Metabolic-associated Fatty Liver Disease as Assessed by the Fatty Liver Index Among Migrant and Non-migrant Ghanaian Populations

Anne-Marieke van Dijk1,10, Sjoerd Dingerink10, Felix Patience Chilunga3,1, Karlijn Anna Catharina Meeks1,2, Silver Bahendeka1, Matthias Bernd Schulze5,6, Ina Danquah6,7, Tracy Bonsu Osei7, Erik Serné8, Charles Agymang2 and Adriaan Georgius Holleboom1

1Department of Vascular Medicine, Amsterdam UMC, location AMC, Amsterdam, the Netherlands; 2Department of Public Health, Amsterdam UMC, location AMC, Amsterdam Public Health Research Institute, Amsterdam, the Netherlands; 3Center for Research on Genomics and Global Health, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA; 4MKGMS-Uganda Martyrs University, Kampala, Uganda; 5Department of Molecular Epidemiology, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany; 6Institute of Nutritional Science, University of Potsdam, Nuthetal, Germany; 7Heidelberg Institute of Global Health (HIGH), Universitätsklinikum Heidelberg, Heidelberg, Germany; 8Department of Vascular Medicine, Amsterdam UMC, location VUMc, the Netherlands

Abstract

Background and Aims: Metabolic-associated fatty liver disease (MAFLD) is driven by high caloric intake and sedentary lifestyle. Migration towards high income countries may induce these driving factors; yet, the influence of such on the prevalence of MAFLD is clearly understudied. Here, we investigated the Fatty Liver Index (FLI), a proxy of steatosis in MAFLD, after migration of Ghanaian subjects.

Methods: Cross-sectional data of 5292 rural, urban and migrant participants from the Research on Obesity and Diabetes among African Migrants (also known as RODAM) study were analyzed with logistic regression for geographical differences in FLI and associations with type 2 diabetes mellitus (T2DM), waist-to-hip ratio, and 10-year predicted risk of atherosclerotic cardiovascular disease (ASCVD).

Results: Both FLI and the proportion with an FLI indicative of MAFLD steatosis (FLI ≥60) were higher in migrants compared with non-migrants. Prevalence of elevated FLI (FLI ≥60) in non-migrant males was 4.2% compared to 28.9% in migrants. For females, a similar gradient was observed, from 13.6% to 36.6% respectively. Compared to rural residents, the odds for a FLI ≥60 were higher in migrants living in urban Europe (odds ratio [OR] 9.02, 95% confidence interval [CI]: 5.02–16.20 for men, and 4.00, 95% CI: 3.00–5.34 for women). Compared to controls, the ORs for FLI ≥60 were 2.43 (95% CI: 1.73–3.41) for male T2DM cases and 2.02 (95% CI: 1.52–2.69) for female T2DM cases. One-unit higher FLI was associated with an elevated (≥7.5%) 10-year ASCVD risk (OR: 1.051, 95% CI: 1.041–1.062 for men, and 1.020, 95% CI: 1.015–1.026 for women).

Conclusions: FLI as a proxy for MAFLD increased stepwise in Ghanaians from rural areas, through urban areas, to Europe. Our results clearly warrant awareness for MAFLD in migrant population as well as confirmation with imaging modalities.

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Introduction

In recent years, the prevalence of metabolic-associated fatty liver disease (MAFLD) has clearly increased, with an estimated prevalence of 25% worldwide.1 The MAFLD prevalence increases coincide with the global increasing prevalence of type 2 diabetes mellitus (T2DM) and obesity, especially central obesity.2 MAFLD is a spectrum of liver disease ranging from hepatic steatosis through non-alcoholic steatohepatitis (NASH), to fibrosis and cirrhosis.3 MAFLD has a complex pathophysiology, but its root cause is insulin resistance.
resistance and MAFLD is therefore seen as the hepatic component of the metabolic syndrome.\(^5\)\(^,\)\(^6\) In turn, MAFLD itself may contribute to the clinical manifestations of the metabolic syndrome and therefore to atherosclerotic cardiovascular disease (ASCVD), potentially by inducing dyslipidemia through increased secretion of triglyceride (TG)-rich lipoproteins, in combination with low-grade inflammation and hypercoagulability.\(^6\)

