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The impact of interethnic lipidomic variation in falciparum malaria

Wael Abdrabou [a,1], Saruul Zorigt [a], Issiaka Soulama [b,c], Dariga Bolatbay [a], Mame Massar Dieng [a], Jakub Jurkovic [a], Samuel Sindié Sermé [b], Salif Sombié [b], Noëlie Béré Henry [b], Désiré Kargougou [b], Sam Aboubacar Coulibaly [b], Aïssatou Diawara [a], Youssef Idaghdour [a,d,*]

[a] Program in Biology, Division of Science, New York University Abu Dhabi, Abu Dhabi, UAE
[b] Centre National de Recherche et de Formation sur le Paludisme, Ouagadougou, Burkina Faso
[c] Institut de Recherche en Sciences de la Santé, Ouagadougou, Burkina Faso
[d] Center for Genomics and Systems Biology, New York University Abu Dhabi, Abu Dhabi, UAE

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SUMMARY

Background: Shifts in dietary patterns during lifestyle transitions are integral components of the dynamic interactions between humans and their environments. Investigating the link between dietary diversity, the composition of the human lipidome and infection is key to understanding the interplay between diet and susceptibility to pathogens.
Methods: Here we address this question by performing a comparative study of two ethnic groups with divergent dietary patterns: Fulani, who are nomad pastoralists with a dairy-centric diet, and Mossi, who are farmers with a plant-based diet. We generate 196 paired global lipidomes (927 lipid molecules) from both groups before and during natural *Plasmodium falciparum* infection.
Results: Our analysis revealed 211 significantly differentially abundant lipid molecules between the two ethnic groups in both infection states. We show that ethnicity has a greater impact on the lipidome of these children than do *P. falciparum* infection and report inter-ethnic differences that impact pathogenesis. We highlight elevated levels of pentadecanoic acid (C15:0)-containing phospholipids in Fulani and experimentally demonstrate the suppressive effects of lysophosphatidylcholine LysoPC (15:0) on *P. falciparum* gametocyte production.
Conclusion: These findings link the Fulani's dairy-centric diet and lower *P. falciparum* gametocyte densities reported in this group and underscore the intricate links between dietary lipids and the host response to infection.

Introduction

Humans have experienced multiple lifestyle transitions throughout history. Early humans primarily relied on a subsistence strategy of nomadic hunting and gathering until the Neolithic period. This era marked a gradual transition towards agricultural and agrarian-based lifestyles.[1] These transitions have contributed to strong immune genetic and transcriptional signatures of recent positive selection [2,3] as a result of differential pathogen exposures. Lifestyle transitions have also been accompanied by major shifts in dietary consumption patterns which impact the composition of diet and consequently nutrient intake and nutritional status.[4,5] These factors are intricately linked to host immunity, microbiota and pathogens and as a result can influence the onset and course of infections.[6–8]

One notable impact of dietary transitions is the change in lipid composition of diet. Lipids, central components of diet, serve as substrates for cellular structure, energy metabolism and signaling pathways for both host and pathogen, embodying the complex interdependence between lipids, physiology and pathogenicity.[9] The lipid composition of human blood plasma influences blood pathogens like *Plasmodium falciparum*, which develop and circulate within the bloodstream during the blood stage of malaria. The lipid constituents of the host's diet affect the availability of nutrients and metabolites that *P. falciparum* critically depend on for their asexual proliferation and sexual differentiation processes.[10–13] Successful

* Corresponding author at: Program in Biology, Division of Science, New York University Abu Dhabi, Abu Dhabi, UAE.
E-mail address: youssef.idaghdour@nyu.edu (Y. Idaghdour).
[1] Current Address: College of Health Sciences, Abu Dhabi University.

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transmission from the human host to the mosquito vector necessitates a delicate balance between investments in asexual reproduction and gametocyte formation during the intra-erythrocytic developmental cycle.[14–17] These processes are impacted by host conditions and factors including circulating diet-derived molecules.[18,19] Diet exerts a profound influence on the lipid composition of blood plasma and the substantial diversity in dietary patterns among ethnic groups residing in malaria-endemic regions is therefore likely to impact the course of blood stage malaria.

The Fulani and Mossi ethnic groups have coexisted for generations in regions of high malaria prevalence in Burkina Faso, each with a unique lifestyle shaped by distinct dietary choices. Fulani, being pastoralists, follow a dairy-centric diet,[22–24] while Mossi, who are farmers, primarily consume a plant-based diet.[25–27] Multiple comparative studies have established that Fulani are less susceptible to falciparum malaria. Compared to other sympatric ethnic groups with similar *P. falciparum* exposures, Fulani exhibit distinct parasitological, immune [20–22,28–30] and clinical features,[31] including reduced levels of *P. falciparum* gametocyte densities.[32] It remains unclear if these features are related to a heightened immune response, or to other factors such as dietary preferences.

Here, we conducted a comparative lipidomic study of Mossi and Fulani children sampled before and during natural *P. falciparum* infection. The starkly divergent dietary patterns of the two ethnic groups offered an opportunity to investigate the relationship between lipid constituents of diet and response to *P. falciparum* infection. The seasonal pattern of malaria transmission in Burkina Faso provided a unique opportunity to employ a paired study design allowing for an in-depth examination of alterations in lipid composition directly associated with the onset and progression of infection. Our findings uncover a significant impact of ethnicity on a third of the host lipidome and show that this signature is driven by diet-derived lipids. We highlight the elevated levels of dairy derived-pentadecanoic acid (C15:0) and pentadecanoic-containing phospholipids in the less malaria susceptible Fulani. We further demonstrate the suppressive effects of LysoPC (15:0) on *P. falciparum* gametocyte production in vitro during blood stage malaria. These results illustrate the significant influence of dietary intake on the types and amounts of lipids circulating in the bloodstream, which in turn can influence the development of *Plasmodium* parasites within the human host, and link between inter-ethnic diversity in dietary habits and malaria pathogenesis.

