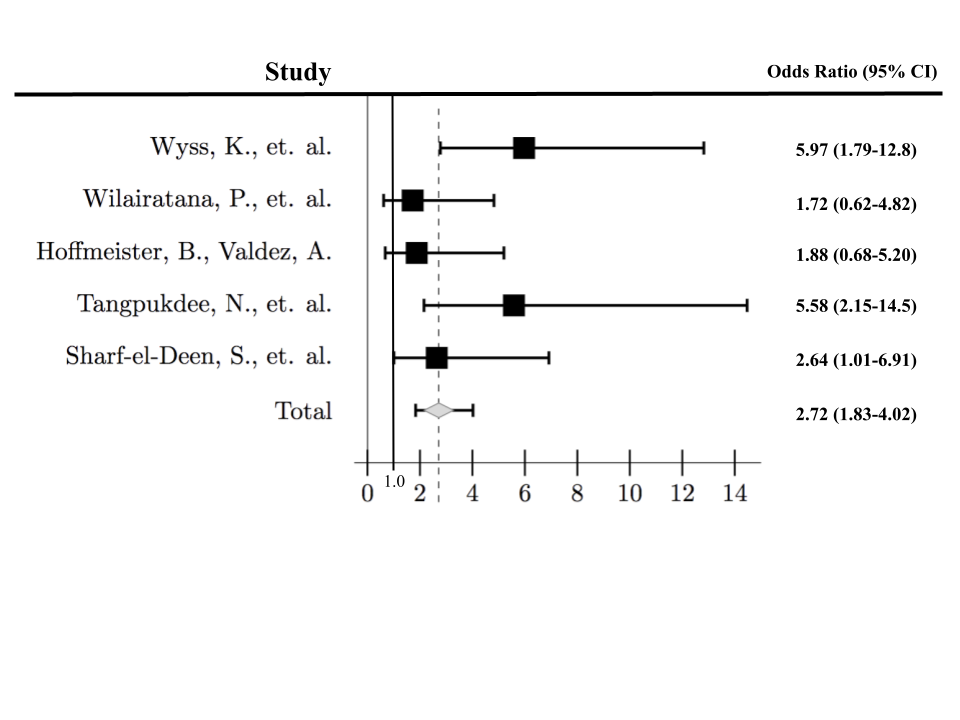
*Percent increase/decrease = |*(*OR - 1.0*)*| x 100%*

The odds ratio and 95% CI results were displayed as forest plots generated using the Overleaf LaTeX editor.

**Results**

*Obesity*

The five studies were analyzed separately for the effect of obesity on severity of malaria infection (Figure 2). Three studies were found to have a significant increase in odds of severe malaria with obesity. The analyses of Wyss, et. al. (2015), Tangpukdee, et. al. (2007), and Sharf-el-Deen, et. al. (2021) resulted in odds ratios of 5.97 (95% CI 2.78-12.8), 5.58 (95% CI 2.15-14.5), and 2.64 (95% CI 1.01-6.91), respectively. The analyses of Wilairatana, et. al. (2019) and Hoffmeister and Valdez (2019) did not result in a significant effect of obesity on the severity of malaria infection. When all subjects of the five studies were combined into a single analysis, the total sample (n=2386) had an odds ratio of 2.72 (95% CI 1.83-4.02), indicating 172% increased odds of developing severe malaria with obesity compared to non-obese BMI categories. The 95% confidence intervals on the analyses of the individual studies were wide ranges for the individual studies, indicating low confidence in the results. The analysis on the combined sample had a narrower confidence interval, indicating a greater confidence in the precision of the odds ratio result.



**Figure 2.** Individual odds ratios and total sample of the effect of obesity (≥30.0) on the severity of malaria infection compared to non-obese BMI categories (<18.5-29.9).

