Fasting Blood Glucose in a Ghanaian Adult is Causally Linked with Malaria Parasite Count: A Mechanistic Case Study Using Convergent Cross Mapping

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Abstract

Background: Adults with diabetes mellitus (DM) in malaria-endemic areas might be more susceptible to *Plasmodium* infection than healthy individuals. Herein, we aimed at verifying the hypothesis that increased fasting blood glucose (FBG) promotes parasite growth as reflected by increased parasite density.

Methods: Seven adults without DM were recruited in rural Ghana to determine the relationships between FBG and malaria parasite load. Socio-economic data were recorded in questionnaire-based interviews. Over a period of 6 weeks, we measured FBG and *Plasmodium spc.* infection in peripheral blood samples photometrically and by polymerase chain reaction (PCR)-assays, respectively. Daily physical activity and weather data were documented *via* smartphone recording. For the complex natural systems of homeostatic glucose control and *Plasmodium spc.* lifecycle, empirical dynamic modelling was applied.

Results: At baseline, four men and three women (median age, 33 years; interquartile range, 30-48) showed a median FBG of 5.5 (5.1-6.0 mmol/L); one participant had an asymptomatic *Plasmodium spc.* infection (parasite density: 240 /µL). In this participant, convergent cross mapping (CCM) for 34 consecutive days, showed that FBG was causally affected by parasite density ($p < 0.02$), while the reciprocal relationship was not discernible ($p > 0.05$). Additionally, daily ambient temperature affected parasite density ($p < 0.01$).

Conclusion: In this study population living in a malaria-endemic area, we successfully piloted time series analyses for the relationships between FBG and *Plasmodium spc.* density. Longer observation periods and larger samples are required to confirm these findings and determine the direction of causality.

Introduction

Infectious diseases such as malaria, HIV and tuberculosis have long been the main contributors to morbidity and mortality in Sub-Saharan Africa (SSA) (Roth et al., 2018). It is encouraging that malaria-related deaths have declined globally from 585,000 in 2010 to 405,000 in 2018. However, malaria still constitutes a major public health threat in SSA with more than 90% of cases and deaths occurring among children under the age of five years (WHO Global, 2019). In Ghana, West Africa, malaria remains highly endemic with an annual incidence of 10,000 per 100,000 at risk (Murray et al., 2014). Notably, it is one of the countries with the highest absolute increase in malaria cases as reported in 2018, compared with 2017 (WHO Global, 2019).

At the same time, non-communicable diseases (NCDs) have gained considerable importance globally and in SSA, including an “epidemic” of diabetes mellitus (DM) (Gouda et al., 2019). Worldwide, 463 million adults are living with DM as of 2019, with 79% residing in low- and middle-income countries. The International Diabetes Federation predicts that worldwide, there will be 700 million people living with DM by 2045 (Duke et al., 2019). Type 2 diabetes mellitus (T2DM) poses a growing health problem on the African continent (Duke et al., 2019; Sinclair, 2019), including Ghana, where 10% of adults have T2DM (Agyemang et al., 2016). The accelerating urbanization in the African region comes along with changes in

dietary behavior and physical activity, which contribute to the observed increase of T2DM (Mbanya et al., 2010). In addition to this, the epidemiologic transition from infectious diseases to NCDs due to increased life-expectancy and lower birth rates progresses slowly in SSA. These factors give rise to the observed double burden of infectious diseases and NCDs in the region. This double burden has been recognized at the country level (Smallman-Raynor & Phillips, 1999) and among individuals (Alicke et al., 2017). Thus, interrelations of malaria and DM in SSA appear logical but have only been insufficiently investigated so far (Kalra et al., 2017).

Previously, we reported a 46% increased odds of *Plasmodium falciparum* infection among Ghanaian adults with T2DM in urban Ghana (Danquah et al., 2010). While this observation warrants independent verification, underlying mechanisms have been proposed. First, patients with DM may be more attractive to the mosquito vector *Anopheles gambiae* due to diabetes-related alterations in olfactory signals and thus, experience increased exposure to infectious bites (Dalton et al., 2004; Takken & Knols, 1999). Second, enhanced transmission of malaria parasites to individuals with DM has been suggested, based on findings in a murine malaria model (Pakpour et al., 2016). Third, immune suppression among individuals with DM may compromise the clearance of infected red-blood cells and thus, prolong the parasites´ lifespan (Muller et al., 2005). Fourth, malaria parasites depend on external glucose (Jensen et al., 1983), which is chronically increased in DM patients and thus, may fuel parasite growth. So far, the latter has been shown only under laboratory conditions and has not been addressed in real-life settings. At the same time, FBG homeostasis and malaria parasite density are tightly regulated, (White et al., 2014), which hampers the investigation of diabetes-malaria-interactions in cross-sectional studies.

