Serum Adiponectin and Leptin Among Ghanaian Migrants in Amsterdam and Their Compatriots in Rural and Urban Ghana: The RODAM Study

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Yaw A Kusi-Mensah[1,2,3,4,5], Charles Hayfron-Benjamin[1,2,3,4], Sean Chetty[5], Eva L van der Linden[1,2], Karlijn AC Meeks[1,6], Erik Beune[1], Frederick Anokye-Danso[7], Rexford S Ahima[7], Bert-Jan van den Born[1,2] and Charles Agyemang[1,7]

[1]Department of Public & Occupational Health, Amsterdam Public Health Research Institute, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands. [2]Department of Vascular Medicine, Amsterdam Cardiovascular Sciences Institute, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands. [3]Department of Physiology, University of Ghana Medical School, Accra, Ghana. [4]Department of Anaesthesia and Critical Care, University of Ghana Medical School, Accra, Ghana. [5]Department of Anaesthesiology and Critical Care, Faculty of Medicine and Health Sciences, Stellenbosch University (Tygerberg Hospital), Cape Town, South Africa. [6]Center for Research on Genomics and Global Health, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA. [7]Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

ABSTRACT

BACKGROUND: The rapidly rising cardiometabolic disease (CMD) burden in urbanizing sub-Saharan African populations and among sub-Saharan African migrants in Europe likely affects serum adiponectin and leptin levels, but this has not yet been quantified.

OBJECTIVES: To compare the serum levels of adiponectin and leptin among migrant, and non-migrant (urban and rural) populations of Ghanaian descent.

METHODS: Cross-sectional analysis of serum leptin and adiponectin in the multi-centre Research on Obesity and Diabetes among African Migrants (RODAM) study. Logistic-regression models were used to examine the association between these adipocyte-derived hormones after stratification (sex, geographic area) and adjustments for potential confounders.

RESULTS: A total of 2518 Ghanaians were included. Rural participants had the highest serum adiponectin and lowest leptin levels compared to Amsterdam and urban Ghanaians ($P < .001$). In fully adjusted models, participants living in urban Ghana had significantly higher odds of hyperleptinemia compared to rural participants (women-odds ratio 2.88; 95% CI, 1.12-7.38, $P = .028$ and men 43.52, 95% CI, 4.84-391.25, $P < .001$). Urban Ghanaian men also had higher odds of elevated leptin: adiponectin ratio (6.29, 95% CI, 1.43-27.62, $P = .015$). The odds of hyperleptinemia were only higher in Amsterdam Ghanaian men (10.56; 95% CI, 1.11-100.85, $P = .041$), but not in women (0.85; 95% CI, 0.30-2.41, $P = .759$). There was no significant association between hypoadiponectinemia and geographical location in both sexes.

CONCLUSION: Urbanization is associated with serum adiponectin and leptin levels after adjusting for confounding covariates in sub-Saharan Africans. These findings serve as a backdrop for further research on the role adipokines play in CMD epidemiology among Africans.

KEYWORDS: Adiponectin, leptin, cardiometabolic disease, obesity, urbanization

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CORRESPONDING AUTHOR: Yaw A Kusi-Mensah, Department of Physiology, University of Ghana Medical School, P.O. Box CT 2004, Cantonments, Accra, Ghana. Emails: y.a.kusimensah@amsterdamumc.nl; ykusimensah@gmail.com

Introduction

The prevalence of cardiometabolic disease (CMD) has more than doubled worldwide in the past 3 decades and is currently the leading cause of death.[1] This is also true for low- and middle-income (LMICs) countries, including Ghana, where CMD and associated mortality is increasing.[2] Although not fully understood, CMD disproportionately affects Africans compared to other ethnic groups.[3] CMD refers to specific interrelated conditions: cardiovascular disease (CVD), type 2 diabetes (T2DM) and chronic renal failure, which all have metabolic derangement as risk factors for their development.[1] Obesity is one of such risk factors, and an important contributor to the increase in CMD among Africans. The association between obesity and CMD is partly mediated by adipocyte-derived hormones, including leptin and adiponectin.[4] Leptin and adiponectin are closely related to obesity and

obesity-associated cardiometabolic complications.[4-7] Leptin is secreted by adipocytes and acts in the brain to regulate feeding and energy metabolism, while adiponectin is reduced in obesity and exerts potent insulin-sensitizing, anti-inflammatory and anti-atherogenic effects.[4,8] Obesity is associated with elevated leptin levels, insulin resistance, chronic inflammation, oxidative stress, and a predisposition toward diabetes and CMD.[6,7] Some studies suggest that in some African populations, adiponectin is causally associated with low-density lipoprotein(LDL) in people with obesity, and high-density lipoprotein and T2DM in populations without obesity.[9] Hyperleptinemia and hypoadiponectinemia are thus associated with insulin resistance, atherosclerosis, and a pro-inflammatory state.[4-8] In addition, a derived parameter, the leptin: adiponectin ratio has been shown to be associated with carotid intima thickness, serving as a marker and predictor of atherosclerosis, a major risk factor associated with CVDs.[4,6]

Urbanization and migration are associated with a higher prevalence of obesity and, potentially affect serum adiponectin and leptin levels.[10] Urbanization, and to a lesser extent international migration, is increasing rapidly in sub-Saharan Africa[11,12] and is associated with dietary modifications (processed foods rich in sugar, fat, and salt) and an increased sedentary lifestyle. In Ghana, rural-to-urban migration has contributed significantly to the obesity epidemic.[10] Evaluating obesity-related endocrine processes in the context of urbanization and migration (both locally and internationally) will provide important insight into the pathophysiology of obesity and related diseases.