Methods

Study design and ethical approval

A total of 53 Fulani and 45 Mossi children from Burkina Faso were recruited for the study. All recruited children reside in the health district of Saponé. The recruitment process took place at the end of the dry season and follow-up continued through the rainy season. Inclusion criteria were as follows: ages between 2 and 12, non-infected with *P. falciparum* at the time of enrollment, no fever (axillary temperature of ≥37.5 °C) in the 48 h preceding enrollment. Children with the following conditions were excluded from the study: suffering from active infection or illness, prior use of anti-malarial treatment within the two weeks preceding enrollment, use of any immune-modifying drugs within the six months preceding enrollment, receipt of a blood transfusion within the three months preceding enrollment, and a history of immunosuppressive or chronic diseases. Community consultations and engagement through household visits and interviews confirmed the plant- and dairy-based dietary choices of the Mossi and Fulani families. The study was granted approval by the Ethics Committee for Health Research of Ministry of Health of Burkina Faso (Protocols number 2015–02-018 and 2018–5-062) and the institutional review board of New York University Abu Dhabi (Protocols number 011–2015 and 0142018R).

Sample and data collection

Peripheral blood samples were obtained from study participants prior to the onset of, and during, *P. falciparum* infection. Subsequent to sampling during infection, the children were administered artemether/lumefantrine antimalarial treatment (Coartem). A total of 106 and 90 blood samples were collected from the same group of 53 Fulani and 45 Mossi children, respectively, resulting in 100% matching of samples before and during *P. falciparum* infection. Each participant provided 8 ml of peripheral blood split between SST and EDTA tubes for serum processing and hematological testing, respectively. *P. falciparum* infection status was initially determined by the SD BIOLINE Malaria Ag P.f/Pan rapid detection test, and confirmed using bright field microscopy and PCR analysis using *P. falciparum* specific primers.[33] Parasitemia was determined using Giemsa staining of blood smears following the World Health Organization guidelines. Clinical parameters of study participants were measured and recorded by a pediatrician and their clinical team (Supplementary Table 1).

Serum sample preparation and lipidomics profiling

Serum samples were isolated by centrifugation of blood samples in SST tubes for 30 min at 1500 RCF. Separated serum aliquots of 0.5 ml were stored in cryovials immediately at −80 °C prior to shipping to Metabolon Inc. (Durham, NC, USA) in dry ice for global lipidomic profiling. At Metabolon, lipids were extracted in conjunction with deuterated internal standards using an automated BUME extraction.[34] Lipid extracts were dried using nitrogen, and reconstituted in 0.25 ml of dichloromethane:methanol solution containing 10 mM ammonium acetate (50:50). Infusion-MS analysis was performed on a Shimadzu LC with nano PEEK tubing and the Sciex SelexIon-5500 QTRAP via both positive and negative mode electrospray for each sample. The 5500 QTRAP was operated in Multiple Reaction Monitoring (MRM) mode with a total of more than 1100 MRMs. Sciex SelexIon-5500 QTRAP is a triple quad instrument that applies a combination of flow injection analysis, differential mobility spectrometry, and multiple reaction monitoring allowing for the identification of complex lipids structure to the individual fatty acid level.[35] Samples were randomized to minimize inter-day variation in instrument tuning.

Complex lipid data curation

The individual lipid molecule concentration was calculated by the ratio of the signal intensity of each molecule to the signal intensity of its assigned internal standard multiplied by the concentration of the internal standard added to each sample. To determine the fatty acid composition of lipid classes containing more than one fatty acid per molecule, such as PC and PE, the proportion of each class composed of individual fatty acids (FAs) was calculated. Triglycerides (TAG) concentration was individually calculated based on the neutral loss of FA moieties. Each compound was adjusted in run-day blocks by aligning the medians to equal one and proportionally normalizing each data point. Missing values imputation was done using the observed minimum after normalization.

Lipid molecules annotation

Complex lipids were annotated in the following manner: Lysophospholipids (LysoPC and LPE), sphingolipids, cholesterol esters, and monoacylglycerols were annotated using the sum

composition of number of carbons and number of double bonds such as LPE (16:1), SM (18:0), CE (18:1), and MAG (18:2). TAGs were denoted by their sum composition – number of carbons and double bonds of one of the three FA moieties such as TAG 50:2-FA18:0. Phospholipids, namely PC, PE, PI, and PS, as well as diacylglycerols (DAG), were annotated using the following notion: <lipid class> (<number of carbons in first FA>:<number of double bonds in first FA><>/><number of carbons in second FA>:<number of double bonds in second FA>) such as PC (18:0/14:0) and DAG (14:0/18:0).

Lipidomics data curation and statistical analysis

Complex lipids data were log transformed and IQR normalized, and Principal component analysis (PCA) was performed using SAS/JMP Genomics version 10.0 (SAS Institute Inc., Cary, NC) to explore the correlation structure in the data and global influence of infection and ethnicity on the serum lipidome (Supplementary Fig. 1, Supplementary Table 2 and Mendeley Data). Supervised statistical analyses were carried out using both GraphPad Prism v8.0 and SAS/JMP Genomics version 10.0 (SAS Institute). Inter-ethnic analysis of covariance with repeated measures was used to identify statistically significant differentially abundant complex lipids and FA total concentrations between the Mossi and Fulani before and during infection while accounting for age, sex and hemoglobin levels and ratio of lymphocytes to neutrophils (RLN) using the following model:

$$\text{Lipid abundance} = \mu + \text{ethnicity} + \text{age} + \text{sex} + \text{hemogloboin} + \text{RLN} + \text{individual effect} + \epsilon$$

In this model, μ is the grand mean population sample for the metabolite and a normal distribution was assumed for the error ϵ with a mean of zero. A Benjamini-Hochberg false discovery rate threshold of 10% was used to infer statistical significance. The differences in the lipid abundance between the two groups were assessed using Mann–Whitney tests in GraphPad Prism v8.0.

Parasite culture

P. falciparum line 3D7 cultures were performed as previously described.[36] To prepare an asexual blood stage-rich parasite culture, *P. falciparum* cultures were synchronized twice using a 5% D-sorbitol (Sigma-Aldrich) solution at a 7–10-hour interval as described previously.[37] Cultures were kept at 37 °C in complete RPMI consisting of RPMI 1640 Medium with GlutaMAX™ and HEPES (ThermoFisher Scientific) supplemented with 0.05 mg/ml hypoxanthine (Invitrogen), 2 mg/ml sodium bicarbonate (Invitrogen), and 10 µg/ml gentamicin (Invitrogen), and 0.5% AlbuMAX (Invitrogen) in an atmosphere of 5% O_2, 5% CO_2, and 90% N_2. Cultures were also supplemented daily with 200 µl of erythrocytes that were obtained by collecting venous blood from healthy donors in EDTA tubes after white blood cells were removed through centrifugation at 3000 rpm for 10 min. The erythrocytes were washed using complete RPMI media (CM) and maintained at 50% hematocrit.