*Diabetes Mellitus*

Three studies were analyzed separately for the effect of diabetes mellitus on the severity of malaria infection (Figure 3). Analyses of Wyss, et. al. (2017) and Sharf-el-Deen et. al. (2021) resulted in a significant increase in the odds of developing severe malaria in patients with diabetes mellitus compared to patients without diabetes mellitus, with an odds ratio of 3.71 (1.67-8.24) and 19.5 (5.28-72.1) respectively. Analysis of Hoffmeister and Valdez (2019) did not result in a significant effect of diabetes mellitus on severity of malaria infection. When all the subjects of these three studies were combined into a single analysis, the total sample (n=1577) had an odds ratio of 4.43 (2.58-7.61). indicating 343% increased odds of developing severe malaria for patients with diabetes mellitus compared to patients without diabetes mellitus. The 95% confidence intervals for the analyses of the individual studies were all wide, but the confidence interval for the Sharaf-el-Dean et. al. (2021) study was exceptionally wide, likely due to the small sample size of the study (n=104).

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**Figure 3.** Individual odds ratio and total sample odds ratio of the effect of diabetes mellitus on the severity of malaria infection compared to no diabetes mellitus.

*Hypertension*

Two studies were analyzed separately for the effect of hypertension on the severity of malaria infection (Figure 4). Analysis of Wyss et. al. (2017) and Hoffmeister and Valdez (2019) revealed a significant increase in the odds of developing severe malaria infection in patients with hypertension compared to patients without hypertension, with odds ratios of 3.81 (1.93-7.50) and 3.45 (1.69-7.01) respectively. When the subjects of these two studies were combined into a single analysis, the total sample (n=1577) had an odds ratio of 3.73 (2.29-6.07), indicating 273% increased odds of developing severe malaria for patients with hypertension compared to patients without hypertension.

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**Figure 4.** Individual odds ratio and total sample odds ratio of the effect of hypertension on the severity of malaria infection compared to no hypertension.

*Hyperparasitemia*

The effect of obesity, diabetes mellitus, and hypertension on total parasitemia levels in erythrocytes was analyzed (Table 4). Wyss et. al. (2017) reported parasitemia levels for patients with obesity and diabetes mellitus. The odds ratio for the effect of obesity on hyperparasitemia was 4.02 (95% CI 1.33-12.1) indicating 300% increased odds of developing hyperparasitemia for patients with obesity compared to non-obese patients. However, the confidence interval is wide indicating a low level of precision. The odds ratio for the effect of diabetes mellitus on hyperparasitemia was 2.43 (0.90-6.58) which was insignificant. Hoffmeister and Valdez (2019) reported parasitemia levels for patients with hypertension. The odds ratio for the effect of hypertension on hyperparasitemia was 0.19 (0.03-1.09) which was also insignificant.

**Table 4.** Odds ratios for the effect of obesity, diabetes mellitus, and hypertension on hyperparasitemia. Raw data acquired from Wyss, K., et. al. (2015) and Hoffmeister, B. and Valdez, A. (2019).

|  |  |
| --- | --- |
| **Chronic Disease** | **Odds Ratio (95% CI)** |
| Obesity | 3.95 (1.31-11.9) |
| Diabetes Mellitus | 2.43 (0.90-6.58) |
| Hypertension | 0.19 (0.03-1.09) |

Wilairatana et. al. concluded obesity was a protective factor in preventing severe *Plasmodium falciparum* malaria. The other four studies found that obesity and other cardiovascular health conditions were risk factors for severe infection. Additionally, the odds ratios analyses of the current research found no decreased risk for severe infection with obesity. The statistical analyses performed by Wilairatana et. al. included chi square tests. However, chi square tests cannot account for confounding factors when analyzing the impact of health status on infection. The studies that determined that obesity and other cardiovascular health conditions were risk factors to severe *Plasmodium falciparum* malaria utilized statistical tests like multivariable logistic regressions that accounted for all comorbidities.

Contingency tables for analysis of all variables are included in Appendix 1.

**Discussion**

This study showed that obesity, diabetes mellitus, and hypertension are factors that increase the likelihood of developing severe *Plasmodium falciparum* malaria infection in hospitalized adults compared to having a BMI less than 30.0, no diabetes, or no hypertension. This study also found that having one chronic disease does not significantly increase the odds of developing severe *Plasmodium falciparum* malaria but having two chronic diseases significantly increases the odds of developing severe *Plasmodium falciparum* malaria compared to no chronic disease.