Therefore, the major goal of this study was to establish the causal relationships between FBG concentrations and malaria parasite density using time series analysis of a prospective observational pilot study, among adults in rural Ghana. The specific objectives were i) to determine the time-varying associations between FBG and parasite load, and ii) to identify causal interaction between FBG and *Plasmodium* parasite density.

Methods

Study design and procedures

From September to October 2019, we conducted a prospective observational pilot study with seven adults who resided in Agogo, Ashanti Akim North District, Ashanti Region, Ghana. Subsistence farming, trading and mining are the main income sources in this region (Browne et al., 2000). Eligible individuals were recruited in the vicinity of Agogo Presbyterian Hospital and participated in daily follow-up visits over 6 weeks, except on Sundays. Inclusion criteria comprised adult age, permanent residence in Agogo and written informed consent. Exclusion criteria were plans to travel within the following 6 weeks, known diagnosis of DM, taking glucose-lowering medication, and known pregnancy. Following detailed information on background and procedures of the study, appointments at the hospital were scheduled for the next morning. We instructed the participants on over-night fasting and avoiding physical activity for

at least 8 hours before visiting the hospital. The individual examination comprised the daily collection of fasting peripheral blood samples for glucose measurement and malaria detection every morning, measurement of axillary temperature, and documentation of daily weather conditions and physical activity. Baseline interviews were conducted to assess the participants' socioeconomic background.

The study protocol adhered to the principles laid down in the Declaration of Helsinki and was reviewed and approved by the Committee on Human Research, Publication and Ethics of the School of Medical Sciences/Komfo Anokye Teaching Hospital, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana (CHRPE/AP/507/18). All participants gave written informed consent.

Glucose measurement and malaria detection

FBG was measured in finger-prick fasting blood samples applying a portable HemoCue Glucose 201$^+$ RT device (HemoCue, Germany), providing plasma equivalents of FBG in mmol/L. Malaria parasites were microscopically identified on Giemsa-stained (4%, 30 min., pH 7.2) thick and thin blood films. Parasite density was quantified by examining microscopy fields of the thick film corresponding to 500 white blood cells (WBCs), and the average WBC count was set as 8,000/µL. Thin films served for species differentiation. In addition, venous whole blood samples were collected on filter paper (Whatman cellulose chromatography paper, 3 mm). DNA was extracted using the QIAmp DNA Blood Mini kit (QIAGEN, Germany https://www.qiagen.com). *Plasmodium* species and sub-microscopic infections were then identi□ed by semi-nested multiplex PCR assays (Rubio et al., 2002). For Cp values, that correspond to parasite load, quantitative real-time PCR analyses were performed using commercially available primers and probes for *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae* (TIB MolBiol, https://www.tib-molbiol.com) on a Roche LightCycler 480 device (https://lifescience.roche.com). *Plasmodium* infection was defined by the more sensitive PCR-assay in the absence of current fever (axillary temperature ≥37.5°C) and was not treated during the present study. Clinical malaria was defined as microscopically visible parasites *plus* current fever and was treated according to Ghana Health Service guidelines.

Assessment of covariables

Demographic and socioeconomic data were documented in face-to-face interviews by trained study personnel and comprised age (years), sex (m/f), residence (Agogo or else), known DM status (yes/ no/ unknown), known malaria status (yes/no/unknown), level of formal education (none/ primary/ secondary/ tertiary/ other), current occupation (subsistence farming/ trading/ business/ public servant/ unemployed), and the number of household's physical assets (list of 11 items). Further, meteorological data and physical activity levels were assessed as factors potentially influencing both, FBG (Li et al., 2016) and parasite density (Cella et al., 2019; Pathak et al., 2019). Each participant was supplied with a standard smartphone and pre-installed applications for the assessment of these covariables. We documented daily air humidity (%) and ambient temperature (°C) (accuweather.com) as well as the duration of daily physical activity (min/d) and the step count (steps/d) (Google Fit).