Quantification of gametocytogenesis induction

To evaluate the effect of LysoPC (15:00) on the induction of gametocytogenesis in *P. falciparum*, parasite-conditioned medium (Cond. M) was used to induce sexual conversion. Cond. M was prepared using a separate parasite culture maintained at high parasitemia 24 h prior to the experiment under well-defined conditions as described previously.[38] Two ethanol-dissolved stock solutions of LysoPC (15:0) and LysoPC (18:1) were prepared by dissolving 25 µg of each LysoPC (Avanti Polar Lipids) into ~150 µl of (50%) ethanol. Stock solutions of each LysoPC were then added to Cond. M to a final concentration of 25 µM of each lipid to generate Cond. M+LysoPC medium. Synchronized asexual blood-stage parasites were cultured for 4 days in triplicates in 24-well plates at 3% parasitemia (5% hematocrit) in 500 µls of the following prepared media: (25%) Cond. M +LysoPC (15:0); (25%) Cond. M+LysoPC (18:1); (25%) Cond. M+EtOH (containing an equal volume of 50% ethanol used to dissolve all LysoPCs); and complete media (CM) (as controls). Gametocytemia was assessed and calculated using microscopic counts of thin smears of erythrocyte samples fixed with methanol, stained with Giemsa, and microscopically evaluated on Days 1 and 4 by standard methods.[39] Differences in gametocyte counts between the two time points, and between the different conditions were evaluated using two-tailed paired *t* test and Kruskal-Wallis test, respectively, in GraphPad Prism v8.0. Significance was determined at a B-H FDR adjusted p value < 0.05.

Results

Paired inter-ethnic lipidomic profiling

The study involved meticulously paired sampling of 53 Fulani and 45 Mossi children, both before and during natural *P. falciparum* infection (100% matching) (Fig. 1A and Supplementary Table 1). The two groups were closely matched for key experimental variables, including exposure to *P. falciparum*, sex, age, hemoglobin levels before infection, and levels of parasitemia during infection (Fig. 1B). Sample collection was done for both ethnic groups simultaneously and the samples were randomized in each phase of data generation. A total of 196 global complex lipidomic profiles were generated using complex lipid profiling (Metabolon, Inc.) using a combination of flow injection analysis, differential mobility separation and multiple reaction monitoring (Fig. 1C, see Methods for details of complex lipid profiling). A total of 927 complex lipid molecules spanning 10 lipid classes were identified with the most represented being triacylglycerol (TAG; n = 518), phosphatidylethanolamine (PE; n = 100), and phosphatidylcholine (PC; n = 86). TAG and phospholipids made up 55% and 24% of total lipid molecules detected, respectively (Fig. 1C).

Impact of infection and ethnicity on the lipidome

First, we assessed the relative impact of infection and ethnicity on the lipidome of Fulani and Mossi children. Principal component analysis (PCA) of the full dataset revealed a strong correlation structure in the data, with the first two PCs accounting for 43.8% of the variation and PC1 clearly capturing a strong effect of ethnicity on the lipidome (Fig. 2A). The effect of ethnicity is clearly visible when the dataset is stratified by infection state, with ethnicity explaining approximately half of the variance of PC1 (Figs. 2B and 2C). These findings demonstrate the significant differences in the lipidomes of Fulani and Mossi children irrespective of their infection status, indicating that these differences are likely driven by their divergent diet regimes.

To identify the lipid molecules contributing to the disparity between the two ethnic groups before infection, we performed a pairwise comparison of the normalized concentrations of all lipid molecules in non-infected Fulani and Mossi children while accounting for sex, age, hemoglobin levels and ratio of lymphocytes to neutrophils. The analysis revealed 231 differentially abundant lipid molecules (FC ≥ |1.5|, B-H FDR < 0.1, Fig. 2D and Supplementary Table 2). Among these, 79 lipid molecules were enriched in Mossi, while 152 were enriched in Fulani. Investigating these differences in the infected state revealed 260 differentially abundant lipids between the two ethnic groups (FC ≥ |1.5|, B-H FDR < 0.1, Fig. 2E and Supplementary Table 2), with 81 lipids enriched in Mossi and 152 in Fulani. Notably, 75% (211 lipids) of the significantly differentially abundant lipids between the two ethnic groups were consistent