Of note, the prevalence of MAFLD varies among ethnic groups. Despite a higher prevalence of obesity among ethnic minority groups, especially in women,\(^7\) individuals of African descent are relatively less prone to MAFLD compared to individuals of European, Asian, or Hispanic descent, as assessed in the Multietnic Cohort in the USA.\(^8\) Variance in PNPLA3 has been established to influence susceptibility for MAFLD and may contribute to the observed ethnic difference in MAFLD. The PNPLA3-453A allele, which occurs at a higher frequency in African-ancestry populations (12.5%) compared with other populations (< 1%), is associated with lower hepatic fat content.\(^4\)\(^,\)\(^5\)\(^,\)\(^10\)

Migration-related environmental changes and urbanization may facilitate sedentary lifestyle and obesity, potentially driving MAFLD.\(^1\)\(^1\) Yet, the influence of migration on the prevalence and severity of MAFLD is understudied. In order to address this relevant question, homogeneity of the studied population is imperative to reduce the effects of differences in genetic background. To achieve this, we used data from the Research on Obesity and Diabetes among African Migrants (RODAM) study, representing a relatively homogenous group of Ghanaians which comprises adults originating from the Ashanti Region in Ghana, living in different environmental contexts.\(^12\) Direct measures of hepatic fat content, such as liver biopsy, ultrasound, or Magnetic Resonance Imaging Proton Density Fat Fraction (MRI-PDFF) were unavailable in our study population. Therefore, we used a well-established non-invasive composite proxy to assess the steatotic component of MAFLD: the Fatty Liver Index (FLI).\(^11\) We aimed to study the prevalence of MAFLD as assessed by the FLI among Ghanaian residents in rural and urban Ghana and among Ghanaians in three European cities.

Additionally, we assessed the associations of the FLI with T2DM, as well as predicted 10-year risk of ASCVD. Patients with MAFLD are at 1.5- to 2-fold increased risk for atherosclerotic cardiovascular disease (ASCVD), potentially via the mixed hyperlipidemia often observed in MAFLD patients.\(^5\) Therefore, we included predicted 10-year risk of ASCVD in our study.

**Methods**

**Study design and population**

The RODAM study aims to gain knowledge on the development of obesity and diabetes mellitus among African migrants. Full details of the multicenter RODAM study, initiated in 2012, are published elsewhere.\(^12\) In brief, 5,898 Ghanaian men and women aged 25–70 years, were recruited and physically examined from a population residing in rural Ghana, urban Ghana, and Ghanaians residing in three different European cities (Amsterdam, Berlin, and London). As we aim to study the effects of migration on the FLI, Ghanaians living in Europe were categorized as migrants, of which 97% were first-generation migrants. Ethical approval of the study protocols has been received at all sites. All authors had access to the study data and reviewed and approved the final manuscript. Details on data acquisition, blood sampling and processing procedures can be found in the Supplementary File 1.

**FLI**

The FLI is validated for people aged 18–75 and is calculated by taking into account body mass index (BMI), waist circumference, TGs, and gamma-glutamyltransferase (yGT) according to the algorithm by Bedogni et al.\(^14\) In the RODAM database, TG are measured in mmol/L, whereas the formula for the FLI requires TG expressed as mg/dL. For conversion, the factor 88.57 was used.\(^15\) The FLI varies between 0 and 100, and the <30 is validated by the FLI. Elevated FLI was defined as a score of ≥60, since a cut-off of 60 predicts presence of hepatic steatosis, with a specificity of 82.3%.\(^11\) In our aim to capture MAFLD in the RODAM study, we excluded participants in case of detrival therapy or treatment for hepatitis C and/or excessive alcohol use, defined as >21 units (168 gram alcohol) per week for men and >14 units (112 gram alcohol) per week for women from the current analysis.