These results of this study are of particular importance for travelers to malaria-endemic regions, who might have health conditions that put them at risk for more severe malarial symptoms that could lead to increased morbidity or mortality for patients. For the individual traveler, this information is important so people with any of these conditions are more cognizant of the risks associated with malaria and are encouraged to seek malaria prophylaxis medications to protect them before travel.41 Additionally, if an individual develops any symptoms of either uncomplicated or severe malaria, they should seek treatment immediately. For public health departments, these findings are important to develop the information for travelers at risk of developing severe malaria infection. Results from scientific literature indicate that individuals are at risk of severe *Plasmodium falciparum* infection depending on age, pregnancy, residency, and co-infection with HIV.28 There are little data provided by public health organizations about the increased risk of severe infection for people with chronic diseases, specifically diseases that are increasing in prevalence across the globe. These findings could encourage the public health departments like the Center for Disease Control and the World Health Organization to update their recommendations and list multiple chronic diseases, obesity, and diabetes mellitus, and hypertension as risk factors for severe *Plasmodium falciparum* malaria.

Finally, these results are important beyond the scope of individual travelers and travel recommendations. The increased risk for severe *Plasmodium falciparum* malaria infection associated with chronic health conditions impacts the residents of malaria-endemic regions. Hypertension, obesity, and diabetes mellitus are becoming more prevalent in lower income countries, as these “diseases of affluence” are shifting between socioeconomic groupings.34 These shifts are due to several nutritional, social, and economic factors and have resulted in a rapid increase of cardiovascular related disease in lower income countries. The results of this study can help people living in malaria-endemic regions to understand their increased risk. Even more importantly, this information provides guidance for health care providers and public health programs to appropriately prepare preventative measures and treatments for people at higher risk of severe malaria infection.

**Limitations and Future Considerations**

There are several aspects of this study that offer limits and should be considered for future studies. BMI measurement, sex distribution, age range, and sample size and study location all impact the analysis or offer possible points for consideration for future studies.

*Body Mass Index*

All nutritional statuses including overweight and obese metrics were defined using BMI, a controversial calculation. BMI was used for convenience and commonality across data and was utilized by the chosen studies in their demographic listings. However, there can be several inaccuracies in measuring a person’s adipose make-up solely with height and weight dimensions. For example, one is unable to indicate adipose distribution, fat versus muscle weight, and the disparities between males and females as well. Techniques to determine BMI like underwater weighing, caliper measurements, and Dual Energy X-ray Absorptiometry may be more accurate, they were not used in this study due to lack of public usage. Different BMI measuring techniques would be beneficial for future studies to determine the possible effect of adipose distribution on malaria symptom severity.

*Sex Distribution*

The data from these four studies had nearly double the male participants compared to female participants. The cases were identified through different hospital databases, so it is possible that fewer females infected with malaria were going to the hospital for symptom treatment. It is also be possible that malaria disproportionately affects males compared to females. A study from 2020 found that females had a lower prevalence of infection, but no significant difference in rate of acquiring infection compared to males.42 The authors attributed this difference to faster clearance of infection in females than in males, which could result in fewer females going to the hospital for malaria treatment.

*Age Range*

All data were collected from adults or near adults aged 15 to 60+. Next steps following this study would be to expand data collection to children. Globally, children under five years old are more affected by malaria than any other age group, with 57% of malaria fatalities occurring in this age group.20 Childhood obesity trends parallel those seen in adult populations, with approximately 15% of children in the world overweight or obese.18 In Africa and Asia, where most of the malaria endemic regions are located, childhood obesity is significantly increasing. Additionally, childhood diabetes (both Type 1 and Type 2) is increasing globally.42 Chronic diseases affecting children of young age is of great public health concern and should be considered when identifying risk factors for other diseases. Future studies can identify the risks of childhood obesity and diabetes mellitus on the severity of *Plasmodium falciparum* infection.