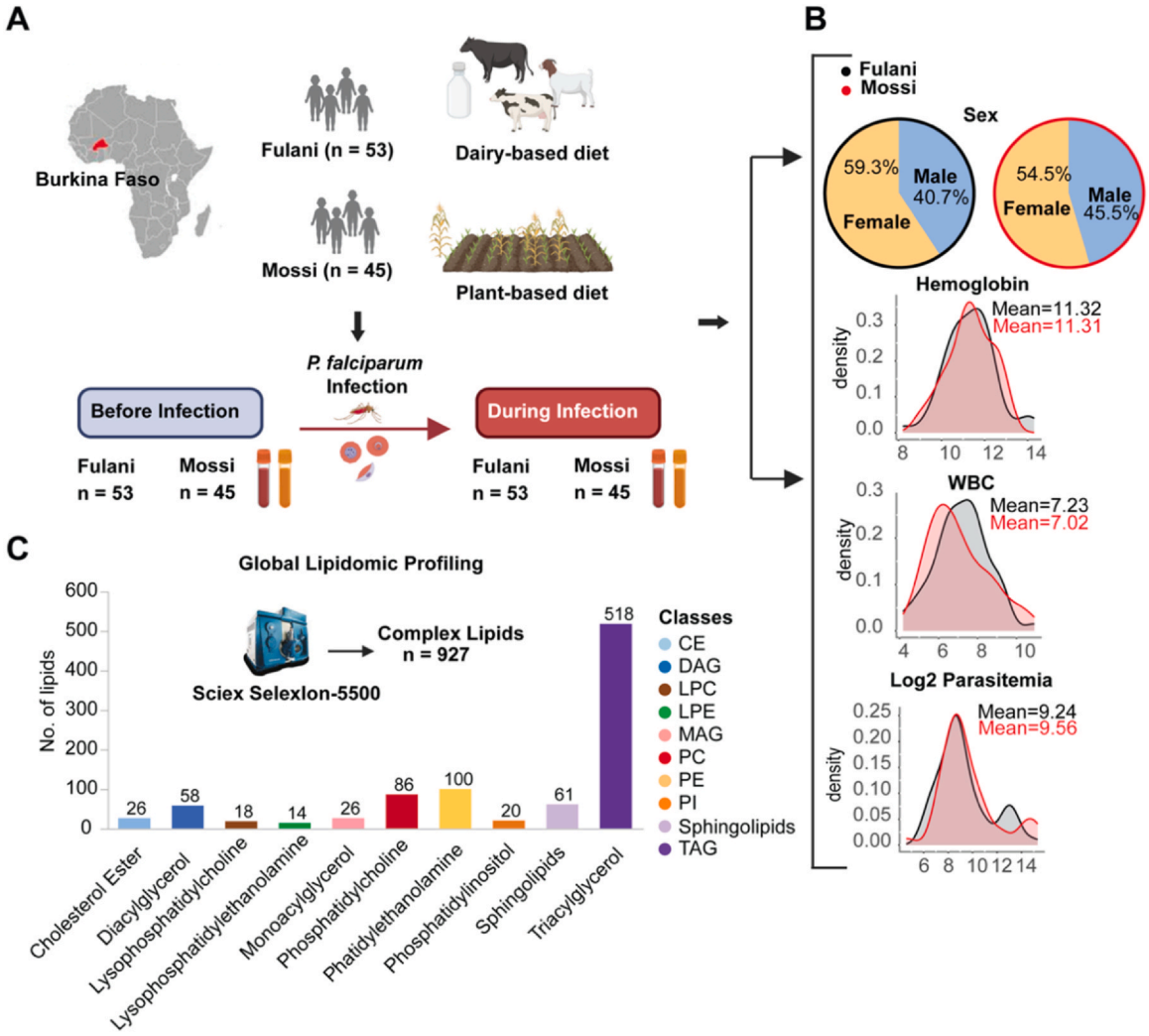

Fig. 1. Matched inter-ethnic comparative lipidomic profiling study of *P. falciparum* malaria. (A) Illustration of the prospective matched pairs study design for two sympatric ethnic groups; Fulani with a dairy-based diet and Mossi with a plant-based diet in Burkina Faso (upper panel). Total blood and serum samples collected from both cohorts are shown (lower panel). (B) Characteristics of Mossi and Fulani children including sex, age, hemoglobin levels, white blood cell count (WBC) and parasitemia. Density plots of age in years, hemoglobin levels and WBC, and its averages before infection (black), and the number of parasites/µl of blood (log2) and its average during infection (red), are shown for Fulani (n = 53) and Mossi (n = 45) children. (C) Global complex serum lipidomic profiling of Mossi and Fulani children revealed 927 complex lipid molecules grouped into 10 major lipid classes. Complex lipids were profiled using a combination of flow injection analysis, differential mobility spectrometry and multiple reaction monitoring.

across both infection states (Supplementary Table 2). These results demonstrate the persistence of most pre-infection inter-ethnic differences in the lipidome of children when they are infected.

A close examination of the differentially abundant lipids revealed striking inter-ethnic differences in the levels of diet-derived lipids, particularly pentadecanoic acid (C15:0)- and omega 3 (n3) docosahexaenoic acid (DHA, 22:6n3)-containing lipids (Figs. 2D and 2E). Pentadecanoic acid is dietary active essential odd chain saturated fatty acid not synthesized de novo by humans.[40,41] It serves as a biomarker for dairy fat intake and exhibits beneficial properties for cardiometabolic, immune and liver health.[41,42] Among the 152 significantly enriched lipids in Fulani before infection, 47% of the essential fatty acid-containing complex lipids (n = 14 out of 30) were pentadecanoic acid (C15:0)-containing lipids (e.g., CE (15:0) and PC (15:0/18:1)). Moreover, all of these lipid molecules remained significantly enriched in Fulani during infection (Fig. 2D-2F and Supplementary Table 1).

Additionally, among the 79 enriched lipids in Mossi before infection, 33 (42%) were DHA-containing lipids (e.g., PC (16:0/22:6), LysoPC (22:6) and DAG (18:0/22:6)) (Fig. 2D-2F and Supplementary Table 2). Of these 33 DHA-containing lipids, 31 (94%) remained enriched during infection (e.g., LysoPC (22:6): before infection FC = 1.88, B-H FDR-adjusted $P = 9.29^{-7}$; during infection FC = 1.99, B-H FDR-adjusted $P = 9.29^{-7}$) (Fig. 2D-2F, Supplementary Fig. 2 and Supplementary Table 2). The sustained presence of the majority of pre-infection differences during infection in both ethnic groups likely reflects the persistence of their general dietary habits when infected.

Next, we tested for association between the abundance of all lipid molecules and parasitemia within each ethnic group. Out of 927 lipid molecules tested, the analysis revealed 8 negatively correlated lipids with parasitemia in Fulani children: 2 LysoPCs, 2 LysoPEs, and 4 PCs ($r < -0.35$, BH FDR-adjusted $P < 0.05$). In Mossi, the analysis revealed 28 lipids including 9 negatively correlated with parasitemia (9 TAGs $r < -0.32$, BH FDR-adjusted $P < 0.05$) and 19 lipid molecules positively correlated with parasitemia (2 TAGs, 2 MAGs, 3 PCs, 2 PEs and 10 CERs, $r > 0.33$ and BH FDR-adjusted $P < 0.05$). The results of this analysis are provided in the Supplementary Table 2. While some of these lipids show potential as biomarkers of disease severity, further validation is required. Larger, longitudinal studies are necessary to confirm their specificity and sensitivity in different ethnic groups and malaria settings. Additionally, the underlying