In addition, body weight to the nearest 100g and height to the nearest cm were assessed in duplicates, using the Person Scale DT602 (Camry, Hong Kong, China) and the statometer SECA 213 (Hamburg,

Germany), respectively. Body mass index (BMI) was calculated as weight (kg) over squared height (m) and is expressed in kg/m^2.

Data analysis

The baseline characteristics of the study population are presented as median and range for continuous variables and as absolute numbers for categorical data.

For establishing causal links between FBG and malaria parasite load, linear statistical methods such as correlation analysis were inappropriate. In fact, the metabolic processes regulating blood glucose and parasite density over time are inherently non-linear (Churcher et al., 2010). Also, linear analyses had the risk of detecting spurious correlations, which might have led to wrong or misleading conclusions (Deyle et al., 2013, 2016; Sugihara et al., 2012). To overcome the problematic setting of cross-sectional assessments for the investigation of time-varying fluctuations in glucose metabolism and parasite growth, we applied the framework of empirical dynamical modelling (EDM) that acknowledges non-linear dynamics (Chang et al., 2017). Here, we used Convergence Cross Mapping (CCM) for the identification of causal coupling between FBG and malaria parasite count (Sugihara et al., 2012). More detail about this method is presented in the **Supplementary material**. In brief, CCM operates on the theory of dynamical systems. This theory acknowledges complex biological interactions in time and space that can be mathematically detected (Packard et al., 1980). Following this idea, we tested if FBG and parasite load as two time series variables were causally coupled (originated from the same dynamical system) by measuring the extent to which the time series of the causal variable has left an imprint in the time series of the affected variable (Sugihara et al., 2012). FBG concentration was defined as the causal variable, and *P. falciparum* density served as the affected variable (here: Cp as a proxy measure).

For significance testing, we generated 100 surrogate time series that were comparable to the measured data but fulfilled the null hypothesis of no relationship between the two time series variables (Kantz and Schreiber, 2006) following the method by Ebisuzaki, 1997. The causal couplings of the empirical time series were defined as significant if the CCM result of the original data outperformed 95% of the CCM results of the surrogate data ($p < 0.05$) (Deyle et al., 2013; Van Nes et al., 2015). Furthermore, the embedding dimension (*E*) for each potential causal combination (from FBG, weather parameters and body temperature to parasite density) in CCM analysis was determined following the procedure of Deyle et al., 2016. This corresponds to a lag nonlinear model, where cross-mapping ρ lagged 1-time step for the largest possible number of points in the surrogate time series. Further, all-time series were normalized to zero mean and unit variance. Due to the paucity of observation points, we performed leave-one-out cross-validation (Glaser et al., 2014). Two missing values for parasite density were imputed by linear interpolation. Time series analysis was performed using the rEDM package (version 0.7.3) of the programming language *R* (Ye et al., 2020).

Results

Study population

Table 1 presents the baseline characteristics of the study population. Among the seven participants, there were four men and three women with an age range between 30 to 48 years. Six participants reported to belong to the Akan tribe. Five individuals permanently resided in Agogo, and six participants had a secondary formal education. All participants worked as sellers or other service personnel in the vicinity of the hospital. The median of household assets was 6 out of 11, and the BMI ranged between 20.7 and 39.1 kg/m^2. The baseline axillary body temperature was in the normal range for all participants (median: 36.3°C; range: 35.3-36.7°C). Also, the baseline FBG was in the normal range (median: 5.5 mmol/L; range: 5.1-6.0 mmol/L).

Table 1
Baseline characteristics of 7 study participants under 6-weeks glucose- and *Plasmodium*-monitoring

Characteristics	**Median (range) / n**
N	7
Age (years)	33 (30-48)
Males : Females	4 : 3
Agogo residence	5
Akan ethnicity	6
Secondary education	6
Occupation	
Street vendor	2
Cleaner	2
Security service	2
Public servant	1
No. of 11 assets	6 (2-7)
Body Mass Index (kg/m^2)	27.8 (20.7-39.1)
Baseline fasting plasma glucose (mmol/L)	5.5 (5.1-6.0)
Baseline axillary temperature (°C)	36.3 (35.3-36.7)
Baseline *P. falciparum* infection	1
Baseline malaria parasite count of infected individuals (GMPD/µL)	240
Baseline physical activity (min/d)	61.8 (16.2-114.6)
Baseline step count (steps/d)	5,728 (1,664-11,072)