**10-year predicted risk of ASCVD**

The standardized and clinically oriented American College of Cardiology (ACC)/American Heart Association (AHA) ASCVD risk score was applied to calculate the 10-year risk of clinical manifest ASCVD. This score can be used to calculate the total 10-year cardiovascular disease risk percentages.\(^16\)\(^,\)\(^17\) It accurately predicts ASCVD risk also in non-European populations.\(^18\) It is scored as a percentage; a score of ≥7.5% is considered elevated risk of developing ASCVD in the next 10 years based on the prior work by Goff et al.\(^16\) More information can be found in the Supplementary File 1. This risk score has been validated for subjects between 40–79 years of age, without prior history of ASCVD. Thus, for the ASCVD analysis, participants below 40 years of age and those with a history of ASCVD were excluded. The RODAM database contained self-reported information on stroke, heart attack, other heart conditions, and peripheral arterial disease. The risk score was calculated with an algorithm that combines age, sex, use of antihypertensive medication, presence of diabetes mellitus, systolic blood pressure, total cholesterol, high-density lipoprotein (i.e. HDL) cholesterol, and smoking status.

**Data analysis**

Data were analyzed using SPSS Statistical software, version 26 (IBM Corp., Armonk, NY). Univariate analyses were conducted separately for men and women due to a statistically significant interaction between FLI and sex. Normally distributed continuous variables were presented as means and standard deviations. Skewed continuous variables were presented as medians and interquartile ranges (IQRs). Categorical variables were presented as proportions. Differences between rural, urban, and migrant participants were assessed by ANOVA, Kruskal-Wallis tests, and χ\(^2\) tests as appropriate. Three models were fitted to adjust for possible confounders. Model 1 was adjusted for age; model 2: model 1 + education; model 3: model 2 + physical activity, alcohol, and T2DM. The results are presented as odds ratios (ORs) and the corresponding 95% confidence intervals (CIs). A p-value of <0.05 was considered statistically significant. In addition, the associations between FLI and elevated 10-year risk of ASCVD were calculated, in which the 10-year risk of ASCVD was the dependent variable. For this ASCVD association, nearly identical models to adjust for potential confounding were used as in the assessment for
The only difference between these models in correcting for confounding was the replacement of T2DM by smoking in model 3.

Results

General characteristics

From a total of 5,898 RODAM participants who underwent physical examination, 5,282 were included in the current analysis, based on age and the criteria of assessing FLI. Of these participants, 951 (18.0%) were rural Ghanaians, 1,432 (27.1%) were urban Ghanaians, and 2,899 (54.9%) were migrants. The majority of participants were female (62.7%). Mean age was higher in men than in women in urban participants and migrants. However, in rural participants, mean age was higher in women than in men. The mean duration of living in urban Europe was 18.6 years (standard deviation [SD]: 9.6) for males and 19.0 years (SD: 9.5) for females, calculated from 2,529 out of 2,899 migrants. Migrants had the highest levels of educational and rural participants had the lowest levels, in both men and women. The prevalence of any alcohol consumption was higher in rural participants in men (53.1%) compared to urban participants (40.6%) and migrants (41.4%). In women, alcohol consumption was lower in urban participants (26.1%) compared to rural participants (30.9%) and migrants (31.2%). The proportion of current smokers was higher in migrants than non-migrants (31.3% in migrant women, and 21.1% in migrant women). Compared to the two other groups, rural participants had the highest levels of physical activity, irrespective of sex. Differences in general characteristics are shown in Table 1.