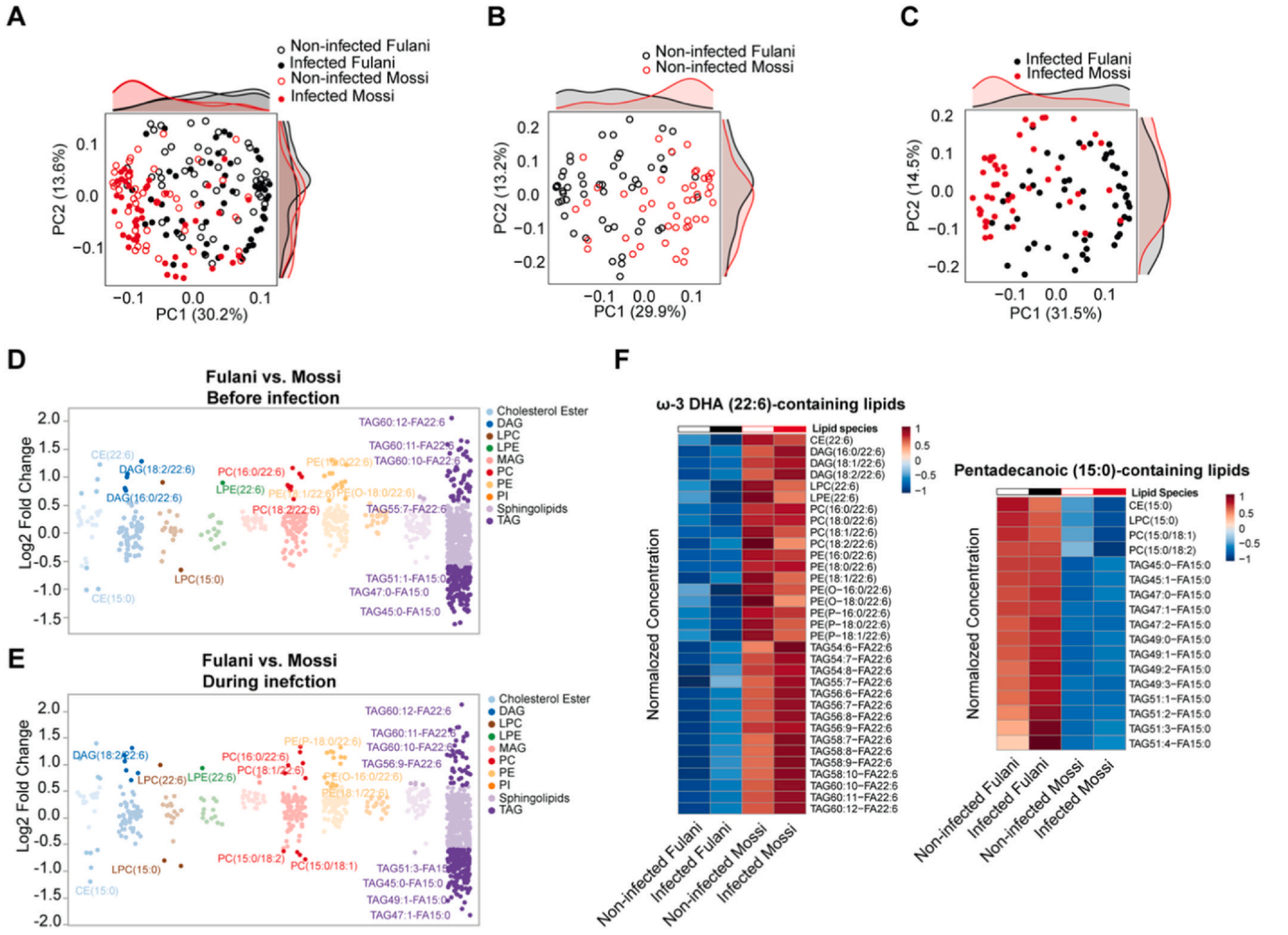

Fig. 2. Impact of ethnicity and infection on Fulani and Mossi plasma lipidomes. PCA of the global lipidome of Fulani children before infection (black circles; n = 53 samples) and during infection (back dots; 45 samples; 100% matched), and Mossi children before infection (red circles; n = 53 samples) and during infection (back dots; 45 samples; 100% matched). (B) PCA of the global lipidome of Fulani (black circles; n = 53 samples), and Mossi children before infection (red circles; n = 53 samples). (C) PCA of the global lipidome of Fulani (back dots; 45 samples), and Mossi children during infection (back dots; 45 samples). (D) Scatter plot disapplying the outcome of the differential lipid abundance analysis (n = 926 lipid molecules) between both cohorts (Fulani; n = 53) and (Mossi; n = 45) before infection. Significant differentially abundant lipids between the two ethnic groups (repeated measures ANCOVA, B-H FDR < 0.1, Fold Change > |1.5|) are highlighted in different colors, each representing a different lipid class, (n = 152 lipid molecules significantly abundant in Fulani relative to Mossi children, and n = 79 lipid molecules significantly abundant in Mossi relative to Fulani children before infection). (E) Scatter plot disapplying the outcome of the differential lipid abundance analysis (n = 926 lipid molecules) between the same two cohorts (100% matched samples) during infection. Significant differentially abundant lipids between the two ethnic groups (repeated measures ANCOVA, B-H FDR < 0.1, Fold Change > |1.5|) are highlighted in different colors, each representing a different lipid class (n = 179 lipid molecules significantly abundant in Fulani relative to Mossi children, and n = 81 lipid molecules significantly abundant in Mossi relative to Fulani children during infection). (F) Two-way clustering of the average concentration of diet-derived DHA-containing lipid molecules (left panel; n = 33) and pentadecanoic acid-containing lipid molecules (right panel; n = 17) in Fulani (n = 53) and Mossi (n = 45) children before and during infection using Ward's method.

mechanisms driving these lipid alterations and their direct involvement in disease outcomes need to be explored further to fully understand their clinical utility.

Inter-ethnic differences in essential fatty acids before and during P. falciparum infection

We expanded our ethnic comparative analysis to assess whether the total concentrations of fatty acids (FAs), irrespective of the complex lipid molecule or class they are part of, differ significantly between Mossi and Fulani using PCA. The analysis included all 32 FAs detected in our dataset and revealed segregation by ethnicity with PC1–2 explaining 61.8% of the variation in the data (Supplementary Fig. 3A). Investigating factor loadings in this analysis identified pentadecanoic acid (C15:0), DHA (C22:6), omega-6 PUFA linoleic acid (LA, C18:2), omega-3 PUFAs and α-linolenic acid (ALA, C18:3) as the most significantly correlated with PC1 and 2, differentiating Mossi and Fulani in both infection states (Supplementary Fig. 3B). Importantly, all of these FAs are diet-derived essential FAs, further supporting the hypothesis that diet plays a substantial role in the observed inter-ethnic lipidomic variation between Mossi and Fulani.