*Sample Size and Location of Data Collection*

The sample sizes of each study selected were large, but there were few patients with the chronic diseases, particularly BMI > 30.0, included in the studies. This sample distribution may be accurate for the demographics of the infected patients in the hospitals where data were collected, but the distribution yielded less precise odds ratio results. It is important to collect demographic data from hospitals in both endemic and non-endemic regions that frequently treat *Plasmodium falciparum* malaria patients to confirm or challenge the current demographic distributions that exist in these selected studies.

**Conclusion**

Obesity, diabetes mellitus, and hypertension were each found to increase the odds of developing severe *Plasmodium falciparum* malaria in hospitalized adults from different hospitals around the globe. Additionally, having obesity increases the odds of hyperparasitemia compared to non-obese patients. As the prevalence of these chronic diseases continues to increase, it is important for individuals and public health organizations to recognize the impacts on communicable disease, like the negative impact on *Plasmodium falciparum* malaria infection.

**Appendix 1**

2x2 Contingency Tables for Analysis:

*The effect of obesity (≥30.0) on the severity of malaria infection compared to non-obese BMI categories (<18.5-29.9).*

**Table A.1.** 2x2 contingency table and odds ratio (95% CI) results for Wyss, K., et. al. (2017)

|  |  |  |
| --- | --- | --- |
|  | Severe Malaria | Uncomplicated Malaria |
| Obese (BMI > 30.0) | 12 | 23 |
| Non-obese (BMI < 30.0) | 43 | 492 |

Odds Ratio: 5.970 (95% CI 2.780-12.82)

**Table A.2.** 2x2 contingency table and odds ratio (95% CI) results for Wilairatana, P., et. al. (2019)

|  |  |  |
| --- | --- | --- |
|  | Severe Malaria | Uncomplicated Malaria |
| Obese (BMI > 30.0) | 7 | 8 |
| Non-obese (BMI < 30.0) | 189 | 372 |

Odds Ratio: 1.722 (95% CI 0.6176-4.821)

**Table A.3.** 2x2 contingency table and odds ratio (95% CI) results for Hoffmeister, B. and Valdez, A. (2019)

|  |  |  |
| --- | --- | --- |
|  | Severe Malaria | Uncomplicated Malaria |
| Obese (BMI > 30.0) | 5 | 19 |
| Non-obese (BMI < 30.0) | 63 | 449 |

Odds Ratio: 1.876 (95% CI 0.6764-5.200)

**Table A.4.** 2x2 contingency table and odds ratio (95% CI) results for Tangpukdee, N., et. al. (2007)

|  |  |  |
| --- | --- | --- |
|  | Severe Malaria | Uncomplicated Malaria |
| Obese (BMI > 30.0) | 3 | 8 |
| Non-obese (BMI < 30.0) | 23 | 566 |

Odds Ratio: 5.583 (95% CI 2.153-14.47)

**Table A.5.** 2x2 contingency table and odds ratio (95% CI) results for Sharf-el-Deen, S., et. al. (2021)

|  |  |  |
| --- | --- | --- |
|  | Severe Malaria | Uncomplicated Malaria |
| Obese (BMI > 30.0) | 13 | 29 |
| Non-obese (BMI < 30.0) | 9 | 53 |

Odds Ratio: 2.640 (95% CI 1.008-6.915)

**Table A.6.** 2x2 contingency table and odds ratio (95% CI) results for combined sample

|  |  |  |
| --- | --- | --- |
|  | Severe Malaria | Uncomplicated Malaria |
| Obese (BMI > 30.0) | 40 | 87 |
| Non-obese (BMI < 30.0) | 327 | 1932 |

Odds Ratio: 2.72 (95% CI 1.83-4.024)

*The effect of diabetes mellitus on the severity of malaria infection compared to no diabetes mellitus.*

**Table A.7.** 2x2 contingency table and odds ratio (95% CI) results for Wyss, K., et. al. (2017)

|  |  |  |
| --- | --- | --- |
|  | Severe Malaria | Uncomplicated Malaria |
| Diabetes Mellitus | 9 | 24 |
| No Diabetes Mellitus | 83 | 821 |