FLI and its determinants by location of current residency

In both men and women, TG levels were highest among urban participants and the lowest among migrants, and γGT was the highest in urban participants and the lowest in rural participants. FLI, BMI, and waist circumference increased stepwise after migration from rural Ghana, through urban Ghana to Europe, whereby the Ghanaian homogenous population living in three distinct environments can be seen as a proxy for migration. This study has three important findings. First, the prevalence of an elevated FLI (FLI ≥60) as an indicator of MAFLD in the Ghanaian population living in rural Ghana, urban Ghana and Europe. The homogenous Ghanaian population living in three distinct environments is used as a proxy for migration. This study has three important findings. First, the prevalence of an elevated FLI (FLI ≥60) as an indicator of hepatic steatosis increased from rural participants, through urban participants, to European migrants, irrespective of sex. Second, T2DM was positively associated with higher odds for FLI in both Ghanaian men and women. Third, an elevated FLI (FLI ≥60) was associated with an elevated 10-year ASCVD risk (≥7.5%) in both men and women, with a more pronounced effect in men.

Discussion of the key findings

Studies of human migration and features of cardiometabolic disease are scarce. Several studies have reported differences in the prevalence of MAFLD among different ethnicities; however, these were performed in participants residing in a single country.15,19 For instance, multiple studies report a lower prevalence of MAFLD in African Americans compared to Hispanic Americans.19–21 The prevalence of MAFLD in migrants of African descent is often lower than the prevalence of MAFLD in the general population of the host country.20,21 Interestingly, this contrasts with the prevalence of morbidity with a close relation to MAFLD, i.e. obesity, T2DM, and hypertension, which are found to be more prevalent among ethnic minorities in Europe, including African groups.20 Factors driving variation in cardiometabolic health across geographical locations are thought to include changes in nutritional patterns, physical inactivity, and stress, in combination with genetic susceptibility and gene-environment interactions.20,22 As MAFLD is driven by insulin resistance and obesity, one would expect the aforementioned factors to play a similar role in the effects of migration on the prevalence of MAFLD.23 Interestingly, in our models, the effect sizes only slightly changed upon adjustment for lifestyle factors, such as physical activity, alcohol consumption, and T2DM. This may fit with the ‘multiple hit’ hypothesis which
van Dijk A.M. et al: FLI as MAFLD proxy in a Ghanaian population

Table 1. General characteristics of rural and urban residing, and migrant participants