Analysis of variance of the 32 FAs by infection state revealed pentadecanoic acid (C15:0) as the most abundant FA in Fulani children both before infection (FC = 2.35, B-H FDR-adjusted $P = 2.91^{-7}$); and during infection (FC = 3.05, B-H FDR-adjusted $P = 2.70^{-7}$ (Fig. 3A, Supplementary Fig. 3C-D, and Supplementary Table 2). Conversely, DHA (C22:6) is the most abundant FA in Mossi children before infection (FC = 1.57, B-H FDR-adjusted $P = 9.28^{-7}$) and during infection (FC = 1.56, B-H FDR-adjusted $P = 2.70^{-8}$) (Fig. 3A, Supplementary Fig. 3C-D and Supplementary Table 2). Collectively, these results demonstrate the substantial impact of ethnicity on the lipidome of Fulani and Mossi children both before and during *P. falciparum* infection prompting further inquiry into whether the observed differences in the levels of lipid molecules contribute to inter-ethnic differences in the response to *P. falciparum* infection.

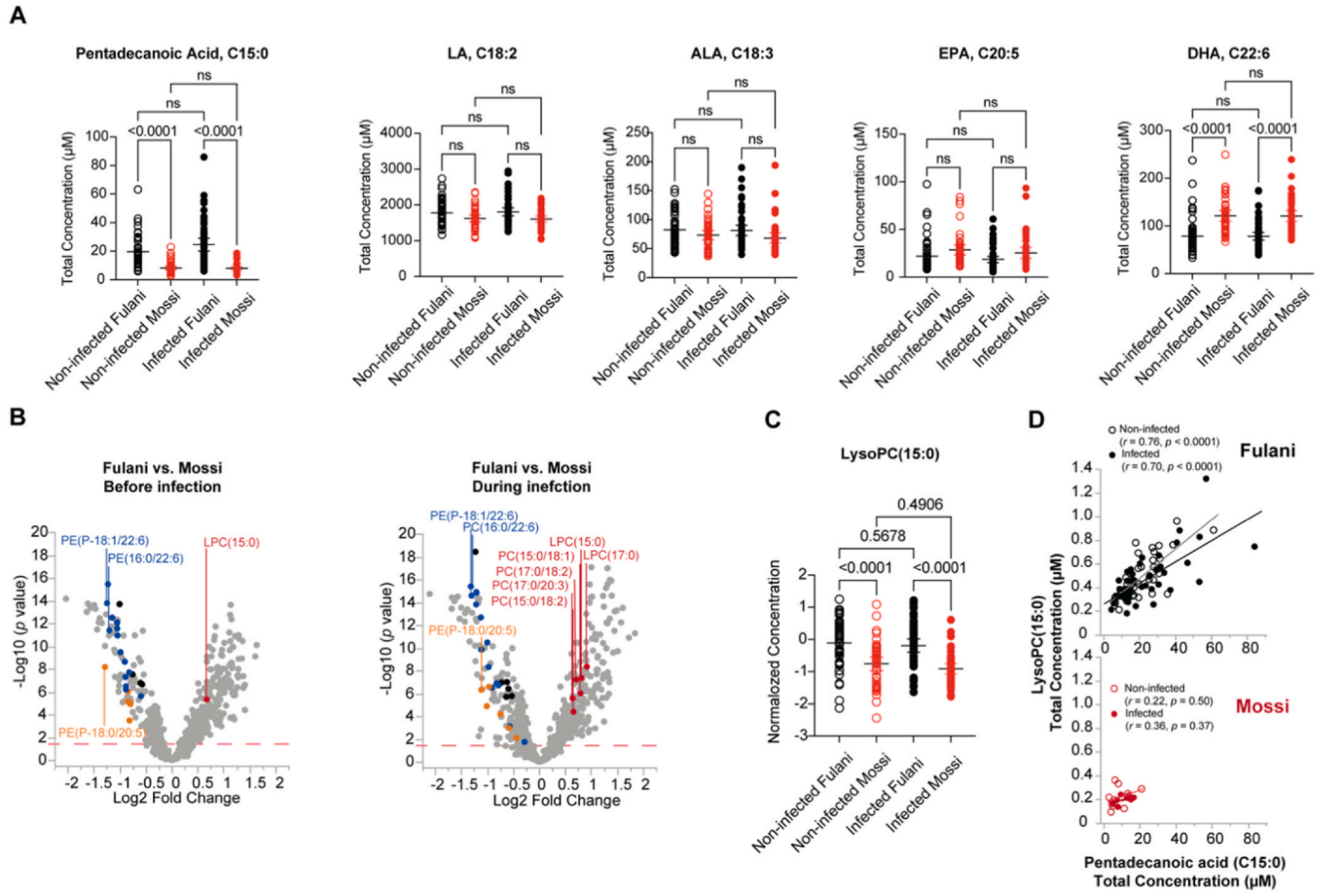

Fig. 3. Diet-derived essential lipids in Mossi and Fulani plasma lipidomes. Total concentration (μM) of pentadecanoic acid (C15:0), LA, ALA, EPA and DHA in Fulani (n = 53) and Mossi (n = 45) children before and during infection. B-H FDR was used to infer statistical significance. Aligned dot plot shows the mean ± SEM as bounds of whiskers. (B) Volcano plots of differential lipid abundance between Fulani and Mossi children before (left panel) and during (right panel) infection. Differentially abundant phospholipids are highlighted. The magnitude (x-axis, Log2(Fold change)) and significance (y-axis, -Log10(*P*)) of differences are shown. The red dashed line indicates the statistical significance threshold (repeated measures analysis of covariance (ANCOVA), B-H FDR 10%). (C) Relative normalized concentration of LysoPC (15:0) before and during infection. B-H FDR was used to infer statistical significance. Aligned dot plot shows the mean ± SEM as bounds of whiskers. (D) Correlation between the total concentration (μM) of pentadecanoic acid (C15:0) and LysoPC (15:0) in both groups; Fulani (Upper panel; non-infected (n = 45), Pearson correlation r = 0.76, *P* < 0.0001; infected (n = 45), Pearson correlation r = 0.70, *P* < 0.0001) and Mossi (Lower panel; non-infected (n = 12), Pearson correlation r = 0.22, *P* = 0.50; infected (n = 8), Pearson correlation r = 0.36, *P* = 0.36).

Dairy-derived pentadecanoic acid associated with lysophospholipid abundance in peripheral blood

Next, we focused our analysis on examining differentially abundant phospholipids between Mossi and Fulani. Delving into their molecular characteristics, we identified 25 differentially abundant phospholipids at the pre-infection state. Remarkably, 84% of these phospholipids (21 molecules) contained essential FAs (FC ≥ |1.5|, B-H FDR < 0.1, Fig. 3B and Supplementary Table 2). Of particular note, only one phospholipid, lysophosphatidylcholine LysoPC (15:0), was significantly enriched in Fulani children before infection (FC = 1.57, B-H FDR-adjusted *P* = 0.00005, Figs. 3B and 3C) and continued to be enriched during infection (LysoPC (15:0): FC= 1.74, B-H FDR-adjusted $P = 8.26e^{-7}$, Figs. 3B and 3C). LysoPC (17:0) was significantly enriched in Fulani but only during infection (LysoPC (17:0): FC = 1.87, B-H FDR-adjusted $P = 1.12e^{-7}$, Fig. 3B and Supplementary Fig. 2).

