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Inverse Association between Iron Deficiency and Glycated Hemoglobin Levels in Ghanaian Adults—the RODAM Study

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ABSTRACT

Background: Glycated hemoglobin (HbA1c) is often used to diagnose type 2 diabetes (T2D), but studies show that iron deficiency (ID) is associated with elevated HbA1c in the absence of hyperglycemia. It is unknown whether ID prevalence varies between sub-Saharan African populations living in different locations and whether ID influences HbA1c levels in these populations.

Objectives: We assessed the prevalence of ID among Ghanaian migrants in Europe and nonmigrant Ghanaians, and the influence of ID on HbA1c categories among Ghanaians without T2D.

Methods: We used the database from the cross-sectional RODAM (Research on Obesity and Diabetes among African Migrants) study. This contained data on 3377 Ghanaian men and women aged 25–70 y living in urban and rural Ghana and Ghanaian migrants living in Amsterdam, London, and Berlin. ID was defined as ferritin < 15 ng/mL or, if C-reactive protein was ≥5 mg/mL, as ferritin < 30 ng/mL according to the WHO. We used binary logistic regression to assess differences in ID between sites and its association with clinically defined HbA1c categories (<5.5%, ≥5.5% to <6.5%, ≥6.5%). Men and women were analyzed separately.

Results: The prevalence of ID was higher in migrant [28.4%; adjusted OR (aOR): 3.08; 95% CI: 2.04, 4.65)] and urban (23.2%; aOR: 2.37; 95% CI: 1.56, 3.59) women than in rural women (11.9%). Among women, ID was associated with higher odds of HbA1c ≥ 5.5% to <6.5% in the absence of hyperglycemia (aOR: 1.43; 95% CI: 1.08, 1.87). This association was not found in men.

Conclusions: Further research is needed to identify factors underlying the high prevalence of ID among urban and migrant Ghanaian women, and the association of ID with HbA1c ≥ 5.5% to <6.5% in women. In addition, our study reinforces the need to consider iron concentrations if interpreting HbA1c among African populations. *J Nutr* 2020;150:1899–1908.

Keywords: HbA1c, iron deficiency, iron deficiency prevalence, ferritin, type 2 diabetes, Ghanaians, migrants in Europe, urban area, rural area

Introduction

Worldwide, the number of people with type 2 diabetes (T2D) is rising. In sub-Saharan Africa (SSA), the number of people living with T2D is expected to more than double to 34.2 million by 2040 (1). These statistics are especially worrisome, considering that only 30 y ago, T2D was rare in West African countries (2). This epidemic also affects SSA migrants residing in Europe, because they are 2.5 times more likely to suffer from T2D than the European host population (3).

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To curb the T2D epidemic, there is a need to properly screen for and treat T2D. Glycated hemoglobin (HbA1c) seems an appropriate choice in this matter because it can be easily obtained and shows less day-to-day variation than the oral-glucose-tolerance test and fasting plasma glucose (FPG) (4). Recently, the WHO approved HbA1c for the diagnosis of T2D (4). However, some research suggests that an increased HbA1c level is not only related to hyperglycemia, but could instead be due to ID, possibly affecting the diagnostic validity of HbA1c for T2D (5–8).

Several hypotheses have been proposed regarding the mechanism through which ID could increase HbA1c. El-Agouza et al. (9) hypothesized that in a state of ID, hemoglobin concentrations decrease while serum glucose continues binding to hemoglobin at the same rate and therefore the absolute amount of HbA1c formed stays the same. HbA1c is measured as the percentage of HbA1c from the total amount of hemoglobin. Thus, in a state of ID the percentage of HbA1c would falsely increase. A second hypothesis states that this process involves malondialdehyde, a biomarker of oxidative damage to lipids. Malondialdehyde is capable of enhancing the glycation of hemoglobin (10, 11). In a state of ID, the amount of malondialdehyde in the body increases which could account for the increased HbA1c associated with ID (10).

Thus far, studies on the association between ID and HbA1c in nondiabetics have shown varying results with some studies showing no association and others an association between ID and increased HbA1c (5–8). However, these studies were mainly based on patients from Korea, India, and the United States. It has not yet been studied whether an association between ID and HbA1c exists in SSA populations. For reasons that remain unknown, ethnic background appears to influence HbA1c value, suggesting that these earlier findings may not be directly applicable to SSA populations (12). It is particularly important to determine whether ID influences HbA1c in SSA people because ID is a major problem in SSA countries. A systematic review determining the ID prevalence in a selection of SSA countries reported a prevalence of ≤25% in women (13). A recent report by Strengthening Partnerships, Results, and Innovations in Nutrition Globally (SPRING) found an even higher prevalence of ID—34%—in Ghanaian women (14). In SSA, it has been found that the prevalence of ID among men ranges from 6% to 31% (15–18).

In addition, over the past few decades, governments in SSA countries have put tremendous effort into combatting ID through the implementation of fortified foods, deworming campaigns, malaria prevention efforts, and hygienic improvements (14, 19, 20). However, more research is needed to determine whether these efforts have affected ID prevalence across different demographic settings. Differences in local factors such as accessibility of these programs and inhabitants' educational status might have influenced the success these policies have had in reducing ID. Furthermore, given that SSA migrants in Europe experience rapid changes in their economic and nutritional status, the prevalence of ID among them is likely to differ from the prevalence among their counterparts in their countries of origin.