Despite the increasing burden of obesity and its related complications, and the increasing rate of urbanization and migration in sub-Saharan Africa, not much is known about the effect of urbanization and migration on the changes in biomarkers, for example, adiponectin and leptin, and their association with CMD in Africans. In addition, the unchanging association of adiponectin and leptin with CVD despite adjustment for confounders, may potentially further explain the disproportionate disease burden amongst Africans. Limited data exist on the serum levels of adiponectin and leptin in sub-Saharan Africans, including Ghanaians. The overall aim of this study was therefore to compare the serum levels of adiponectin, leptin, and the leptin: adiponectin ratio between Ghanaian migrants living in Amsterdam, the Netherlands, and non-migrant Ghanaians living in rural and urban Ghana.

Materials and Methods

Study design, study participants, sample calculation and ethical considerations

A cross-sectional analysis, of baseline data from the multi-centre Research on Obesity and Diabetes among African Migrants (RODAM) study was done. To summarize, the RODAM study is a population-based study that collected baseline data from 2012 to 2015 amongst Ghanaians (aged 25-96 years) living in rural and urban Ghana as well as in Amsterdam, the Netherlands; Berlin, Germany; and London, UK. Data collection of the study was standardized across sites. This cross-sectional analysis was carried out on a subset of the total RODAM study population and included randomly selected 2518 RODAM study participants in Amsterdam and Ghana (both rural and urban), who had their serum leptin and adiponectin measured. The analysis was limited only to participants in Amsterdam and Ghana mainly due to logistic limitations. A detailed overview of participants included in this cross-sectional analysis is illustrated in Figure 1.

The study was designed to look at the upper 95th and lower fifth percentile of leptin and adiponectin respectively to assess the impact of migration on these adipocyte derived hormones. We calculated, using the Vanderbilt University Medical Center Power Sample Size calculator, that we would need at least 800 men and women to demonstrate a 4 times rise in leptin or fall in adiponectin levels considering alpha = 0.05 and a power of 80%.

The approval for the study protocol was granted at all sites from the respective ethical committees: in Ghana (School of Medical Sciences/Komfo Anokye Teaching Hospital Committee on Human Research, Publication & Ethical Review Board, ref. CHRPE/AP/200-12), and in the Netherlands (institutional review board of the Academic Medical Centre, University of Amsterdam, ref. W12_062#12.17.0086). Written informed consent was obtained from each participant before enrollment. For further details, the rationale, conceptual framework, design, and methods of the RODAM study have been extensively described elsewhere.[13] This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Measurement of variables and definitions

Information on demographics, educational level (used as a proxy for socioeconomic status), medical history, dietary intake, and other lifestyle factors was obtained through a structured questionnaire using appropriately validated instruments. Smoking status was categorized into smoker or non-smoker. Alcohol intake (gram per day) and total energy intake(kilocalories per day) were estimated using standard portion sizes, combined with the frequency of intake based on a standardized Food Propensity Questionnaire (Ghana-FPQ). The Ghana-FPQ is based on the multi-language, semi-quantitative European-FPQ, and included Ghanaian foods identified in previous studies.[14] Data on physical activity in metabolic equivalent(MET, hours/week) was derived using the WHO-STEPS questionnaire.[15] Based on the information gathered from the WHO-STEPS questionnaire, participants were classified into a low, moderate, or high level of total physical activity based on the International Physical Activity Questionnaire (IPAQ) classification.[16] Participants were asked to bring their medication, and medication use was verified by a questionnaire. Blood pressure-lowering medications