| Variables                             | Rural (n=951) | Urban (n=1,432) | Migrated (n=2,899) | Total (n=5,282) | P   |
|---------------------------------------|---------------|-----------------|--------------------|-----------------|-----|
| Men, n                                | 356           | 406             | 1,209              | 1,971           |     |
| Age, years                            | 45.8±12.9     | 46.7±11.8       | 47.0±10.4          | 46.7±11.2       | 0.193|
| Education, n (%)                      |               |                 |                    |                 | <0.001|
| Elementary                            | 136 (38.2)    | 89 (21.9)       | 144 (11.9)         | 369 (18.7)      |     |
| Lower secondary                       | 128 (36.0)    | 173 (42.6)      | 453 (37.5)         | 754 (38.3)      |     |
| Higher secondary                      | 47 (13.2)     | 85 (20.9)       | 279 (23.1)         | 411 (20.9)      |     |
| Tertiary                              | 21 (5.9)      | 37 (9.1)        | 250 (20.7)         | 308 (15.6)      |     |
| Alcohol consumption, n (%)            | 189 (53.1)    | 165 (40.6)      | 500 (41.4)         | 854 (43.3)      | <0.001|
| Smoking, n (%)                        |               |                 |                    |                 | 0.023|
| Current                               | 17 (4.8)      | 12 (3.0)        | 76 (6.3)           | 105 (5.3)       |     |
| Past                                  | 48 (13.5)     | 61 (15.0)       | 131 (10.8)         | 240 (12.2)      |     |
| Physical activity, n (%)              |               |                 |                    |                 | <0.001|
| Low levels                            | 37 (10.4)     | 85 (20.9)       | 287 (23.7)         | 409 (20.8)      |     |
| Medium levels                         | 54 (15.2)     | 72 (17.7)       | 176 (14.6)         | 302 (15.3)      |     |
| High levels                           | 238 (66.9)    | 223 (54.9)      | 457 (37.8)         | 918 (46.6)      |     |
| WHR                                   | 0.89±0.06     | 0.90±0.06       | 0.93±0.07          | 0.91±0.07       | <0.001|
| WHR ≥0.90, n (%)                      | 126 (35.4)    | 222 (54.7)      | 785 (64.9)         | 1,133 (57.5)    | <0.001|
| T2DM, n (%)                           | 15 (4.2)      | 46 (11.3)       | 158 (13.1)         | 219 (11.1)      | <0.001|
| BMI, kg/m²                             | 21.0±3.0      | 24.1±3.8        | 27.0±3.9           | 25.4±4.4        | <0.001|
| AST/ALT ratio                         | 1.99±0.82     | 1.70±0.72       | 1.44±0.56          | 1.60±0.68       | <0.001|
| Waist circumference, cm               | 76.9±8.4      | 84.7±10.3       | 92.6±10.9          | 88.1±12.0       | <0.001|
| TG, mmol/L, median (IQR)              | 0.96 (0.7–1.3)| 1.02 (0.8–1.3)  | 0.89 (0.67–1.19)   | 0.92 (0.70–1.23)| <0.001|
| γGT, mmol/L, median (IQR)             | 33.1 (24.3–51.6)| 39.5 (27.8–56.6)| 36.7 (27.7–50.1) | 36.5 (27.0–51.5)| 0.003|
| FLI, median (IQR)                     | 11.7 (6.6–21.8)| 27.0 (12.3–47.5)| 42.6 (21.8–64.6) | 31.8 (14.3–56.7)| <0.001|
| FLI, categorized                      |               |                 |                    |                 | <0.001|
| <30, n (%)                            | 298 (83.7)    | 214 (52.7)      | 426 (35.2)         | 938 (47.6)      |     |
| ≥60, n (%)                            | 15 (4.2)      | 66 (16.3)       | 349 (28.9)         | 430 (21.8)      |     |
| Women, n                              | 595           | 1,026           | 1,690              | 3,311           |     |
| Age, years                            | 46.9±12.6     | 44.7±11.2       | 46.1±9.5           | 45.8±10.7       | <0.001|
| Education, n (%)                      |               |                 |                    |                 | <0.001|
| Elementary                            | 367 (61.7)    | 520 (50.7)      | 427 (25.3)         | 1,314 (39.7)    |     |
| Lower secondary                       | 154 (25.9)    | 367 (35.8)      | 571 (33.8)         | 1,092 (33.0)    |     |
| Higher secondary                      | 18 (3.0)      | 87 (8.5)        | 362 (21.4)         | 467 (14.1)      |     |
| Tertiary                              | 11 (1.8)      | 28 (2.7)        | 186 (11.0)         | 225 (6.8)       |     |
| Alcohol consumption, n (%)            | 184 (30.9)    | 268 (26.1)      | 527 (31.2)         | 951 (28.7)      | 0.014|
| Smoking, n (%)                        |               |                 |                    |                 | <0.001|
| Current                               | 0 (0)         | 0 (0)           | 21 (2.1)           | 21 (0.6)        |     |
| Past                                  | 5 (0.8)       | 21 (2.0)        | 67 (4.0)           | 93 (2.8)        |     |
| Physical activity, n (%)              |               |                 |                    |                 | <0.001|
| Low levels                            | 130 (21.8)    | 406 (39.6)      | 406 (24.0)         | 942 (28.5)      |     |
| Medium levels                         | 126 (21.2)    | 158 (15.4)      | 289 (17.8)         | 582 (17.6)      |     |
| High levels                           | 294 (49.4)    | 434 (42.3)      | 577 (34.1)         | 1,305 (39.4)    |     |