Only one individual had microscopically visible *Plasmodium falciparum* infection at low parasite density (baseline: 240 parasites/µL). This infection was asymptomatic throughout the study period. As shown in Figure 1a, this person had two peaks in microscopically detected parasite density on day 2 (560 parasites/µL) and on day 24 (600 parasites/µL). Corresponding Cp values as a measure of (submicroscopic) parasite load showed similar peak time points and constant parasite load throughout the course of the study (Figure 1b**)**. For this participant, baseline FBG was normal (5.5 mmol/L) but varied considerably between 3.0 and 6.8 mmol/L (Figure 1c). None of the remaining participants was subsequently infected during the study period.

Relationships of fasting blood glucose with malaria parasite density

For the one participant with asymptomatic malaria infection, Cp values remained stable when FBG ranged between 4.5 to 5.5 mmol/L. The time series of FBG and parasite density (Fig. 1a and 1b) indicated that parasite density lagged FBG. However, this was not discernible for the relationship between FBG and Cp values (Fig. 1a and 1c). In fact, any drop in FBG appeared to follow a peak in Cp (Fig. 1a and 1c). The results of the CCM analysis supported this observation. As shown in Figure 2, we detected that Cp causally affected FBG concentration ($p<0.01$) but not vice versa. The surrogate data for no relationship between Cp and FBG were outperformed by 95% of the empirical time series for these two variables.

Relationships with covariables

To test the robustness of the CCM analysis in this dynamical system of FBG homeostasis and regulation of parasite density, we examined additional relationships with relevant covariables. Regarding causal links with Cp values, weather parameters and body temperature were assessed for the participant with asymptomatic malaria infection. The mean daily ambient temperature was 25.2°C (SD=1.9°C) with the maximum recorded being 31°C and the minimum 23°C. The results of the CCM analysis for air temperature and Cp values in this participant are shown in Figure 3. Cp lagged daily ambient temperature ($p<0.01$). The mean relative humidity was 84.0% (SD=9.1%) ranging between 97% and 61%. There was no relationship between humidity and Cp ($p>0.05$). Also, in this asymptomatic participant, we did not detect a causal relationship between body temperature and Cp ($p>0.05$).

Regarding causal relationships with FBG, we analyzed the duration of physical activity (min/day) and step count (steps/day) among all study participants. As shown in Table 2, various lag times were tested (0-5 days). Among four participants, the empirical CCM results outperformed the surrogate time series for physical activity and FBG, indicating that both, duration of physical activity and step count, affected FBG ($p<0.05$).

Table 2
Convergence cross-mapping detects causal effects of physical activity (min/day) and step count (steps/day) on fasting blood glucose (FBG) concentration

Patient number	Affected variable	Effecting variable	Time lag (day)	Kendall's τ	p_τ
1	FBG	Activity in min	0	0.929	<0.0001
1	FBG	Activity in min	3	1	<0.0001
1	FBG	Step count	0	0.937	<0.0001
1	FBG	Step count	3	1	<0.0001
2	FBG	Activity in min	2	0.974	<0.0001
2	FBG	Step count	2	0.974	<0.0001
3	FBG	Step count	1	0.918	<0.0001
6	FBG	Step count	5	1	<0.0001
7	FBG	Activity in min	5	1	<0.0001
7	FBG	Step count	5	1	<0.0001

Discussion

In this prospective observational study among 7 adults living in rural Ghana, we analyzed the causal relationships between time series of FBG and measures of malaria parasite load. During the course of the study, only one individual had an asymptomatic malaria infection at low parasite density. In this participant, CCM results showed that Cp values (as a measure of submicroscopic parasite density) affected FBG concentrations. But FBG did not affect Cp. In addition, temperatures affected parasite density, and more physical activity led to lower FBG.