Therefore, we used data of the RODAM (Research on Obesity and Diabetes among African Migrants) study *1*) to estimate the prevalence of ID among rural and urban Ghanaians and Ghanaian migrants in Europe and to assess whether these differ, and *2*) to determine whether there is an association between ID and clinically defined HbA1c categories among Ghanaians without diabetes.

Methods

Study design and population

We used the RODAM study database for the present analysis. The rationale and the design of the RODAM study have been described in detail elsewhere (21). In short, the RODAM study is a multicenter cross-sectional study that recruited 6385 Ghanaians aged between 25 and 70 y from a homogeneous population residing in rural and urban Ghana and Ghanaians that had migrated to 3 European cities, namely Berlin (Germany), London (United Kingdom), and Amsterdam (Netherlands). In Berlin and London, Ghanaian individuals were identified through member lists of Ghanaian organizations and churches and randomly selected from these lists. In Amsterdam, Ghanaians were randomly identified from the Amsterdam Municipal register, which contains data on country of birth for all registered inhabitants (including noncitizens) in Amsterdam and the country of birth of their parents. In Ghana, 15 villages and 2 purposively chosen cities (Kumasi and Obuasi) in the Ashanti region were used as rural and urban recruitment sites, respectively. Participants were mobilized with the help of local health and community authorities. RODAM team members set up mini-clinics and then resided within the community for 1–2 wk to collect data. The participation rates were 76% and 74% in rural and urban Ghana, respectively. In Amsterdam, London, and Berlin, the participation rates were 53%, 75%, and 68%, respectively.

The study was approved by the respective ethics committees at all the study sites in Ghana, Germany, Netherlands, and the United Kingdom. In addition, informed written consent was obtained from every participant before enrolment in the study.

Measurements

Of the 6385 Ghanaians recruited, 5898 were physically examined. To ensure identical data collection at every location, standardized protocols were put in place. Participants underwent physical examinations, completed questionnaires, and provided blood samples. Depending on the participant's preference, questionnaires were either self-administered or completed with the help of a trained, ethnically matched research assistant. Validated devices were used for the physical examinations. Participants' weight was measured to the nearest 0.1 kg without shoes and in light clothing with a SECA 877 scale. Height was measured without shoes to the nearest 0.1 cm with the SECA 217 stadiometer. All measurements were taken twice and the mean of the 2 measurements was calculated. BMI was calculated as kg/m^2. Fasting blood samples were drawn by trained laboratory and research assistants. Immediately after collection at the research location, blood samples were divided into aliquots and underwent cryopreservation to prevent degradation. They were then transported to local laboratories for registration and stored at −80°C. From there 2 aliquots of blood samples and a 2-mL EDTA-coated whole blood sample for each participant were sent to Berlin for

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Abbreviations used: aOR, adjusted OR; AT, α-thalassemia; CKD, chronic kidney disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; G6PD, glucose-6-phosphate dehydrogenase; HbA1c, glycated hemoglobin; HIC, high-income country; HMB, heavy menstrual bleeding; ID, iron deficiency; RODAM, Research on Obesity and Diabetes among African Migrants; SSA, sub-Saharan Africa/African; T2D, type 2 diabetes.

biochemical analysis. All samples were biochemically analyzed at the same laboratory in Berlin to avoid variations in measurements due to interlaboratory differences; only HbA1c was determined in a laboratory in Amsterdam. For the purposes of the present study, we used serum ferritin, FPG, HbA1c, serum creatinine, and plasma C-reactive protein (CRP). HbA1c was measured with an ion-exchange HPLC analyzer. The other biochemical indexes were measured using an ABX PENTRA 400 (Horiba ABX).

We defined HbA1c categories according to WHO criteria with normal HbA1c < 5.5%, prediabetes HbA1c ≥ 5.5% to <6.5%, and diabetic HbA1c ≥ 6.5% (4). Iron status was based on plasma ferritin, the preferred indicator of iron status according to WHO recommendations, and defined as deficient or normal (22, 23). ID was defined as ferritin < 15 ng/mL if CRP was <5 mg/mL; otherwise, if CRP was ≥5 mg/mL, ID was defined as ferritin < 30 ng/mL to account for the inflammatory properties of ferritin. We excluded individuals with the hemoglobin variants HbAS and HbAC because they can lead to unreliable HbA1c measurements ($n = 1345$) and we excluded those without data on HbA1c level ($n = 414$) (24). For the analysis on the association between ID and HbA1c distribution, participants with T2D were excluded ($n = 289$) because of the potential bias by the effect of impaired glucose tolerance on HbA1c. We defined diabetes based on self-report, use of hypoglycemic medication, or an FPG > 7 mmol/L, according to WHO criteria (25). Lastly, we excluded participants with stage III–V chronic kidney disease (CKD), ferritin > 200 ng/mL (men) or >150 ng/mL (women), or missing data on these indexes ($n = 523$). We excluded patients with stage III–V CKD because we used ferritin as the single measure of ID, and ferritin has been shown not to be a reliable indicator of iron status in these patients (26). CKD was defined based on estimated glomerular filtration rate (eGFR) using the CKD Epidemiology Collaboration formula. Reduced eGFR was defined as eGFR < 60 mL · min^{-1} · 1.73 m^{-2}. We excluded participants with increased ferritin concentrations because this can be an indication of hemochromatosis which carries an increased risk of developing T2D (27). Finally, 3377 diabetic and nondiabetic participants remained for the main analyses (**Figure 1**). To determine the association between ID and HbA1c, data of 3088 nondiabetic participants were used.