The primary source of pentadecanoic (C15:0) is dairy fat.[43,44] Our findings suggest that the biosynthesis of LysoPC (15:0) hinges on the availability of diet-derived pentadecanoic acid (C15:0) in blood plasma. Consequently, a positive correlation between the total concentration of pentadecanoic acid (C15:0) and LysoPC (15:0) is anticipated. Testing this association in Fulani before and during infection revealed a significant correlation between serum C15:0 and LysoPC (15:0) concentrations in both infection states (before infection: Pearson correlation *r* = 0.76, *P* < 0.0001, and during infection: Pearson correlation *r* = 0.70, *P* < 0.0001, Fig. 3D), thereby supporting our hypothesis of the use of pentadecanoic acid in the biosynthesis of LysoPC (15:0). Conversely, and in line with our observation, no such association was observed in Mossi children (before infection: *P* = 0.50, and during infection: *P* = 0.37, Fig. 3D), further reinforcing this hypothesis.

Diet-derived LysoPC (15:0) suppresses P. falciparum gametocyte production

The Fulani population exhibits lower gametocyte densities in their blood during infection compared to other ethnic groups, such as Mossi, a phenomenon that remains poorly understood.[32] In this context, the abundance of circulating LysoPCs is of particular intertest, since this class of molecules have been shown to regulate *P. falciparum* gametocytogenesis.[18]

To investigate whether LysoPC (15:0) enriched in Fulani children impacts parasite sexual commitment, we conducted a series of controlled synchronized asexual blood stage parasite cultures, using parasite-conditioned medium to induce sexual conversion (Fig. 4A) (see Methods). We tested the effect of supplementing conditioned medium with 20 μM of LysoPC (15:0) on gametocyte production. Parasites grown in conditioned medium supplemented with 20 μM

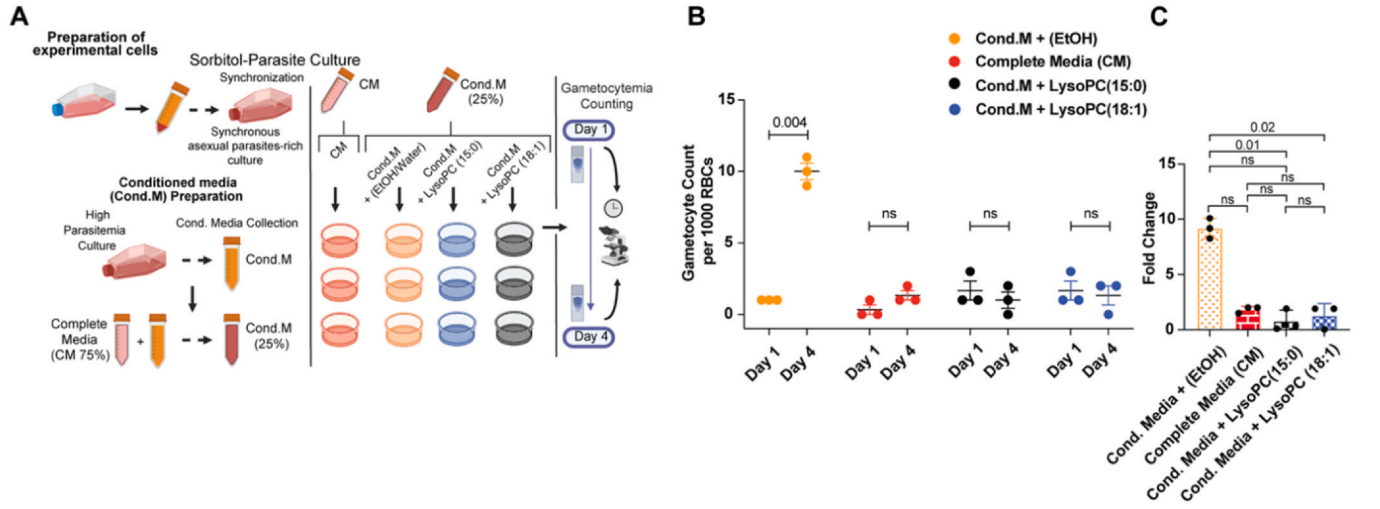

Fig. 4. Impact of LysoPC (15:0) on gametocyte production. (A) Illustration of gametocytogenesis induction experiments using synchronized asexual *P. falciparum* in vitro culturing in conditioned media (Cond. M) supplemented with or without LysoPC (15:0). Cond. M supplemented with LysoPC (18:1) and complete media (CM) were used as positive and negative controls for gametocytogenesis induction, respectively. Three independent culture sets were maintained for four days. (B) Gametocyte counts per 1000 RBCs quantified using Giemsa staining and microscopy on days 1 and 4 of the experiment for three independent cultures. (C) Bar blots showing fold change in gametocytemia between days 1 and 4 the experiment (n =3). Whiskers represent mean ± SEM. Kruskal-Wallis test was used to assess the differences between experimental conditions and controls. Significant *P* values are shown.

of LysoPC (18:1) served as a control for inhibition of gametocytogenesis[18] (Fig. 4A). Gametocytemia was determined using microscopy of thin smears and evaluated on Days 1 and 4 using standard methods.[39] As expected, we observed a 10-fold increase in gametocytemia in conditioned medium, with no significant change in the complete medium condition. On the other hand, supplementing conditioned medium with LysoPC (15:0) resulted in blocking *P. falciparum* parasite sexual commitment, with no induction of gametocyte production, similar to the inhibition control condition (Figs. 4B and 4C and Supplementary Table 3). These results affirm that LysoPC (15:0), found in higher levels among Fulani children, suppresses *P. falciparum* gametocyte production.