Odds Ratio: 3.709 (95% CI 1.669-8.244)

**Table A.8.** 2x2 contingency table and odds ratio (95% CI) results for Hoffmeister, B. and Valdez, A. (2019)

|  |  |  |
| --- | --- | --- |
|  | Severe Malaria | Uncomplicated Malaria |
| Diabetes Mellitus | 2 | 14 |
| No Diabetes Mellitus | 66 | 454 |

Odds Ratio: 0.9827 (95% CI 0.2184-4.421)

**Table A.9.** 2x2 contingency table and odds ratio (95% CI) results for Sharf-el-Deen, S., et. al. (2021)

|  |  |  |
| --- | --- | --- |
|  | Severe Malaria | Uncomplicated Malaria |
| Diabetes Mellitus | 11 | 4 |
| No Diabetes Mellitus | 11 | 78 |

Odds Ratio: 19.50 (95% CI 5.278-72.05)

**Table A.10.** 2x2 contingency table and odds ratio (95% CI) results for combined sample

|  |  |  |
| --- | --- | --- |
|  | Severe Malaria | Uncomplicated Malaria |
| Diabetes Mellitus | 22 | 42 |
| No Diabetes Mellitus | 160 | 1353 |

Odds Ratio: 4.429 (95% CI 2.578-7.610)

*The effect of hypertension on the severity of malaria infection compared to no hypertension.*

**Table A.11.** 2x2 contingency table and odds ratio (95% CI) results for Wyss, K., et. al. (2017)

|  |  |  |
| --- | --- | --- |
|  | Severe Malaria | Uncomplicated Malaria |
| Hypertension | 13 | 35 |
| No Hypertension | 79 | 810 |

Odds Ratio: 3.808 (95% CI 1.935-7.496)

**Table A.12.** 2x2 contingency table and odds ratio (95% CI) results for Hoffmeister, B. and Valdez, A. (2019)

|  |  |  |
| --- | --- | --- |
|  | Severe Malaria | Uncomplicated Malaria |
| Hypertension | 13 | 30 |
| No Hypertension | 55 | 438 |

Odds Ratio: 3.451 (95% CI 1.699-7.010)

**Table A.13.** 2x2 contingency table and odds ratio (95% CI) results for combined sample

|  |  |  |
| --- | --- | --- |
|  | Severe Malaria | Uncomplicated Malaria |
| Hypertension | 26 | 65 |
| No Hypertension | 134 | 1248 |

Odds Ratio: 3.725 (95% CI 2.286-6.072)

*The effect of one chronic condition on the severity of malaria infection compared to no chronic conditions for individual studies and total sample.*

**Table A.14.** 2x2 contingency table and odds ratio (95% CI) results for Wyss, K., et. al. (2017)

|  |  |  |
| --- | --- | --- |
|  | Severe Malaria | Uncomplicated Malaria |
| One Chronic Disease | 17 | 122 |
| No Chronic Diseases | 75 | 723 |

Odds Ratio: 1.343 (95% CI 0.7670-2.3525)

**Table A.15.** 2x2 contingency table and odds ratio (95% CI) results for Hoffmeister, B and Valdez, A. (2019)

|  |  |  |
| --- | --- | --- |
|  | Severe Malaria | Uncomplicated Malaria |
| One Chronic Disease | 11 | 50 |
| No Chronic Diseases | 57 | 418 |

Odds Ratio: 1.613 (95% CI 0.7940-3.278)

**Table A.16.** 2x2 contingency table and odds ratio (95% CI) results for combined sample

|  |  |  |
| --- | --- | --- |
|  | Severe Malaria | Uncomplicated Malaria |
| One Chronic Disease | 28 | 172 |
| No Chronic Diseases | 132 | 1141 |

Odds Ratio: 1.407 (95% CI 0.9080-2.181)

*The effect of two chronic conditions on the severity of malaria infection compared to no chronic conditions for individual studies and total sample.*