(continued)
postulates that multiple factors act together in inducing MAFLD, and adjustment for a few of these factors would not have a major effect.24 In addition to physical inactivity and genetic susceptibility, gut microbiota have been suggested to play a role. Several studies report the interaction between liver and gut as a critical player in the onset of MAFLD.25–27 Dietary factors may alter the composition of the gut microbiota, which in turn may contribute to the development of MAFLD.28 Evidence for these changed dietary factors in an urban population compared to a rural population was found in a prospective cohort study that was conducted in South Africa. The nutrition intakes of urban-residing men and women were consistently higher than those of their rural counterparts.29 This is often accompanied by a nutrition transition to a Westernized diet, frequently high in fat and sugar.30 This reported change in dietary factors could also play a role in our study population. Taken together, the sizeable disparity in FLI in our study between similar populations living in different environments suggests a more significant role for environmental factors such as dietary changes and alterations in the gut microbiome, in driving the prevalence of MAFLD than for genetic susceptibility.

Of note, we found a strong relation of the FLI with the presence of T2DM. The interplay between T2DM and MAFLD is complex. T2DM is an important risk factor for developing MAFLD, and vice versa, MAFLD may contribute to insulin resistance. Insulin resistance is a central mechanism that leads to lipolysis in peripheral adipose tissue and an increased hepatopetal flux of free fatty acids, driving lipotoxicity in the liver, with subsequent inflammation and hepatocyte injury.4,31 A higher prevalence of MAFLD in patients with T2DM has been found.23,32 In turn, ectopic fat accumulation in MAFLD is thought to affect T2DM. This ectopic fat accumulation is associated with increased gluconeogenesis, decreased glycogen synthesis and inhibition of insulin signalling.32

We observed a significant association of FLI with 10-year risk of ASCVD, bolstering the notion that patients with MAFLD may have increased ASCVD. The relation between MAFLD and ASCVD is supported by studies of subclinical atherosclerosis, such as carotid intima-media thickness.

![Table 1. (continued)](image)

| Variables          | Rural (n=951) | Urban (n=1,432) | Migrated (n=2,899) | Total (n=5,282) | P       |
|--------------------|--------------|-----------------|--------------------|-----------------|---------|
| WHR                | 0.89±0.07    | 0.90±0.06       | 0.88±0.08          | 0.89±0.07       | <0.001  |
| WHR ≥0.85, n (%)   | 444 (74.6)   | 829 (80.8)      | 1,153 (68.2)       | 2,426 (73.3)    | <0.001  |
| BMI, kg/m²         | 23.7±4.5     | 28.0±5.5        | 30.3±5.1           | 28.4±5.6        | <0.001  |
| AST/ALT ratio      | 1.96±0.75    | 1.87±0.62       | 1.62±0.49          | 1.76±0.60       | <0.001  |
| Waist circumference, cm | 83.8±11.2 | 90.4±11.9       | 95.7±12.0          | 92.1±12.6       | <0.001  |
| TG, mmol/L, median (IQR) | 0.97 (0.74–1.34) | 1.01 (0.74–1.36) | 0.73 (0.57–0.98) | 0.85 (0.64–1.16) | <0.001  |
| γGT, mmol/L, median (IQR) | 26.6 (20.5–36.7) | 29.5 (22.8–38.5) | 27.3 (21.3–36.9) | 27.9 (21.6–37.3) | <0.001  |
| FLI, median (IQR)  | 16.7 (8.3–36.2) | 40.9 (19.3–69.6) | 46.6 (25.4–71.7) | 39.1 (18.5–67.4) | <0.001  |
| FLI, categorized    |              |                 |                   |                 | <0.001  |
| <30, n (%)         | 402 (67.6)   | 388 (37.8)      | 514 (30.4)         | 1,304 (39.4)    |         |
| ≥60, n (%)         | 81 (13.6)    | 331 (32.3)      | 619 (36.6)         | 1,031 (31.1)    |         |

Data presented as mean±SD unless stated otherwise. SD, standard deviation; WHR, waist-to-hip ratio; T2DM, type 2 diabetes; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TG, triglycerides; γGT, gamma-glutamyltransferase; FLI, fatty liver index; IQR, interquartile ranges.