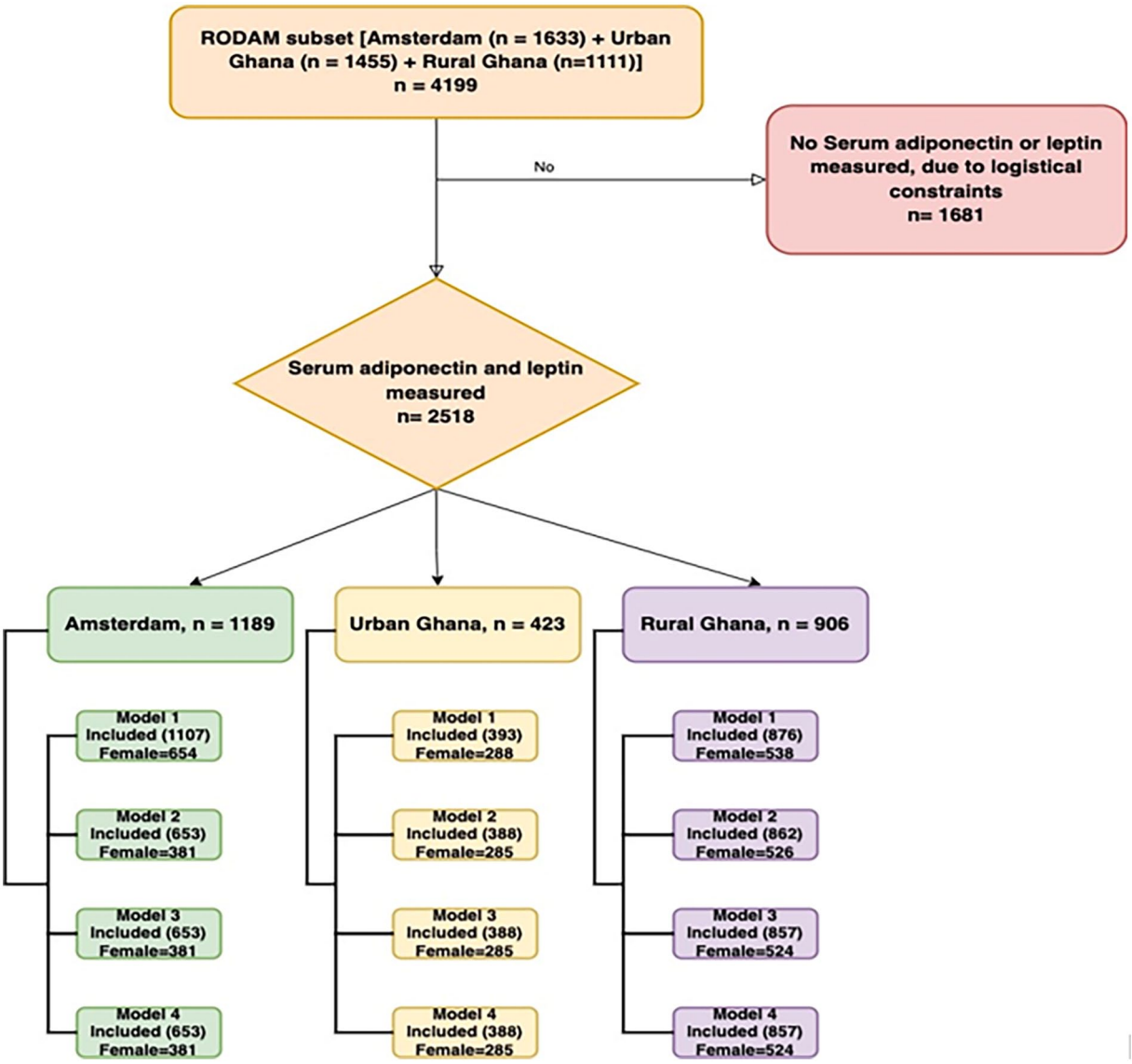

Figure 1. Flow chart of participants included for analysis.

(BP-lowering medication) were then classified based on the Anatomical Therapeutical Chemical (ATC) classification.

Physical examination was done with validated devices according to standardized operational procedures across all study sites. Weight in kilograms, and height in meters, were measured in light clothing without shoes using SECA 877 weighing scales and SECA 217 portable stadiometers, respectively (manufactured by SECA, Hamburg, Germany). Body Mass Index (BMI, kg/m^2) was calculated by dividing the weight in kilograms by the squared height in meters. Waist circumference(cm) and hip circumference(cm) were measured using a standard measuring tape. For waist circumference, the measurement was taken at the midpoint between the lower rib and the upper margin of the iliac crest, and hip circumference was measured around the major trochanter. Waist-to-hip ratio (WHR) was calculated by dividing waist circumference by hip circumference. All anthropometric measurements were performed twice and the average of the 2 measurements was used for the analysis. Blood pressure(BP) was determined using the non-invasive Microlife Watch BP home device (Microlife WatchBP AG, Widnau, Switzerland), with appropriately sized cuffs after at least 5 minutes of rest while seated. The BP for each participant was measured 3 times and the mean of the last 2 measurements was used in the analyses. Hypertensive was defined as systolic BP $\geqslant$ 140 mmHg and/or diastolic BP $\geqslant$ 90 mmHg, and/or current use of antihypertensive agents based on the ATC classification/ medication list.

Trained research assistants took fasting (overnight fast of at least 10 hours) venous blood samples at all locations. All samples were processed and divided into aliquots immediately after collection (within 1 hour to a maximum of 3 hours of the vena puncture), and then temporarily stored at the local research location at −20°C. The separated samples were then transported to the local research centres' laboratories, where they were checked and registered and stored at − 80°C, before being

shipped to their final destination for analysis. All samples were taken to Berlin, Germany for the analysis to avoid inter-laboratory bias. After the analysis, samples were then randomly selected from the Amsterdam and Ghanaian participants and sent to the Endocrinology Research Laboratory at the Johns Hopkins University School of Medicine, for measurement of adiponectin and leptin. Adiponectin and leptin were measured in duplicate samples using enzyme-linked immunosorbent assay(ELISA) kits (Crystal Chem, Elk Grove, Illinois, USA): Adiponectin, Cat No. 80571 (RRID:AB_2800326), sensitivity 0.3 ng/ml, intra-assay CV 3.8%, inter-assay CV 5.7%; Leptin, Cat No. 80968, sensitivity 0.42 ng/ml, intra-assay CV 4.5%, inter-assay CV 4.7%. The leptin: adiponectin ratio was calculated by dividing the measured serum leptin concentration by the adiponectin concentration for each participant. Hypoadiponectinemia was defined as serum adiponectin values below the fifth centile, hyperleptinemia and high leptin: adiponectin ratios were defined as serum leptin values or leptin: adiponectin ratios above the 95th centile specific for the population per sex.[17] Information on fasting plasma glucose (FPG) concentration was obtained using an enzymatic method (hexokinase method by colorimetry). Diabetes was defined as self-reported diabetes and/or use of a hypoglycemic agent and/or fasting blood glucose >7mmol/L and/or HBA1C > 48 mmol/mol or >6.5%. The Mercodia ELISA kit (Mercodia, Uppsala, Sweden) was used to measure plasma insulin levels. Based on the fasting plasma glucose and the plasma insulin, insulin resistance was assessed using the Homeostatic Model Assessment for Insulin Resistance(HOMA-IR) method.[18] Fasting serum total cholesterol and glucose were measured using enzymatic colorimetric assays (ABX Pentra 400 chemistry analyzer, HORIBA ABX, Germany).