**Table A.17.** 2x2 contingency table and odds ratio (95% CI) results for Wyss, K., et. al. (2017)

|  |  |  |
| --- | --- | --- |
|  | Severe Malaria | Uncomplicated Malaria |
| Two Chronic Diseases | 11 | 29 |
| No Chronic Diseases | 81 | 816 |

Odds Ratio: 3.821 (95% CI 1.840-7.934)

**Table A.18.** 2x2 contingency table and odds ratio (95% CI) results for Hoffmeister, B. and Valdez, A. (2019)

|  |  |  |
| --- | --- | --- |
|  | Severe Malaria | Uncomplicated Malaria |
| Two Chronic Diseases | 9 | 20 |
| No Chronic Diseases | 59 | 448 |

Odds Ratio: 3.417 (95% CI 1.487-7.854)

**Table A.19.** 2x2 contingency table and odds ratio (95% CI) results for combined sample

|  |  |  |
| --- | --- | --- |
|  | Severe Malaria | Uncomplicated Malaria |
| Two Chronic Diseases | 20 | 49 |
| No Chronic Diseases | 140 | 1264 |

Odds Ratio: 3.685 (95% CI 2.129-6.378)

**References**

1. World Health Organization. (2020, December 9). The Top 10 Causes of Death. *World Health Organization*, https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death
2. Gupta H. D., Choudhury R.G., (2001). Neonatal disorders and obstetricians. *J Indian Med Assoc.*, 99(5), 262-266. https://pubmed.ncbi.nlm.nih.gov/11676112/
3. Transportation Security Administration. (2022, March 27). TSA Checkpoint Travel Numbers: Current Year versus Prior Year(s)/Same Weekday. *TSA Checkpoint Travel Numbers,* https://www.tsa.gov/coronavirus/passenger-throughput
4. Centers for Disease Control and Prevention. (2021, December 16). CDC - Malaria - Malaria Worldwide - Impact of Malaria. *Centers for Disease Control and Prevention*, https://www.cdc.gov/malaria/malaria\_worldwide/impact.html#:~:text=Nearly%20half%20the%20world's%20population,in%20the%20WHO%20African%20Region
5. World Health Organization. (2021). World malaria report 2021. *World Health Organization*, https://apps.who.int/iris/handle/10665/350147
6. Centers for Disease Control and Prevention. (2020, October 6). CDC - Dpdx - Malaria.” *Centers for Disease Control and Prevention*, https://www.cdc.gov/dpdx/malaria/index.html
7. Zekar, L. (2021). *Plasmodium Falciparum Malaria*. U.S. National Library of Medicine.
8. Centers for Disease Control and Prevention. (2020, July 16). CDC - Malaria - about Malaria - Biology. *Centers for Disease Control and Prevention*, https://www.cdc.gov/malaria/about/biology/#:~:text=General%20Information,%E2%8%9Cvectors%E2%80%9D)%20in%20nature
9. Mawson, A. R. (2013). The Pathogenesis of Malaria: A New Perspective. *Pathogens and Global Health*, 107(3), 122–129. https://doi.org/10.1179/2047773213y.0000000084
10. Bartoloni, A., & Zammarchi, L. (2012). Clinical Aspects of Uncomplicated and Severe Malaria. *Mediterranean Journal of Hematology and Infectious Diseases*, 4, (1), https://doi.org/10.4084/mjhid.2012.026
11. Idro, R., Marsh, K., & John, C*.* (2010). Cerebral Malaria: Mechanisms of Brain Injury and Strategies for Improved Neurocognitive Outcome. *Pediatr Res* 68,267–274. https://doi.org/10.1203/PDR.0b013e3181eee738
12. Luzolo, A., & Ngoyi, D. (2019). Cerebral malaria. *Brain Research Bulletin*, 145(1), 53-58. https://doi.org/10.1016/j.brainresbull.2019.01.010
13. Centers for Disease Control and Prevention. (2022, March 22). CDC - Malaria - about Malaria - Disease. *Centers for Disease Control and Prevention*, https://www.cdc.gov/malaria/about/disease.html