Relationships of fasting blood glucose with malaria parasite load

Our results agree with the fact that *Plasmodium spc.* lack the ability to store energy in the form of polysaccharides such as glycogen. Therefore, the parasite relies on exogeneous glucose supply (Dasgupta, 1960; Homewood, 1977; Olszewski & Llinás, 2011; Scheibel & Miller, 1969; Srivastava et al., 2016). With enough glucose supply, parasite growth and proliferation are enhanced. Vice versa, when glucose supply is interrupted or drops below 5.5 mmol/l, parasite growth and proliferation are greatly impaired (Humeida & Pradel, 2011), giving further weight to our finding that Cp values remained stable when FBG ranged between 4.5 to 5.5 mmol/L. Interestingly, to ease the availability of glucose, infected erythrocytes exhibit a substantial increase in erythrocyte membrane permeability to low molecular weight sugar. In fact, these erythrocytes utilize up to two orders of magnitude more glucose than their non-infected counterparts (Egée et al., 2015; Olszewski & Llinás, 2011; Tewari et al., 2020), leading to

hypoglycemia – a common symptom of clinical malaria (White et al., 2014). In the present study, this is reflected as a drop in FBG following a peak in Cp.

Even though CCM did not detect the reciprocal relationship between FBG and Cp, this observation could be explained by the fact that we could only detect and follow-up malaria parasite load in one participant, thereby increasing the chances for type II error. Clearly, verification in a larger sample and with a longer observation period is required. Still, it remains plausible that individuals with regularly increased blood glucose concentration might experience enhanced malaria parasite growth as compared to subjects with a healthy glucose metabolism.

Interrelations with weather parameters and physical activity

The relationships between weather parameters and parasite load have not been sufficiently explored. However, in SSA, a statistically significant variation of mean parasite density (P-value <0.01) has been previously reported to be influenced by different seasons (Mayengue et al., 2020). In the present study, daily ambient temperatures were associated with Cp. Further CCM confirmed the causality of this relationship, pointing towards an important role of temperature in parasite growth. Therefore, this weather parameter could modulate the relationship between FBG and Cp, as has been seen in the *Anopheles* vector (Pathak et al., 2019).

Also, the observed relationship between physical activity and FBG accords with existing scientific evidence. Physical activity has a glucose-lowering effect (Grace et al., 2017) wherefore it is recommended for the prevention of T2DM and as one of the first-line T2DM treatments (IDF, 2017). Physical exercise induces glucose uptake into skeletal muscles (Henriksen, 2001), and supports the stabilization of plasma blood glucose in the postprandial response, thereby limiting hyperglycemic peaks (Manders et al., 2010).

Our findings underline the necessity of strong adherence to malaria protective measures among individuals with chronically increased blood glucose. This may have implications for patients with poor blood glucose control living in SSA. In fact, only 37% of adults with T2DM in rural Ghana receive glucose-lowering medication, and of these, only 63% have good glucose control (Bijlholt et al., 2018). In addition, children with more severe type 1 DM may be particularly affected, because poor glucose control and lack of semi-immunity against malaria parasites may support the proliferation of *Plasmodium spc.* Lastly, travelers with DM should be encouraged to adhere to their glucose-lowering medication and malaria prophylaxis.

Strengths and limitations

This is the first study, in which time series analysis has been applied, to determine the causal relatedness of FBG to *Plasmodium spc.* density. However, the results of our study need to be interpreted with caution. Even though the number of participants was fair enough for time series analysis, only one individual developed *Plasmodium spc.* infection, thereby leading to type II error and thus limiting our ability to verify the hypothesis that higher FBG leads to higher parasite load. No examinations were conducted on Sundays, which interrupted the time series assessments. Yet, for the participant with asymptomatic

infection, we have overcome any issues arising from missing data by leave-one-out cross validation and linear interpolation. Still, independent studies with longer observation periods and larger sample size are warranted for better in-depth explanation of this causal relationship and to verify the direction of causality.

Conclusion

In conclusion, we have applied CCM to investigate whether FBG among Ghanaian adults is causally linked with malaria parasite density. Since metabolic processes regulating blood glucose and malaria parasite growth are inherently non-linear, we applied the EDM framework for non-linear dynamics in time series data. In this healthy study population without DM, we have verified the common observation of malaria-related hypoglycemia. Yet, the confirmation of our original hypothesis is pending until longer and larger time series analysis can provide causal links between chronically increased FBG and malaria parasite growth.

Declarations

Ethics approval and consent to participate

This study was approved by the committee on Human Research, Publication and Ethics board of the School of Medical Sciences/Komfo Anokye Teaching Hospital under the reference number CHRPE/AP/507/18.