Data analysis

The data were analyzed using RStudio version 2021.09.1 Build 372 for Mac Os and IBM SPSS version 26 for Windows. All analyses were stratified by sex, as several studies have shown significant differences in adiponectin and leptin levels between women and men. Data on continuous variables were presented as mean with 95% confidence interval(CI) and p-values for normally distributed data, and as median with interquartile range(IQR) for non-normally distributed data (normality was determined graphically with histograms and QQ-plot). Data on categorical variables were presented as frequencies and percentages (proportions) with p-values determined using a Chi-square test to assess differences between the geographic locations. The Kruskal-Wallis test was used to compare the median values of serum adiponectin, leptin, and the leptin: adiponectin ratio amongst Ghanaians in Amsterdam, Urban Ghana, and Rural Ghana(non-migrants). A follow-up pair-wise comparison of sites was done to determine where the differences between the 3 locations existed. Age-standardized prevalence rates of hypoadiponectinemia and hyperleptinemia were calculated using the direct method, using the overall RODAM population as reference, and compared between migrant and non-migrant peers. Since the literature extensively describes the association between hypoadiponectinemia and hyperleptinemia and CMD, multivariable logistic regression models were used to examine the association between hypoadiponectinemia, hyperleptinemia and high leptin: adiponectin ratio and geographical location with adjustments for traditional risk factors (age, socioeconomic status, smoking and alcohol intake), markers of adiposity (BMI, WHR) and cardiometabolic risk factors (hypertension, total cholesterol, and insulin resistance). These covariates were chosen based on the prior known literature about these variables and their potential effect on serum adiponectin and leptin levels. To assess the potential role of confounding factors and mediators and based on the results of the DAG (Directed acyclic graph), see at https://www.dagitty.net/dags.html, 4 regression models were used. Model 1 was adjusted for age and socioeconomic status; Model 2 was adjusted for age, socioeconomic status, smoking, alcohol intake, hypertension, total cholesterol, BMI and WHR; Model 3 was adjusted for model 2 plus insulin resistance; and Model 4 (full model)—was adjusted for model 3 plus T2DM. In all the models, the rural Ghana population served as the reference group. Interaction between variables was assessed using the interaction plot line graph, whilst multicollinearity was determined using the Variance Inflation Factor (VIF), with a cut-off of <5 deemed as no significant multicollinearity. No interaction, between all independent variables, was seen and no multicollinearity existed between BMI and WHR, and between insulin resistance and T2DM when assessed. Missing values in each model were handled by listwise deletion, with participants with complete data deemed representative of the total sample following subset analysis. Details of participants included in each model are illustrated in Figure 1.

Results

Population baseline characteristics (demographics, medical history, and physical characteristics)

Details of all baseline characteristics are shown in Table 1. Of the 2518 participants who had their serum adiponectin and leptin measured, 1570 (62.35%) were women. Among women, the mean age differed significantly per geographical location, with Amsterdam-Ghanaian women and Urban-Ghanaian women being slightly younger than their rural counterparts. In general, rural Ghanaians had a better cardiometabolic risk profile compared to urban Ghanaians and Ghanaians living in Amsterdam.

Serum adiponectin and leptin

As expected, women and men living in rural Ghana had a more favorable adipokine profile, with the highest median serum adiponectin ($P < .001$) and the lowest median serum leptin($P < .001$) (Table 2). Despite a higher degree of urbanization in Amsterdam, median serum adiponectin and leptin

Table 1. Baseline characteristics of the included population (n = 1570 (women) and n = 948 (men)).