Data analysis

For statistical analysis, we used SPSS Statistics version 24 (IBM Corporation). To calculate age-standardized prevalence we used R Studio (RStudio, Inc., Boston, MA) version 1.1.453. All analyses were stratified by sex because of the expected difference in ID prevalence between men and women and we therefore anticipated a differential association with HbA1c (23). In our descriptive table, we presented data on age, BMI, CRP, FPG, HbA1c, family history of T2D (yes/no/I do not know), smoking (current/former/never), alcohol (yes/no), and educational level (never or elementary only/lower vocational/intermediate vocational/university). We used frequencies and percentages to present categorical data, means ± SDs to present normally distributed continuous data, and medians [IQRs] to present nonnormally distributed data. Chi-square test, *t* test, and Mann–Whitney *U* test were used to assess differences between groups, respectively. In case expected count was <5, we used Fisher's exact test instead of the chi-square test.

We calculated age-standardized prevalence of ID across locations and HbA1c categories. We used the direct method, with the age distribution of the total RODAM population as the standard population. Binary logistic regression was used to determine the odds of ID in migrant and urban Ghanaians compared with rural Ghanaians with adjustment for the covariates age, BMI, CRP, smoking, alcohol, and education because these variables have been shown to influence ferritin (22, 23, 28–31). Even though we implemented different ferritin cutoffs to define ID in the presence of inflammation, we still felt it necessary to adjust for CRP to take variations into account (23). **Figure 2** depicts an overview of our hypotheses regarding factors influencing ID prevalence, in a directed acyclic graph. Furthermore, binary logistic regression was used to determine the odds of a participant with ID having an HbA1c ≥ 5.5% to <6.5% or ≥6.5% with HbA1c < 5.5% as reference, compared with participants without ID. We further adjusted for the covariates FPG and family history of T2D because these variables have been shown to influence HbA1c (4, 32). Data were expressed as ORs and their corresponding 95% CIs.

Results

Characteristics of the study population

The prevalence of ID was 5.5% among men and 24.4% among women (**Table 1**). In both men and women, FPG was slightly but significantly lower in those with than in those without ID (men: 5.0 mmol/L compared with 5.1 mmol/L; women: 4.9 mmol/L compared with 5.0 mmol/L, respectively). For both men and women BMI did not differ significantly between those with and without ID (men: 26.8 compared with 27.1; women: 27.4 compared with 27.2, respectively). In addition, men with ID were less likely to consume alcohol than men without ID. The difference in mean HbA1c between men with and without ID was nonsignificant. Among women, individuals with ID were on average 5 y younger (41.4 y) and had a higher mean HbA1c (5.6%) than women without ID (46.1 y and 5.5%, respectively). Women with ID had a higher level of education than women without ID.

Prevalence of ID by site

In men, the prevalence of ID did not differ significantly between migrant Ghanaians and Ghanaians in rural or urban Ghana (**Figure 3**, **Table 2**). Among women, however, ID prevalence was significantly higher in migrant and urban Ghanaians, with age-standardized prevalence rates (95% CIs) of 28.4% (25.4%, 31.7%) and 23.2% (19.6%, 27.2%), respectively, compared with 11.9% (8.3%, 16.5%) among women in rural Ghana. After adjustment for covariates, we found that migrant women still had significantly greater odds of ID than their rural counterparts (OR: 3.08; 95% CI: 2.04, 4.65; $P < 0.001$) (Table 2). The same was true when comparing urban women with rural women (OR: 2.37; 95% CI: 1.56, 3.59; $P < 0.001$). In men, the differences in ID prevalence rates across sites remained nonsignificant after adjustment for covariates. When the analysis was stratified by site within Europe, the age-standardized prevalence of ID was markedly higher among Ghanaian men in London (11.1%; 95% CI: 7.4%, 16.1%) than among their counterparts in Amsterdam (2.1%; 95% CI: 0.9%, 4.3%) (Figure 3). The same was true when comparing the prevalence of ID among women in London (35.0%; 95% CI: 29.3%, 41.5%) with the prevalence among women in Amsterdam (23.6%; 95% CI: 19.9%, 27.8%). The prevalence rates among Berlin men (4.4%; 95% CI: 1.7%, 9.2%) and women (29.6%; 95% CI: 22.1%, 39.1%) were also higher than in their Amsterdam peers although these differences were nonsignificant.

Association between ID and HbA1c

The age-standardized prevalence of ID did not differ significantly across HbA1c categories (**Figure 4**). However, after adjustment for covariates, we found that women with ID had greater odds of HbA1c ≥ 5.5% to <6.5% than women without ID (OR: 1.43; 95% CI: 1.08, 1.87; $P < 0.01$) (**Table 3**). Among men, there was no association between ID and HbA1c ≥ 5.5% to <6.5% after adjustment for covariates. There was also no association between ID and HbA1c ≥ 6.5% in both men and women (Table 3).