Consent for publication

Not applicable

Availability of data and material

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

ID, FPM and GBA conceived and designed the study. YAA and RKN collected the data. FG and AT analyzed the data and contributed to interpretation. CAA drafted the article. All authors critically revised the manuscript and approved the final version to be published.

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Figures

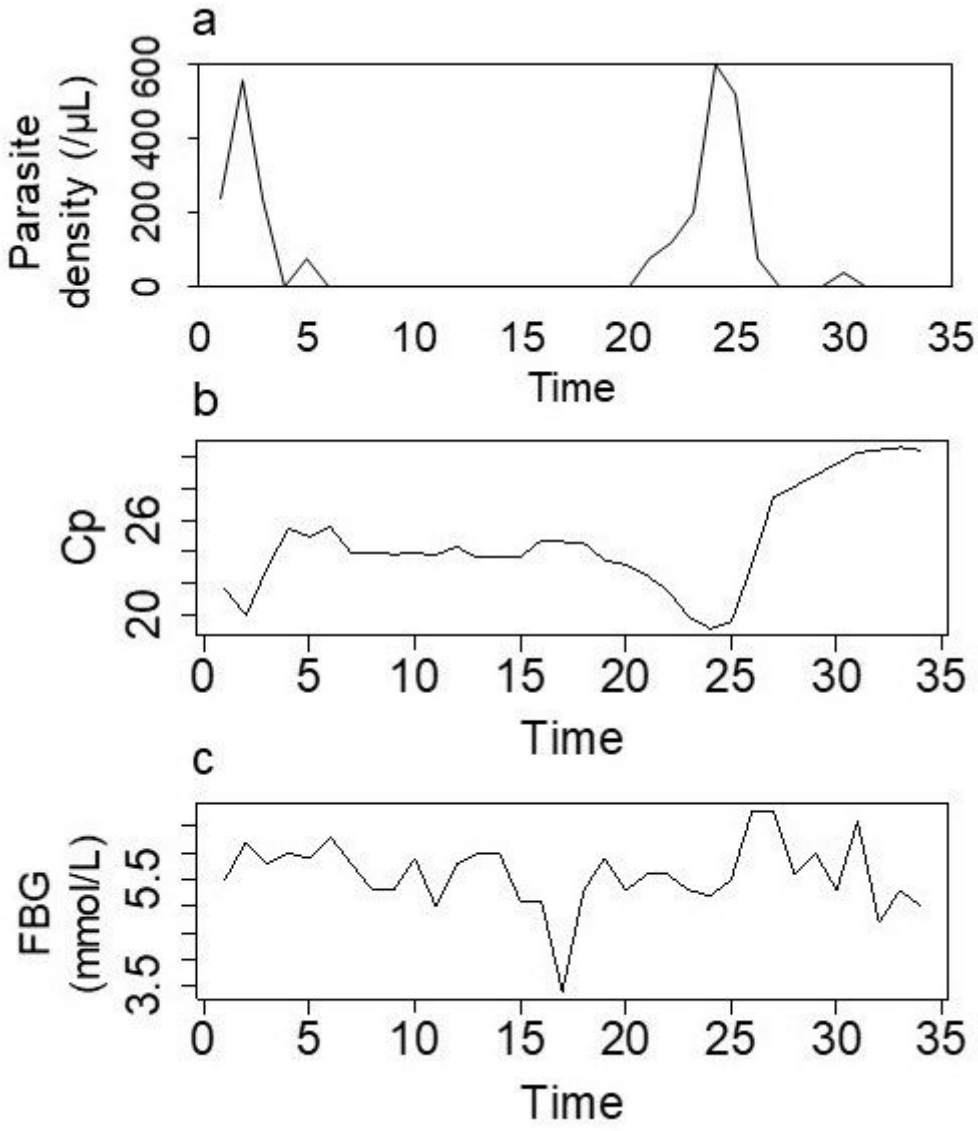

Figure 1

Empirical time series of patient #2. Shown are (a) Plasmodium falciparum density, (b) Cp as a measure of parasite density by PCR, and (c) fasting blood glucose (FBG), as a function of time.