	TOTAL*, N	AMSTERDAM-GHANAIANS	URBAN-GHANAIANS	RURAL-GHANAIANS	*P*-VALUE
Women					
Site, n (%)	1570	710 (45.2)	303 (19.3)	557 (35.5)	
Age, years, mean (SD)	1568	44.06 (10.09)	45.98 (11.17)	49.05 (14.49)	<.001
Educational level, %	1481	655 (44.2)	288 (19.4)	538 (36.3)	<.001
None or Elementary		40.0	58.0	69.9	
Lower Secondary		33.6	31.9	25.3	
Higher Secondary		22.0	7.6	3.2	
Tertiary		4.4	2.4	1.7	
Migrant generation					
First generation, %		97.5	-	-	
Second generation, %		2.5	-	-	
Currently smoking, %	1462	1.4	0.0	0.0	<.001
Alcohol use, g/day, median (IQR)	1266	0.73 (3.12)	**0.06** (0.58)	**0.06** (0.58)	<.001
Total energy intake, median (IQR) kcal/day	1266	2317.66 (1304.95)	2169.90 (763.60)	2532.71 (1271.62)	<.001
Physical activity, %	1271	444 (34.9)	288 (22.7)	538 (42.4)	<.001
Low level		19.4	45.5	26.9	
Moderate level		22.7	15.6	22.8	
High level		57.9	38.9	50.1	
BMI, kg/m^2, mean (95% CI)	1565	29.67 (29.29-30.05)	27.96 (27.36-28.57)	23.55 (23.17-23.93)	<.001
Mean Waist-to-hip ratio, mean (95% CI)	1568	0.89 (0.88-0.89)	**0.90** (0.89-0.91)	**0.90** (0.89-0.91)	<.001
Obesity$^{\alpha}$, %	1565	43.4	32.7	8.1	<.001
Hypertensive$^{\varepsilon}$, %	1570	51.7	42.2	37.0	<.001
Diabetic$^{\phi}$, %	1570	11.1	11.9	6.6	.010
Biochemistry					
Insulin resistance (HOMA-IR), mean (95% CI)	1555	1.86 (1.76-1.94)	2.18 (1.99-2.37)	1.43 (1.32-1.54)	<.001
Mean Total Cholesterol, mmol/L (95% CI)	1557	5.01 (4.93-5.09)	5.27 (5.14-5.39)	4.71 (4.61-4.81)	<.001
Men					
Site, n (%)	948	479 (50.5)	120 (12.7)	349 (36.8)	
Age, years, mean (SD)	948	47.61 (10.94)	47.38 (11.82)	48.54 (14.65)	.505
Educational level, %	896	453 (50.6)	105 (11.7)	338 (37.7)	<.001
None or Elementary		21.4	24.8	43.5	
Lower Secondary		42.2	39.0	36.4	

(Continued)

Table 1. (Continued)

	TOTAL*, N	AMSTERDAM-GHANAIANS	URBAN-GHANAIANS	RURAL-GHANAIANS	*P*-VALUE
Higher Secondary		28.3	21.0	13.0	
Tertiary		8.2	15.2	7.1	
Migrant generation					
First generation, %		97.0	-	-	
Second generation, %		3.0	-	-	
Currently smoking, %	880	7.8	1.9	5.6	.100
Alcohol use, g/day, median (IQR)	760	3.15 (10.16)	**0.11** (1.55)	**0.58** (3.33)	<.001
Total energy intake, median (IQR) kcal/day	760	**2537.04** (1365.32)	2331.59 (908.68)	**2595.23** (1255.22)	.004
Physical activity, %	730	292 (40.0)	104 (14.2)	873 (45.8)	<.001
Low level		22.3	34.6	14.7	
Moderate level		17.1	18.3	18.3	
High level		60.6	47.1	67.1	
BMI, kg/m^2, mean (95% CI)	947	26.97 (26.63-27.32)	24.11 (23.40-24.82)	20.80 (20.49-21.12)	<.001
Mean Waist-to-hip ratio, mean (95% CI)	947	0.94 (0.94-0.95)	0.91 (0.89-0.92)	0.89 (0.88-0.90)	<.001
Obesity$^{\alpha}$, %	947	19.6	8.3	1.1	<.001
Hypertensive$^{\varepsilon}$, %	948	61.6	49.2	28.7	<.001
Diabetic$^{\phi}$, %	948	17.3	10.8	4.9	<.001
Biochemistry					
Insulin resistance (HOMA-IR), mean (95% CI)	941	**1.87** (1.72-2.02)	**1.56** (1.33-1.80)	0.87 (0.73-1.01)	<.001
Mean Total Cholesterol, mmol/L (95% CI)	944	**5.07** (4.97-5.17)	**5.10** (4.87-5.33)	4.20 (4.10-4.31)	<.001

Abbreviations: SD, standard deviation; CI, confidence interval; IQR, interquartile range; BMI, body mass index; HOMA-IR, homeostatic model assessment for insulin resistance.
Values are presented as mean (SD or 95% CI), median (IQR), n (%) or percentages (%) per site.
*Missing data in category excluded in analysis. **Bold font**—no differences between groups following paired-wise analysis. α- Obesity defined as BMI >30 kg/m^2 ε- Hypertensive defined as systolic BP ⩾ 140 mmHg and/or diastolic BP ⩾ 90 mmHg, and/or current use of antihypertensive agents. ϕ- defined as self-reported diabetes and/or use of a hypoglycemic agent and/or fasting blood glucose >7 mmol/L and/or HBA1C > 48 mmol/mol or >6.5%.

values were similar based on the pair-wise analysis, between Ghanaians living in Amsterdam and urban Ghanaian dwellers, with differences only seen in the median adiponectin amongst women. The median leptin value in men living in rural Ghana was remarkably lower compared to women living in the same location. Rural Ghanaian participants had the lowest leptin: adiponectin ratio, however, among men, there was no significant difference in the leptin: adiponectin ratio between Ghanaians living in Amsterdam and urban Ghanaian dwellers.