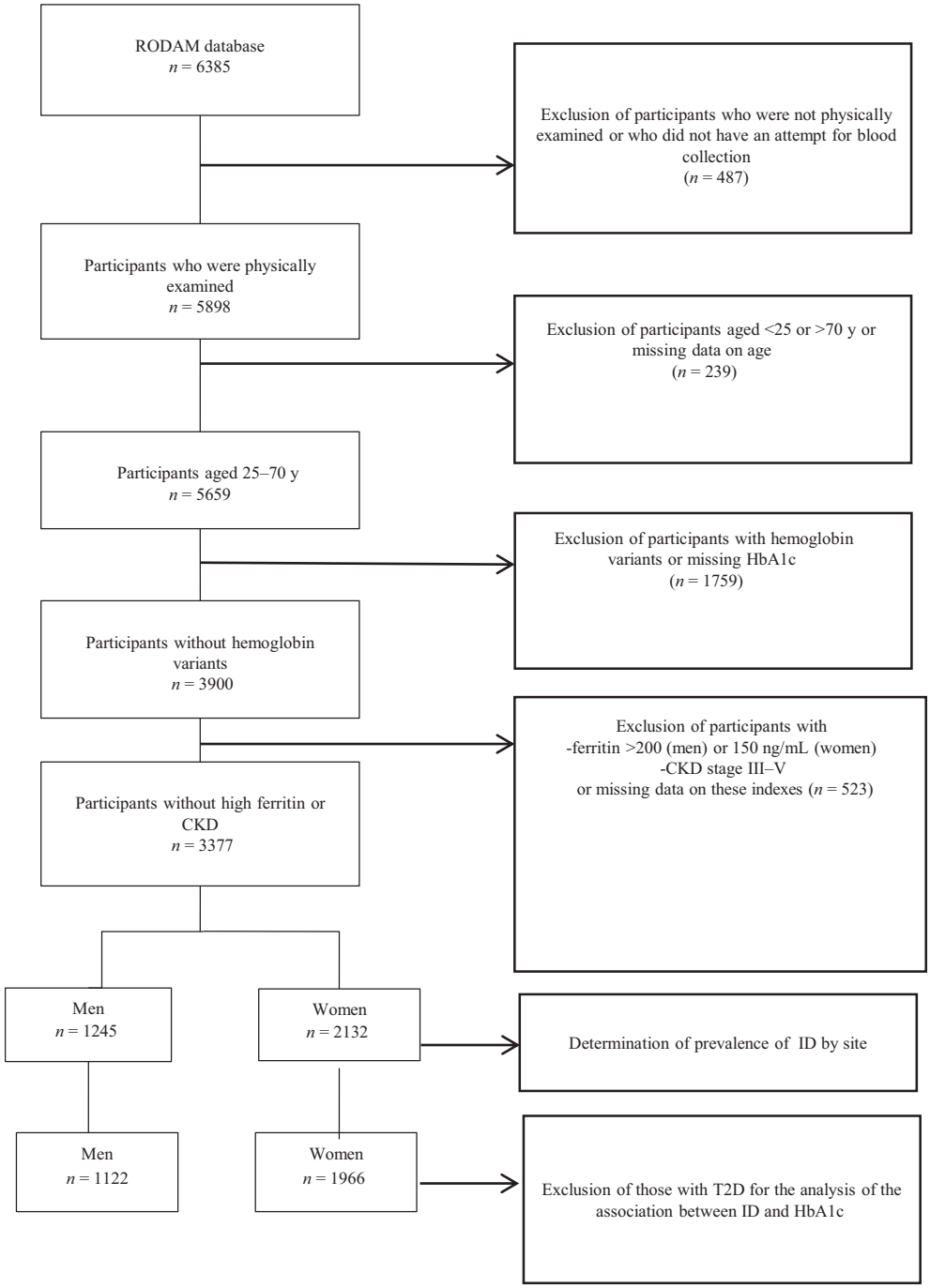

FIGURE 1 Inclusion flow diagram. CKD, chronic kidney disease; HbA1c, glycated hemoglobin; ID, iron deficiency; RODAM, Research on Obesity and Diabetes among African Migrants; T2D, type 2 diabetes.

Discussion

Key findings

In our study we found that ID is more prevalent among migrant and urban Ghanaian women than among their rural counterparts. Among Ghanaian men, ID was less prevalent than among Ghanaian women and rates did not differ across migrant, urban, and rural participants. Among migrant men and women in London, ID was more prevalent than among their counterparts in Amsterdam. Our study findings also show that after adjustment for covariates, ID was associated with HbA1c $\geq$ 5.5% to <6.5% in the absence of hyperglycemia, in women only. There were no associations between ID and HbA1c $\geq$ 6.5% in both men and women.

Discussion of key findings

Previous research on ID prevalence in Ghana has mainly focused on children and pregnant women. These studies reported ID prevalence in urban and rural pregnant women of 16% and 46%, respectively (33, 34). In urban and rural children ID prevalence rates $\leq$10% and 68% have been reported, respectively (35, 36). However, we cannot directly apply these findings to men and nonpregnant women because the causes