14. Luzzatto, L. (2012) Sickle Cell Anaemia and Malaria. *Mediterranean Journal of Hematology and Infectious Diseases*, 4(1), 1-6. https://doi.org/10.4084/mjhid.2012.065
15. Wyss, K, Wangdahl, A., Vesterlund, M., Hammar, U., Dashti, S., Naucler, P., & Farnet, A. (2017). Obesity and Diabetes as Risk Factors for Severe Plasmodium Falciparum Malaria: Results from a Swedish Nationwide Study. *Clinical Infectious Diseases*, 65(6), 949–958. https://doi.org/10.1093/cid/cix437
16. Wilairatana, P., Tangpukdee, N., Krudsood, S., Wilairat, N., Wilairat, P., & Thebpatipat, P. (2019). Overweight and Obesity as Protective Factors in Severe Falciparum Malaria. *Southeast Asian Journal of Tropical Medicine and Public Health,*50(3), 421-427. https://colorado.idm.oclc.org/login?url=https://www.proquest.com/scholarly-journals/overweight-obesity-as-protective-factors-severe/docview/2554644793/se-2?accountid=14503
17. Hoffmeister, B., & Valdez, A. (2019). Hypertension Is Associated with an Increased Risk for Severe Imported Falciparum Malaria: A Tertiary Care Hospital Based Observational Study from Berlin, Germany. *Malaria Journal*, 18(410), 1-10. https://doi.org/10.1186/s12936-019-3007-4
18. World Health Organization. (2022, March 4). Obesity. *World Health Organization*, https://www.who.int/health-topics/obesity#tab=tab\_1
19. Centers for Disease Control and Prevention. (2022, January 21). Adult BMI Calculator. *Centers for Disease Control and Prevention*, https://www.cdc.gov/healthyweight/assessing/bmi/adult\_bmi/english\_bmi\_calculator/bm\_calculator.html
20. Ritchie, H., & Roser, M. (2017, August 11) Obesity. Our World in Data. https://ourworldindata.org/obesity
21. Falagas, M., & Kompoti, M. (2006). Obesity and infection. *The Lancet Infectious Diseases*, 6(7), 438-446. https://doi.org/10.1016/S1473-3099(06)70523-0
22. Csige, I., Ujvarosy, D., Szabo, Z., Lorincz, I., Paragh, G., Harangi, M., & Somodi, S. (2018). The Impact of Obesity on the Cardiovascular System. *Journal of Diabetes Research*, 2018(1), 1–12. https://doi.org/10.1155/2018/3407306
23. Heredia, F., Gómez-Martínez, S., & Marcos, A. (2012). Obesity, inflammation and the immune system. *Proceedings of the Nutrition Society,* 71(2), 332-338. https://doi.org/10.1017/S0029665112000092
24. Pahwa R, Goyal A, Jialal I. (2021). *Chronic Inflammation.* StatPearls Publishing.
25. World Health Organization. (2021, August 25). Hypertension. *World Health Organization*, https://www.who.int/health-topics/hypertension#tab=tab\_1
26. Beevers, G. (2001). ABC of Hypertension: The Pathophysiology of Hypertension. *BMJ*, 322(7291), 912–916. https://doi.org/10.1136/bmj.322.7291.912
27. Centers for Disease Control and Prevention. (2021, May 18). High Blood Pressure Symptoms and Causes. *Centers for Disease Control and Prevention*, https://www.cdc.gov/bloodpressure/about.htm
28. Lüthi, B., & Schlagenhauf, P. (2015). Risk factors associated with malaria deaths in travellers: A literature review. *Travel Medicine and Infectious Disease*, 13(1), 48-60. https://doi.org/10.1016/j.tmaid.2014.04.014
29. Etyang, A., Smeeth, L., Cruickshank, K., & Scott, A. (2016). The Malaria-High Blood Pressure Hypothesis. *Circulation Research*, 119(1), 36–40., https://doi.org/10.1161/circresaha.116.308763
30. World Health Organization. (2021, November 15). Diabetes. *World Health Organization*, https://www.who.int/health-topics/diabetes#tab=tab\_1