Although urban Ghanaian women had the highest age-standardized prevalence rate (6.5%) of hypoadiponectinemia (serum adiponectin <2.36 ug/ml), this was not significantly different from rural Ghanaian dwellers (3.9%) or Ghanaians living in Amsterdam (5.5%) (P=.223) (Figure 2). However, urban Ghanaian women had a significantly higher prevalence rate (10.39%) of hyperleptinemia (serum leptin >72.56 ng/ml) compared to their migrant (6.21%) and rural counterparts (1.22%) (P<.001) (Figure 3). For men, participants living in Amsterdam had a higher age-standardized prevalence rate (6.14%) of hypoadiponectinemia (serum adiponectin <1.39 ug/ml) compared with Ghanaians living in urban (2.68%) and rural Ghana (3.78%), but this was not statistically significant (P=.082) (Figure 2), while men living in urban Ghana had a significantly higher age-standardized prevalence (12.34%) of hyperleptinemia (serum leptin >28.72 ng/ml) compared to their counterparts living in rural Ghana (0.40%) and Amsterdam (6.62%) (P<.001) (Figure 3).

Table 2. Serum leptin, leptin: adiponectin ratio and serum adiponectin of the included population (n = 1570 (women) and n = 948(men)).

	TOTAL*, N	AMSTERDAM-GHANAIANS	URBAN-GHANAIANS	RURAL-GHANAIANS	*P*-VALUE
Women					
Site, n (%)	1570	710 (45.2)	303 (19.3)	557 (35.5)	
Serum leptin, ng/ml, median (IQR)	1570	**28.23** (16.15-41.64)	**27.50** (12.50-47.32)	10.57 (4.10-23.44)	<.001
Leptin: Adiponectin median (IQR)	1570	3.48 (1.48-6.63)	4.18 (1.62-10.02)	1.00 (0.28-3.02)	<.001
Serum adiponectin, ug/ml, median (IQR)	1570	8.50 (5.23-12.95)	6.18 (4.06-9.48)	9.79 (6.26-15.62)	<.001
Men					
Site, n (%)	948	479 (50.5)	120 (12.7)	349 (36.8)	
Serum leptin, ng/ml median (IQR)	946	**5.89** (2.58-11.45)	**4.83** (1.00-12.26)	0.27 (0.11-1.19)	<.001
Leptin: Adiponectin median, (IQR)	946	**1.42** (0.44-3.10)	**0.97** (0.16-3.63)	0.04 (0.01-0.19)	<.001
Serum adiponectin, ug/ml (median IQR)	948	**4.65** (2.68-8.17)	**4.98** (3.41-7.99)	6.79 (4.06-11.30)	<.001

Abbreviation: IQR, interquartile range.
Values are presented as median (IQR) or n (%).
*Missing data in category excluded in analysis. **Bold font**—no differences between groups following paired-wise analysis.

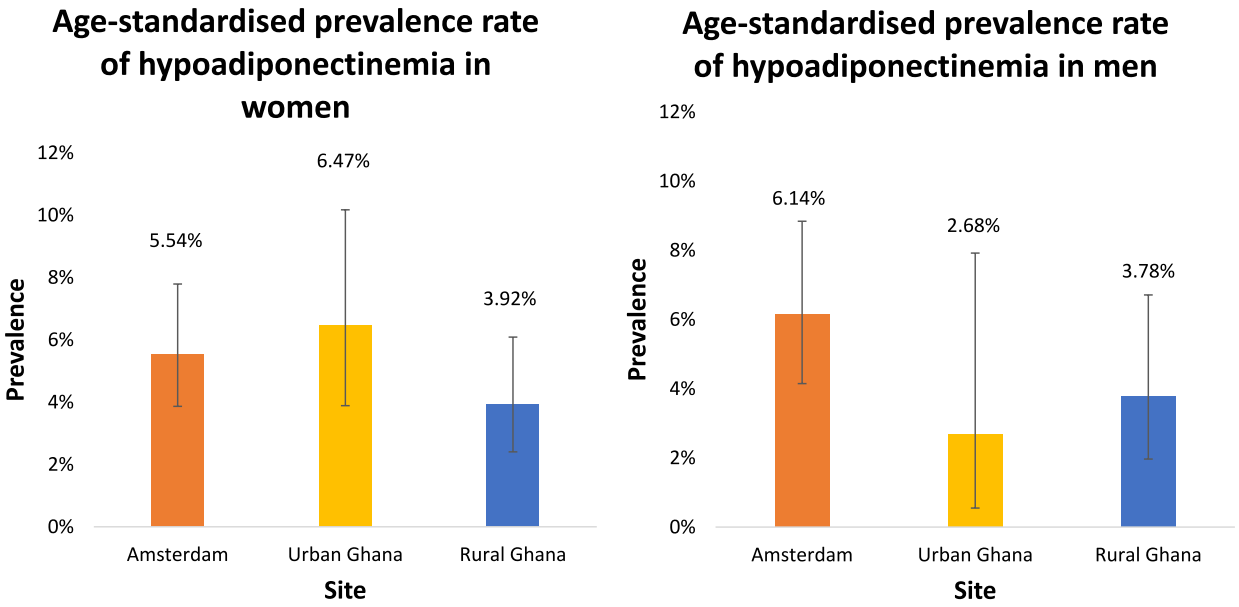

Figure 2. Age-standardized prevalence rates with 95% confidence interval of hypoadiponectinemia in women and men per site.