Discussion

The lipidome of humans is a complex and dynamic system influenced by a combination of biotic and abiotic factors.[9] Our survey of global lipidomic variation of Mossi and Fulani children has unveiled a distinct signature of ethnicity on the lipidome. Dietary practices emerge as the primary factor behind the observed inter-ethnic differences in our data, emphasizing the critical role of nutritional intake in shaping lipid composition and metabolism. However, we acknowledge that while diet plays a predominant role, other factors such as genetics, physical activity levels, and gut microbiota composition could also contribute to the observed lipidomic variations.[45] While their impact in our study may be relatively minor compared to diet, they might nonetheless exert some influence and should be considered for a comprehensive understanding of lipid metabolism diversity.

The divergent dietary patterns of the Mossi and Fulani communities lead to variations in the intake of essential fatty acids, as supported by our data. Our findings highlight pentadecanoic acid (C15:0), an odd-chain saturated essential fatty acid,[40–42] predominantly found in whole-fat milk and dairy products [46] constituting approximately 1% to 3% of dairy fat.[47] Multiple studies have highlighted a positive correlation between dietary dairy fat intake and the levels of pentadecanoic acid levels in human plasma and in RBCs.[48–51] Elevated dietary intake and circulating plasma levels of pentadecanoic acid are associated with reduced risks of numerous heath conditions.[42,52] Pentadecanoic acid attenuates inflammation, anemia, dyslipidemia, and fibrosis in vivo, potentially by interacting with key metabolic regulators and restoring mitochondrial function.[42,53–56] Pentadecanoic acid also activates AMPK and inhibits mTOR, both of which are core components of the human longevity pathway.[40,57–59] Our results expand the benefits of pentadecanoic acid to include its impact on malaria pathogenesis.

P. falciparum's sexual development during the intra-erythrocytic developmental cycle is a key phase for blood stage malaria progression. Our results point to the involvement of pentadecanoic acid-containing LysoPC in influencing parasite sexual commitment in Fulani. This process entails the commitment of a subset of asexual blood-stage schizonts to produce male and female gametocytes, essential for the progression of the sexual phase in the midgut of *Anopheles* mosquitoes.[60,61] The parasite response to host-derived LysoPC in its microenvironment plays a crucial role in regulating its sexual proliferation.[15] *P. falciparum* parasites metabolize LysoPC and use it to synthesize choline and fatty acids required for the *de novo* biosynthesis of phosphatidylcholine (PC).[18] Under LysoPC-limiting conditions, the expression of choline kinase, the first enzyme of the Kennedy pathway is inhibited, and the expression of ethanolamine kinase and phosphoethanolamine methyltransferase enzymes is induced as an essential compensatory metabolic response needed for PC biosynthesis during gametocyte development.[18,62] This response involves metabolic competition for the methyl donor S-adenosylmethionine between phosphoethanolamine methyltransferases and histone methyltransferases, which is responsible for histone methylation-mediated silencing of *ap2-g*, the master transcriptional switch of the parasite sexual proliferation.[63] Thus, under LysoPC-limiting conditions, S-adenosylmethionine is used mostly for PC biosynthesis, activating *ap2-g* and triggering sexual commitment.[63]

The regulation of LysoPC biosynthesis is intricately tied to the availability of a critical precursor pool of choline.[62] Studies have shown that PUFAs such as DHA, EPA and arachidonic acid stimulate the incorporation of choline into total cellular phospholipids.[64] Our findings indicate that elevated levels of pentadecanoic acid (C15:0) act as a catalyst for LysoPC (15:0) production, leading to increased LysoPC (15:0) levels that alter gametocytogenesis in Fulani. This conclusion is supported by the experimental evidence showing that supplementing LysoPC (15:0) to gametocytogenesis-inducing conditioned media is sufficient to suppress *P. falciparum* gametocyte production in vitro. These processes reflect the complexity of *P.*

falciparum sexual development and the multifaceted interplay of diet, epigenetic and metabolic factors that regulate it. However, the molecular mechanism underlying the incorporation of pentadecanoic acid (C15:0) in lysophosphatidylcholine biosynthesis requires further investigation through detailed molecular studies.

While our current findings support the hypothesis that diet plays a significant role in shaping the lipid profiles of the Fulani and Mossi ethnic groups and consequently their control of gametocyte densities, we recognize that a controlled dietary intervention study would provide the most conclusive evidence. This approach would enable direct comparisons of lipid profiles and molecules before and after dietary modifications or supplementation, while assessing their subsequent influence on gametocyte densities. Such studies are essential to further validate our hypothesis and elucidate the mechanistic links between diet and lipid profile variations across populations.

The substantial dietary-driven divergence in lipidomic abundance, with up to a third of the lipidome differing between Mossi and Fulani, underscores the limited genetic impact on lipidomic variation. The prevalence of lifestyle-driven variation in lipids should be considered in genotype-phenotype mapping studies often conducted in a single environment, which fails to capture dietary effects. Equally important, most comparative studies do not account for dietary variation and risk confounding main study variables with diet differences. We thus advocate the use of lipidomic profiling in association mapping and integrative genomic studies to capture dietary effects and link molecular genetics to human ecology.

From an evolutionary perspective, shifts in lifestyles have allowed humans to adapt to most environments on earth. These shifts were accompanied by marked changes in dietary consumption patterns which impact the development and pathophysiology of infectious disease.[4,8] At the molecular level, our results illustrate how inter-ethnic differences in lipid constituents of diet can modulate host-parasite interactions and consequently alter the outcome of infection. The interplay between diet and malaria pathogenesis is of public health relevance and underlines the importance of addressing nutritional aspects alongside conventional antimalarial interventions. In this context, pentadecanoic acid is a natural dietary component making it a feasible and potentially safe option for supplementation to complement existing antimalarial measures. Whether inter-ethnic variations in diet-derived lipids exert broader effects on other host-parasite processes or pleiotropic effects on other conditions and traits remain topics for investigation.

Author contributions

YI conceived and supervised the study. IS supervised field and clinical work. WA, IS, MMD, AD, DA, SSS, SS, HN and DK performed field work, sample processing and data collection. WA, SZ, DB, and JJ carried out in vitro work and analyzed the data. WA and YI wrote the manuscript with contributions from all authors.

Data availability

All normalized lipidomics data are available in the main text or the supplementary datasets. The Mossi and Fulani complex lipid concentrations datasets generated are available at Mendeley data (DOI: 10.17632/bgr6rbmfhw.2; Access link: https://data.mendeley.com/preview/bgr6rbmfhw?a=7f4eecb5-cdcc-4480-9234-b2A2A3011d30).

Declaration of Competing Interest

All authors declare no competing interests.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106396.

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