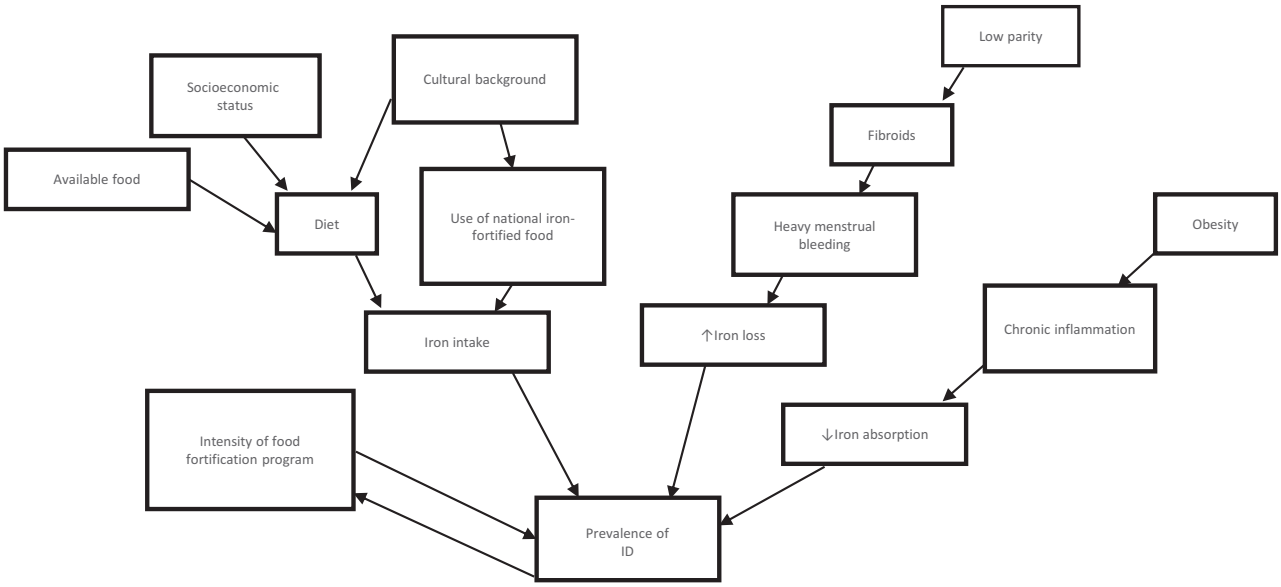

FIGURE 2 Directed acyclic graph of hypothesized factors contributing to ID prevalence. ID, iron deficiency.

of ID in pregnant women and children can be different. In addition, data on ID prevalence among first-generation SSA migrants residing permanently in high-income countries (HICs) are lacking. Owing to the scarcity of data, it is difficult to speculate why, in our study, ID prevalence is highest among migrant women. It is common belief that ID anemia is more prevalent in rural settings and therefore it is often assumed, perhaps incorrectly, that ID (with or without anemia) is also more prevalent in these areas (23, 37). This contradicts our study finding of the highest ID prevalence rates being among migrant women in Europe, migrant men in London, and urban women in Africa. A previous study using the RODAM database identified dietary patterns associated with migrant, urban, and rural settings (38). This study showed differences in iron content between these dietary patterns. In this study a "mixed pattern" consisted of high intakes of whole-grain cereals, sweet spreads, dairy products, potatoes, vegetables, poultry, coffee and tea, sodas and juices, olive oil, margarine, and condiments. Iron intake was higher among individuals who adhered to this mixed pattern than among individuals who did not adhere

TABLE 1 Characteristics of participants by sex and iron status[1]

	Men			Women		
	Iron deficient	Non–iron deficient	*P* value	Iron deficient	Non–iron deficient	*P* value
n	68	1177		520	1612	
Age, y	47.4 ± 12.5	46.4 ± 11.1	0.453	41.4 ± 8.8	46.1 ± 10.6	<0.001
BMI, kg/m^2	26.8 ± 5.2	27.1 ± 5.5	0.647	27.4 ± 5.3	27.2 ± 5.5	0.577
CRP, mg/mL	0.6 [0.1–1.2]	0.4 [0.1–1.4]	0.950	0.9 [0.2–3.1]	1.0 [0.3–3.1]	0.081
FPG,* mmol/L	5.0 ± 0.7	5.1 ± 0.6	0.049	4.9 ± 0.6	5.0 ± 0.6	<0.001
Family history of T2D*			0.851			0.487
Yes	12 (23.1)	200 (22.1)		84 (19.0)	252 (19.4)	
No	35 (67.3)	596 (65.7)		285 (64.3)	858 (66.2)	
I do not know	5 (9.6)	11 (12.2)		74 (16.7)	186 (14.4)	
Smoking			0.319			0.892
Yes	1 (1.6)	73 (6.7)		3 (0.6)	11 (0.7)	
Never	53 (85.5)	882 (80.6)		464 (96.5)	1434 (95.8)	
Former smoker	8 (12.9)	139 (12.7)		14 (2.9)	52 (3.5)	
Educational level			0.779			<0.001
Never or elementary school only	9 (15.3)	209 (18.9)		158 (32.5)	652 (43.3)	
Lower vocational	23 (39.0)	460 (41.7)		185 (38.1)	527 (35.0)	
Intermediate vocational	15 (25.4)	244 (22.1)		88 (18.1)	230 (15.3)	
University	12 (20.3)	190 (17.2)		55 (11.3)	97 (6.4)	
Alcohol			0.002			0.996
No	51 (75.0)	656 (55.7)		362 (69.6)	1122 (69.6)	
Yes	17 (25.0)	521 (44.3)		158 (30.4)	490 (30.4)	
Mean HbA1c,* mmol/L	38.6 ± 7.1	36.9 ± 7.2	0.088	37.7 ± 5.5	36.8 ± 6.2	0.002
Mean HbA1c,* %	5.7 ± 0.7	5.5 ± 0.7		5.6 ± 0.5	5.5 ± 0.6	

[1] Values are means ± SDs, medians [IQRs], or *n* (%) unless otherwise indicated. Iron deficiency is defined as ferritin < 15 ng/mL or, in case CRP > 5 mg/mL, as ferritin < 30 ng/mL. *Participants with T2D excluded. CRP, C-reactive protein; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; T2D, type 2 diabetes.