For women, living in urban Ghana or Amsterdam was associated with significantly higher odds for hyperleptinemia OR 8.69, 95% CI 3.72 to 20.29 and OR 4.24, 95% CI 1.82 to 9.92 compared to those living in rural Ghana, (Table 3). In the fully adjusted model, however, the odds for hyperleptinemia (OR 2.88, 95% CI 1.12-7.38) were only significantly higher for women living in urban Ghana. Further, in the minimally adjusted model for women, living in urban Ghana compared to rural Ghana was associated with a higher odds of high leptin: adiponectin ratio (OR 4.54, 95% CI 2.32-8.89), however, this association was not significant in the fully adjusted model. For men, compared to living in rural Ghana, living in Amsterdam or urban Ghana was associated with higher odds of hyperleptinemia (OR 10.56, 95% CI 1.11-100.85 and OR 43.52, 95% CI 4.84-391.25) respectively, in the fully adjusted model, and this association was seen in all models (Table 3). With regards to the high leptin: adiponectin ratio, men living in Amsterdam had higher odds (OR 7.06, 95% CI 2.12-23.55) compared to their counterparts in rural Ghana. However, this difference was no longer significant in the fully adjusted model. In addition, compared to their rural counterparts, men living in urban Ghana had significantly high odds of high leptin: adiponectin ratios even in the fully adjusted model (OR 6.29,

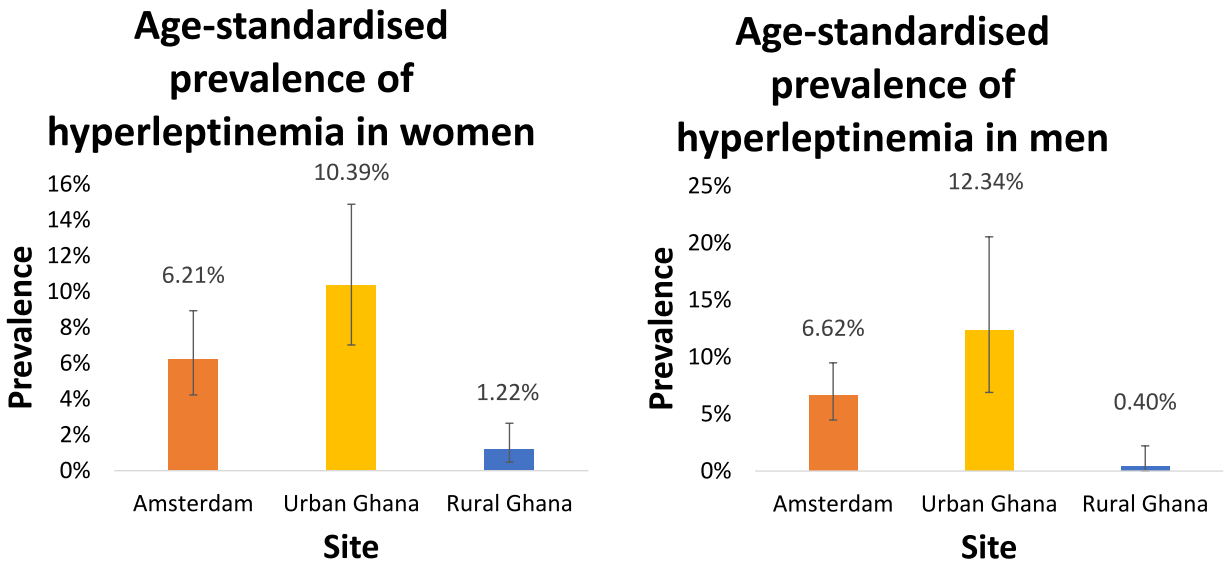

Figure 3. Age-standardized prevalence rates with 95% confidence interval of hyperleptinemia in women and men per site.

95% CI 1.43-27.62). In all the models, there was no significant association between hypoadiponectinemia and geographical location for both men and women. Finally, in models where, hypertension, insulin resistance, T2DM and total cholesterol were excluded, similar results were obtained (see Supplemental Analysis).

Discussion

Key findings

Key findings in this homogenous population of Ghanaians living in rural and urban Ghana and Amsterdam were: serum adiponectin concentrations were lower, and serum leptin concentrations were higher in Ghanaians living in Amsterdam and urban Ghana compared with Ghanaians living in rural Ghana; geographic differences in known cardiometabolic risk factors, including BMI,WHR, T2DM and insulin resistance could fully explain the differences in serum adiponectin, for both women and men, and serum leptin in women living in Amsterdam, however, the differences in serum leptin in men and women living in urban Ghana could only be partly explained by the geographic differences in known cardiometabolic risk factors; and urbanization was associated with a high leptin: adiponectin ratio in men living in urban Ghana even after adjusting for confounders.

Discussion of key findings

Rural participants having high serum adiponectin and low serum leptin compared to their counterparts living in Amsterdam and urban Ghana as demonstrated in this study followed an expected pattern based on their obesity, insulin resistance and T2DM profile. Obesity and the accompanying dysfunctional adipose tissue is the most relevant determinant of adiponectin and leptin production.[19] Adiponectin is downregulated, and leptin is upregulated in the presence of obesity.[4,5] Insulin resistance and T2DM are associated with hypoadiponectinemia and hyperleptinemia.[4,5] Results from the previous RODAM study and this current analysis strongly suggest that the BMI, insulin resistance and T2DM in Ghanaians correlates positively with migration from rural Ghana to urban Ghana and then to high-income countries.[10] A similar association between hypoadiponectinemia and hyperleptinemia, and markers of adiposity and insulin resistance was also seen in a Dutch population.[20] The findings of this study, therefore, reinforce the strong association between markers of adiposity as well as other conventional risk factors for CMD and adiponectin and leptin.