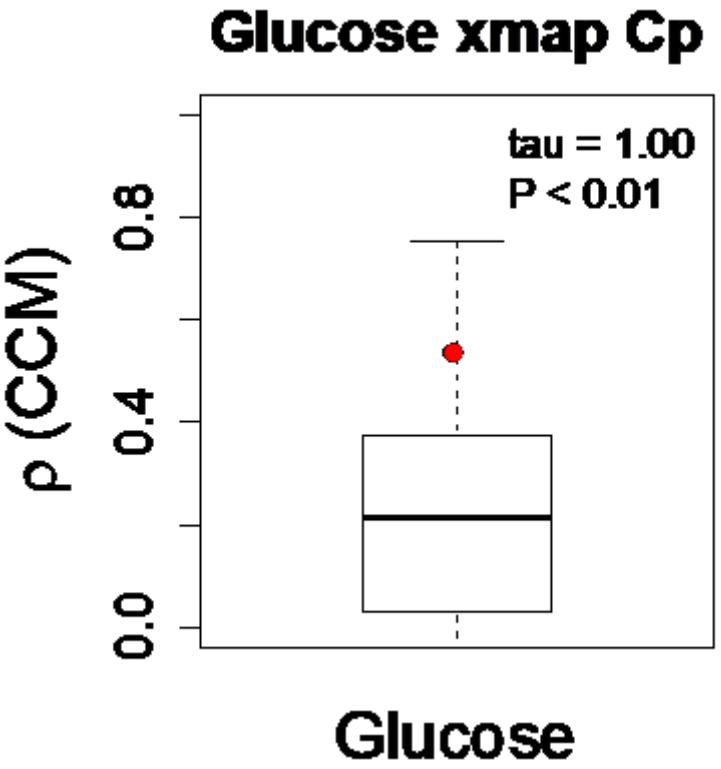

Figure 2

Convergence cross-mapping (CCM) detects a causal effect of Cp (=measure of Plasmodium falciparum density) on fasting blood glucose concentration in patient #2. Shown are the CCM results ρ of the empirical time series (red dot) as well as the results of the surrogate time series (box plot). The empirical result ρ=0.538 outperforms over 95% of the surrogates. A significant Kendall's τ quantifies the convergence of ρ for increasing library size.

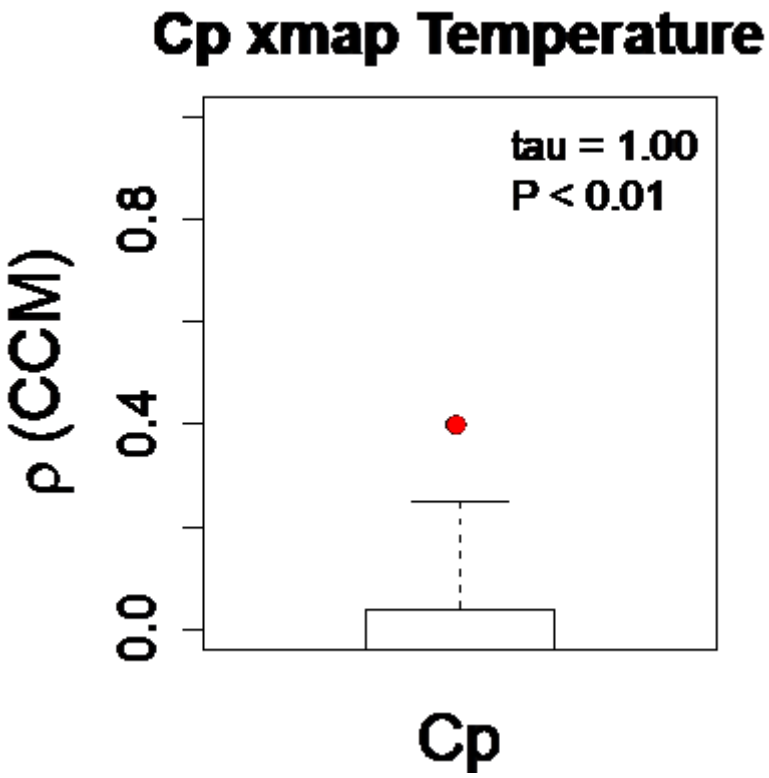

Figure 3

Convergence cross-mapping (CCM) detects a causal effect of temperature on Cp (measure of Plasmodium falciparum density).

Supplementary Files

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