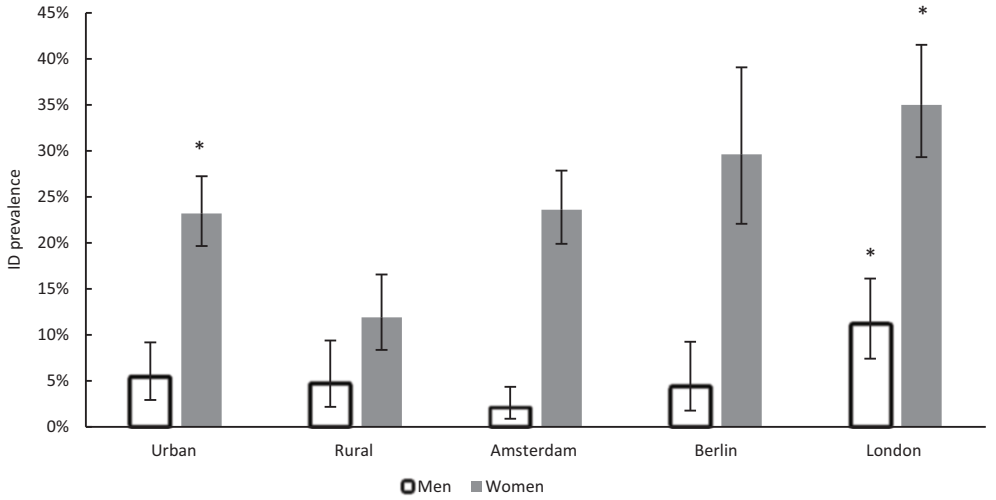

FIGURE 3 Age-standardized prevalence of ID by locality and sex—the RODAM (Research on Obesity and Diabetes among African Migrants) study. Urban Ghana ($n = 263$ men, $n = 650$ women), rural Ghana ($n = 189$ men, $n = 317$ women), Amsterdam ($n = 364$ men, $n = 592$ women), Berlin ($n = 177$ men, $n = 169$ women), London ($n = 252$ men, $n = 404$ women). Error bars represent 95% CIs. Age-standardized prevalence rates (95% CIs) of ID were as follows. For men: urban Ghana, 5.4% (1.8%, 9.4%); rural Ghana, 4.7% (1.2%, 9.4%); Amsterdam, 2.1% (0.9%, 4.3%); Berlin, 4.4% (1.7%, 9.2%); London, 11.1% (7.4%, 16.1%); for women: urban Ghana, 23.2% (19.6%, 27.2%); rural Ghana, 11.9% (8.3%, 16.5%); Amsterdam, 23.6% (19.9%, 27.8%); Berlin, 29.6% (22.1%, 39.1%); London, 35.0% (29.3%, 41.5%). ID, iron deficiency. * indicates a significantly increased ID prevalence compared to the reference group (rural Ghana for urban Ghana, and Amsterdam for London and Berlin).

to mixed patterns. By contrast, decreasing iron intake with higher adherence to the roots, tubers, and plantain pattern was observed. There were no differences in iron intake with higher adherence to the rice, pasta, meat, and fish pattern. But these differences in iron intake between dietary patterns were small and probably not large enough to be clinically significant. However, it is probable, at least in part, that owing to the common belief that ID prevalence is higher in rural areas, fortification programs implemented by the Ghanaian government may be carried out more intensely in rural Ghana. This in turn could have resulted in increased use of fortified products in these areas compared with urban areas and thus supplementary iron intake (14, 19). A cross-sectional study investigating the use of iodized salt in Hohoe Municipality, Ghana, showed that rural households were more inclined to use iodized salt than urban households (39). The same may be true for iron-fortified products, thus leading to a lower prevalence of ID in rural areas than in urban areas.

The high prevalence of ID in migrant women is surprising, especially considering that in HICs the prevalence of ID among nonmigrant women is estimated to be between 15% and 20% (40, 41). This relatively low prevalence of ID in HICs may be partially attributed to iron-fortification of wheat, a widely consumed product in European countries (20). In Ghana, on the other hand, wheat consumption is low, but vegetable oil is iron-fortified on a large scale (19). Migrants tend to eat the food of their country of origin, which could mean that Ghanaian migrants consume little iron-fortified European wheat, but at the same time do not have access to the iron-fortified Ghanaian vegetable oil (42). In addition, foods naturally rich in iron such as meat and fresh fruit are costly and some migrants do not always have the economic resources to purchase these products (43, 44). This may partially explain the higher ID rate found among migrants than among the host population. Unfortunately, data on factors influencing dietary behaviors of first-generation SSA migrants in Europe are limited. Therefore, further research is needed to validate this hypothesis and determine possible other factors contributing to the high ID prevalence in migrant Ghanaian women.