![Fig. 1. Continuous FLI. (A) FLI in rural Ghana, urban Ghana and Ghanaian migrants in males. (B) FLI in rural Ghana, urban Ghana and Ghanaian migrants in females. FLI, fatty liver index.](image)
van Dijk A.M. et al: FLI as MAFLD proxy in a Ghanaian population

**Strengths and limitations**

The FLI is a surrogate marker validated against ultrasonography by Bedogni et al. in a Caucasian population and replicated by others. Potential anthropometric and laboratory data were used in a logistic regression model to obtain a simple and accurate algorithm for the prediction of increased liver fat content, after exclusion of participants with hepatitis B and C. Due to this anthropometric and laboratory data, FLI is not directly based on liver fat content; yet, Bedogni et al. reported an area under the receiver operating characteristic curve of 0.85. In the RODAM study, no imaging modalities of hepatic steatosis, such as abdominal ultrasound or MRI-PDFF, or liver biopsies, were available to validate our findings with the FLI. When using the applied cut-off value of 60, in order to validate the FLI in a population-based study, the likelihood ratio was 5.10 for the presence of MAFLD. Additionally, a cut-off of ≥60 showed a specificity of 91%. Unfortunately, blood platelets were not included in the RODAM study; hence, liver fibrosis proxies, such as Fibrosis-4 and aspartate to aminotransferase to platelet ratio (APRI) could not be included in our current analysis. We excluded other liver conditions in our calculations, as much as possible. We were able to exclude participants that used an excessive amount of alcohol and participants that used medication for hepatitis B and retroviral therapy. However, no data on untreated participants was available in the RODAM study. A great strength of the study is the homogeneity of the studied population, which provides a unique opportunity to investigate the metabolic effects of migration.

**Conclusion**

In conclusion, our study shows that, compared to rural areas, the prevalence of MAFLD as assessed by the FLI in the...
Fig. 3. ORs with 95% CIs for elevated FLI (FLI ≥60) in urban Ghana and Ghanaian migrants compared with rural Ghana in women. Model 1 adjusted for age; model 2: model 1 + education; model 3: model 2 + physical activity, alcohol, and T2DM. OR, odds ratio; CI, confidence interval; FLI, fatty liver index; T2DM, type 2 diabetes.

Fig. 4. FLI in male (black) and female (grey) participants with and without T2DM. FLI, fatty liver index; T2DM, type 2 diabetes.
Ghanaian RODAM population was higher in urban areas and even higher in Europe. In addition, FLI was strongly correlated with T2DM and ASCVD risk. This sheds light on MAFLD in this African population, and highlights the possible influence of migration on the prevalence of MAFLD, providing a clear rationale for future prospective studies with imaging modalities.

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Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Design of the study (AMD, SD, FPC, CA, AGH), preparation of the draft of the protocol and drafting of the manuscript (AMD, SD), statistical analyses and interpretation (AMD, SD, FPC, CA), and revision of the manuscript (AMD, SD, AGH, CA). All authors reviewed and critically revised the manuscript.

Data sharing statement

The data that support the findings of this study are available from the corresponding author, AMD, upon reasonable request.

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Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Design of the study (AMD, SD, FPC, CA, AGH), preparation of the draft of the protocol and drafting of the manuscript (AMD, SD), statistical analyses and interpretation (AMD, SD, FPC, CA), and revision of the manuscript (AMD, SD, AGH, CA). All authors reviewed and critically revised the manuscript.

Data sharing statement

The data that support the findings of this study are available from the corresponding author, AMD, upon reasonable request.

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