31. Centers for Disease Control and Prevention (2021, April 27). Diabetes Symptoms. *Centers for Disease Control and Prevention*, https://www.cdc.gov/diabetes/basics/symptoms.html
32. Danquah, I., Bedu-Addo, G., & Mockenhaupt, F. (2010). Type 2 Diabetes Mellitus and Increased Risk for Malaria Infection. *Emerging Infectious Diseases*, 16(10), 1601–1604, https://doi.org/10.3201/eid1610.100399
33. Mohapatra, M. (2001). Profile of Severe Falciparum Malaria in Diabetics. *International Journal of Diabetes in Developing Countries,* 21(1), 156-161, https://www.springer.com/journal/13410/
34. Ezzati, M., Hoorn, S., Lawes, C., Leach, R., James, W., Lopez, A., Rodgers, A., & Murray, C. (2005). Rethinking the ‘Diseases of Affluence’ Paradigm: Global Patterns of Nutritional Risks in Relation to Economic Development. *PLoS Medicine*, 2(5), 404-412. https://doi.org/10.1371/journal.pmed.0020133
35. Sharaf-el-Deen, S., Mahdy, A., Elshafey, O., El-Ghaffar, M., El-Melegy, M., & Ammar, A. (2021). Sequence Analysis of K13 Propeller Gene Polymorphism of *Plasmodium Falciparum*-infected Patients in Egypt. *Journal of the Egyptian Society of Parasitology*, 51(3), 423-430. https://jesp.journals.ekb.eg/article\_210411\_4d91a08ea286b42eb2be4a3a86edb203.pdf
36. Tangpukdee, N., Krudsood, S., Thanachartwet, V., Duangdee, C., Paksala, S., Chonsawat, P., Srivilairit, S., Looareesuwan, S., & Wilairatana, P. (2007). Predictive Score of Uncomplicated Falciparum Malaria Patients Turning to Severe Malaria. *The Korean Journal of Parasitology*, 45(4), 273–282. https://doi.org/10.3347/kjp.2007.45.4.273
37. World Health Organization. (2014, September). Who Severe Malaria TMIH Supplement 2014. *Tropical Medicine and International Health*, https://www.who.int/malaria/publications/atoz/who-severe-malaria tmih-supplement-2014.pdf
38. World Health Organization. (2021, December 6). Fact Sheet about Malaria. *World Health Organization*, https://www.who.int/news-room/fact-sheets/detail/malaria
39. Doolan, D. L., Dobano, C., & Baird, J. (2009). Acquired immunity to malaria. *Clinical microbiology reviews,* 22(1), 13-36, https://doi.org/10.1128/CMR.00025-08
40. Szumilas, M. (2010). Explaining Odds Ratios. *Journal of the Canadian Academy of Child and Adolescent Psychiatry*, 19(3), 227-229. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2938757/
41. Centers for Disease Control and Prevention. (2018, November 15). CDC - Malaria - Travelers - Choosing a Drug to Prevent Malaria. *Centers for Disease Control and Prevention*, https://www.cdc.gov/malaria/travelers/drugs.html
42. Centers for Disease Control and Prevention. (2021, February 8). Diabetes in Youth. *Centers for Disease Control and Prevention*, https://www.cdc.gov/diabetes/library/reports/reportcard/diabetes-in-youth.html#:~:text=Of%20the%20estimated%2026.9%20million,younger%20than%20age%2020%20years.&text=The%20increasing%20frequency%20of%20both,clinical%20ad%20public%20health%20concern
43. Briggs, J., Teyssier, N., Nankabirwa, J., Rek, J., Jagannathann, P., Arinaitwe, E., Bousema, T., Drakeley, C., Murray, M., Crawford, E., Hathaway, N., Staedtke, S., Smith, D., Rosenthal, P., Kamya, M., Dorsey, G., Rodriguez-Barraquer, I., & Greenhouse, B. (2020). Sex-Based Differences in Clearance of Chronic Plasmodium Falciparum Infection. *eLife*, 9(1), 1-10. https://doi.org/10.7554/elife.59872