Moreover, sex differences in ID rates across sites may be explained by factors that affect women in urban and migrant settings more than rural women. The occurrence of ID in women is largely related to iron loss through menstruation (45, 46), which may explain why women with ID in our study were on average younger than women without ID. The risk of ID increases with heavy menstrual bleeding (HMB) (45). A common cause for HMB is uterine fibroids (47). Some studies have shown that increased parity is associated with decreased risk of fibroids (47, 48). Parity in rural settings tends to be higher than in urban settings (49). Perhaps urban and migrant women therefore have a higher incidence of fibroid-related HMB. In addition, the incidence of obesity is higher among

TABLE 2 ORs of iron deficiency by locality and sex—the RODAM (Research on Obesity and Diabetes among African Migrants) study[1]

	Men			Women		
	n	Unadjusted	Adjusted[2]	*n*	Unadjusted	Adjusted[2]
Rural Ghana	189	1.00	1.00	317	1.00	1.00
Urban Ghana	263	1.01 (0.44, 2.32)	0.77 (0.31, 1.89)	650	2.31 (1.57, 3.41)***	2.37 (1.56, 3.59)***
Migrants	793	1.05 (0.52, 2.13)	0.82 (0.37, 1.79)	1165	3.00 (2.08, 4.33)***	3.08 (2.04, 4.65)***

[1]Values are ORs (95% CIs) unless otherwise indicated. ***$P < 0.001$.
[2]Adjusted for age, BMI, C-reactive protein, smoking, alcohol, and educational level.

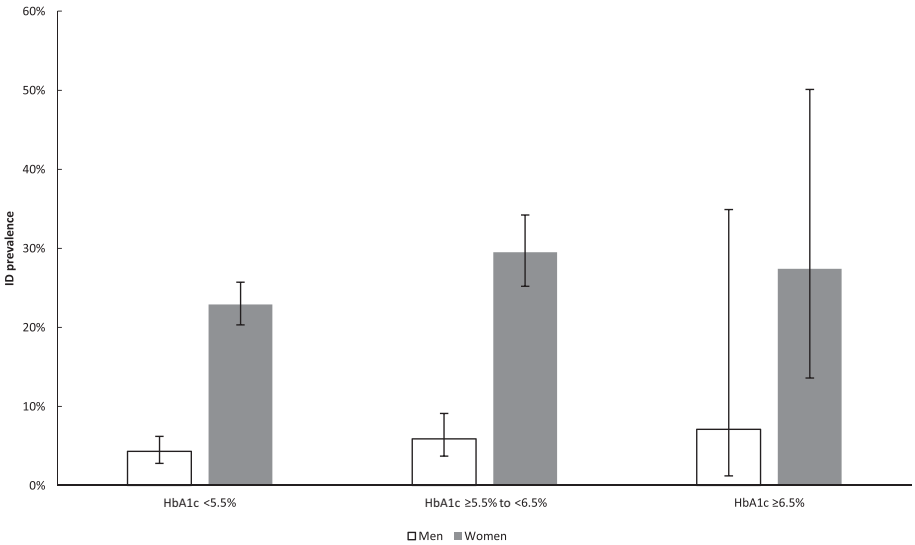

FIGURE 4 Age-standardized prevalence of ID by HbA1c category and sex—the RODAM (Research on Obesity and Diabetes among African Migrants) study. HbA1c < 5.5% (659 men and 1213 women), HbA1c ≥ 5.5% to <6.5% (422 men and 686 women), HbA1c ≥ 6.5% (31 men and 50 women). Error bars represent 95% CIs. Age-standardized prevalence rates (95% CIs) of ID were as follows. For men: HbA1c < 5.5%, 4.3% (2.8%, 6.2%); HbA1c ≥ 5.5% to <6.5%, 5.9% (3.7%, 9.1%); HbA1c ≥ 6.5%, 7.1% (1.2%, 35.0%); for women: HbA1c < 5.5%, 22.9% (20.3%, 25.8%); HbA1c ≥ 5.5% to <6.5%, 29.5% (25.2%, 34.2%); HbA1c ≥ 6.5%, 27.4% (13.7%, 50.2%). HbA1c, glycated hemoglobin; ID, iron deficiency.

migrant and urban women than among rural women (50). It has been proposed that obesity-induced chronic inflammation could cause ID owing to decreased intestinal iron absorption (51). Thus, it is possible that HMB, in combination with obesity-induced decreased intestinal iron absorption and low iron intake, might contribute to the high ID prevalence in urban and migrant female participants in our study. Unfortunately, we did not have any data on menstrual pattern and we only had a single measurement of CRP which is insufficient to determine chronic inflammation. Therefore, additional research is necessary to investigate the contribution of these factors to ID.

Furthermore, analysis showed that Ghanaian migrants residing in London are especially burdened by ID. Noteworthy is the much higher ID rate among Ghanaian migrant men in London than among Ghanaian migrant men in Amsterdam. Data on ID rates among SSA migrants in the United Kingdom, Germany, and the Netherlands are lacking. Although ID rates in the general population of these 3 countries cannot be compared directly owing to heterogeneity among studies, it is probable that ID rates are similar between these populations because iron intakes across these 3 countries are comparable (52–55). This seems to suggest that other factors may contribute to the uneven distribution of ID prevalence among migrants living in different European countries. Perhaps decreased intestinal iron absorption due to obesity-induced inflammation can partially explain the high prevalence of ID in London migrants, because this group also has the highest obesity rate (50, 51). Unfortunately, our sample size did not allow us to further test this theory by controlling for BMI and CRP. Further research is needed to identify additional contextual factors that may contribute to ID in migrant populations.

The second key finding of our study is that Ghanaian women with ID show greater odds of having HbA1c ≥ 5.5% to <6.5% than women without ID. This increased HbA1c level in women with ID could not be attributed to hyperglycemia because the FPG in this group was not increased and was even slightly lower than in women without ID. Our finding is in line with English et al.'s study (5). In that study, the authors found that HbA1c increases in nondiabetic men and women with ID, although we only found this increase to be significant in women. This sex difference has been reported before, in a large cross-sectional study by Kim et al. (6) who found women, but not men with ID to have greater odds of HbA1c ≥ 5.5% to <6.5% than women without ID. We hypothesize that the sex difference we found might be due to a difference in the prevalence of ID between men and women. Owing to the low prevalence of ID in men, an even larger sample size may be necessary to generate enough statistical power to detect a significant association between ID and HbA1c ≥ 5.5% to <6.5% in men. Our study found no association between ID and HbA1c ≥ 6.5%, which is in contrast with Shanthi et al. (8), who found that ID was associated with diabetic HbA1c levels of ≥6.5%. However, Shanthi et al. only included patients with ID anemia, whereas we did not take hemoglobin concentrations into account owing to a lack of data on hemoglobin concentrations in our study. Perhaps a decrease in hemoglobin to anemic concentrations can raise HbA1c even further and lead to levels ≥6.5%. It is possible that we included participants with nonanemic hemoglobin concentrations, which could account for the difference in the studies' findings. This explanation is in line with the aforementioned hypotheses regarding the mechanism by which ID causes HbA1c to increase. When taking into consideration El-Agouza et al.'s (9) hypothesis, the presence of both ID and anemia could cause a larger decrease in hemoglobin concentration than ID without anemia. This might result in an even stronger falsely increased HbA1c level, perhaps to ≥6.5%. Regarding the second hypothesis, perhaps more malondialdehyde is present in ID anemia than in ID alone, thereby increasing HbA1c even more (10).

Strengths and limitations

One of the major strengths of our study lies in the large database we used, which allowed us to have a good representation of the population under study, especially for the determination of

TABLE 3 ORs for HbA1c ≥ 5.5% to <6.5% and HbA1c ≥ 6.5% for those with iron deficiency by sex[1]

	Men						Women					
		HbA1c ≥ 5.5% to <6.5%			HbA1c ≥ 6.5%			HbA1c ≥ 5.5% to <6.5%			HbA1c ≥ 6.5%	
	n	Unadjusted	Adjusted[2]	*n*	Unadjusted	Adjusted[2]	*n*	Unadjusted	Adjusted[2]	*n*	Unadjusted	Adjusted[2]
Iron deficient compared with non–iron deficient	1081	1.31 (0.75, 2.28)	1.47 (0.68, 3.17)	690	2.33 (0.67, 8.10)	2.48 (0.23, 26.41)	1899	1.17 (0.94, 1.44)	1.43 (1.08, 1.87)**	1263	1.00 (0.51, 1.93)	1.26 (0.39, 4.06)

[1]Values are ORs (95% CIs) unless otherwise indicated. HbA1c < 5.5% as reference. HbA1c, glycated hemoglobin. ** $P < 0.01$.
[2]Adjusted for age, site, BMI, C-reactive protein, fasting plasma glucose, smoking, alcohol, educational level, and family history of type 2 diabetes.

ID prevalence among Ghanaians. In addition, we gathered all samples through standardized protocols and analyzed all data on HbA1c in Amsterdam and all other biochemical parameters in Berlin, thereby eliminating the chance of confounding due to interlaboratory differences. Another strength of our study is that we used a homogeneous population in which participants possessed hemoglobin phenotypes that also occur in other West African countries. Therefore, our findings might have important implications for other West African countries (56, 57).

One of the limitations of our study lies in the fact that we did not have data on hemoglobin; we could therefore only investigate the association between HbA1c and ID instead of ID anemia. In addition, we were only able to determine ID through ferritin. Although this is a WHO-validated definition, we would have liked to use additional parameters, especially because we hypothesized that obesity-related ID could play a role in the high ID rates found among migrants. Because obesity is linked to low-grade chronic inflammation, and because ferritin is an inflammatory marker, using an additional parameter to determine ID would have strengthened our study (51). Moreover, we were only able to distinguish which participants suffered from HbAS and HbAC, but we could not identify those with α-thalassemia (AT) and glucose-6-phosphate dehydrogenase (G6PD) deficiency. Müller et al. (58) determined the prevalence of these 2 pathologies among the Ghanaian migrants from our study residing in Berlin. She reported that 30% of this population had AT and 25% of this population had G6PD deficiency. Thus far, little is known of the influence these pathologies have on HbA1c, which makes speculating about the way they might confound our results difficult. Another limitation of our study is that we had a sizeable amount of missing data on family history of T2D, educational level, and smoking. We calculated the mean HbA1c for each of the 3 groups of missing cases and compared it with the mean HbA1c for the corresponding group with known outcomes. These means did not differ significantly, thus we labeled the cases missing at random.

Conclusions

The results of our study suggest that ID is a significant problem especially among migrant and urban Ghanaian women. This is an important finding because, especially for migrants in HICs, there is a paucity of migrant-specific programs that combat ID. Thus, the finding from this research could be a stepping stone for future research to look into the causes of ID in migrants in HICs and urban SSA settings. In addition, ID is associated with HbA1c ≥ 5.5% to <6.5% even when FPG is not impaired. This seems to suggest that when HbA1c levels in this range are found in Ghanaian women, these might be unreliable and could be due to ID instead of hyperglycemia. This suggests the need to take ID status into account when determining HbA1c results in women. Further studies are needed to identify factors driving the association between ID and HbA1c ≥ 5.5% to <6.5% in women.

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for the final content; and all authors: read and approved the final manuscript.

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