Conventional risk factors for CMD, such as obesity have been shown to be a much stronger determinant of serum adiponectin levels compared to serum leptin levels,[21] this could potentially explain why in this study, variations in serum adiponectin were fully explained by differences in conventional risk factors of CMD. In addition, Yang et al demonstrated a 46% increase in plasma adiponectin levels following a 21% reduction in mean BMI, suggesting that adiposity is the main driver of variations in serum adiponectin.[22] In this study, however, variations in serum leptin in women living in urban Ghana and men living in Amsterdam and urban Ghana could not be fully explained by the conventional risk factors for CMDs such as obesity, insulin resistance and T2DM. In a similar study done in a population of Cameroonians, markers of adiposity and insulin resistance did also not fully explain the variations in the leptin: adiponectin ratio in the study population.[23] In Benin, Bonaventure et al demonstrated that only 43% to 58% of the variations in serum leptin in the study participants could be explained by differences in BMI, waist circumference, fasting insulin and HOMA-IR, implying other factors might have affected serum leptin levels. These studies reinforce the findings demonstrated in this current study and corroborate the need to further investigate other potential factors associated

Table 3. Odds ratios for hypoadiponectinemia, hyperleptinemia and high leptin: adiponectin ratio among Ghanaian women and men living in Amsterdam and urban Ghana compared with rural Ghana.

	OR (95% CI), *P*-VALUE			
	MODEL 1	MODEL 2	MODEL 3	MODEL 4
Women				
Hyperleptinemia				
Amsterdam	4.24 (1.82-9.92), .001	0.85 (0.30-2.37), .754	0.83 (0.29-2.33), .717	0.85 (0.30-2.41), .759
Urban Ghana	8.69 (3.72-20.29), <.001	2.91 (1.14-7.45), .026	2.89 (1.13-7.42), .027	2.88 (1.12-7.38), .028
Rural Ghana	1.00	1.00	1.00	1.00
High leptin: adiponectin ratio				
Amsterdam	1.69 (0.85-3.38), .137	0.42 (0.17-1.03), .057	0.45 (0.18-1.10), .079	0.42 (0.17-1.03), .058
Urban Ghana	4.54 (2.32-8.89), <.001	1.76 (0.84-3.70), .136	1.69 (0.80-3.57), .172	1.68 0.80-3.55), .173
Rural Ghana	1.00	1.00	1.00	1.00
Hypoadiponectinemia				
Amsterdam	1.25 (0.70-2.24), .448	0.73 (0.34-1.57), .422	0.78 (0.36-1.69), .531	0.72 (0.33-1.56), .399
Urban Ghana	1.67 (0.88-3.17), .120	1.06 (0.52-2.14), .875	0.98 (0.48-1.99), .957	0.95 (0.47-1.93), .884
Rural Ghana	1.00	1.00	1.00	1.00
Men				
Hyperleptinemia				
Amsterdam	20.24 (2.72-150.64), .003	10.95 (1.14-105.27), .038	11.43 (1.19-110.28), .035	10.56 (1.11-100.85), .041
Urban Ghana	48.45 (6.25-375.85), <.001	42.82 (4.71-389.09), .001	44.40 (4.85-406.78), .001	43.52 (4.84-391.25), .001
Rural Ghana	1.00	1.00	1.00	1.00
High leptin: adiponectin ratio				
Amsterdam	7.06 (2.12-23.55), .001	2.75 (0.63-12.08), .180	2.62 (0.59-11.66), .206	2.62 (0.59-11.65), .207
Urban Ghana	9.88 (2.60-37.55), .001	6.35 (1.45-27.84), .014	6.29 (1.43-27.65), .015	6.29 (1.43-27.62), .015
Rural Ghana	1.00	1.00	1.00	1.00
Hypoadiponectinemia				
Amsterdam	1.60 (0.80-3.19), .185	0.85 (0.31-2.37), .760	0.81 (0.29-2.29), .691	0.81 (0.29-2.29), .690
Urban Ghana	0.46 (0.10-2.09), .313	0.29 (0.06-1.50), .139	0.29 (0.06-1.48), .137	0.30 (0.06-1.52), .146
Rural Ghana	1.00	1.00	1.00	1.00

The odds ratios were generated using logistic regression, with rural participants as the reference population. Hypoadiponectinemia was defined as serum adiponectin values below the fifth centile, hyperleptinemia and high leptin: adiponectin ratios were defined as serum leptin values or leptin: adiponectin ratios above the 95th centile all specific for the population per sex. Model 1—adjusted for age and socioeconomic; Model 2—adjusted for age, socioeconomic status, smoking, alcohol intake; hypertension, total cholesterol, BMI and WHR; Model 3—adjusted for age, socioeconomic status, smoking, alcohol intake; hypertension, total cholesterol, BMI, WHR and insulin resistance. Model 4—adjusted for age, socioeconomic status, smoking, alcohol intake; hypertension, total cholesterol, BMI, WHR, insulin resistance and type 2 diabetes.

with serum leptin such as gut microbiome and stress, in addition to migration and urbanization.

In this study, migration and urbanization were shown to be independently associated with hyperleptinemia in women living in urban Ghana and men, but not hypoadiponectinemia in the entire population even after adjusting for conventional risk factors for CMD. In addition, urbanization was shown to be independently associated with a high leptin: adiponectin ratio in men living in urban Ghana. Migration and urbanization have been demonstrated in previous studies to significantly impact health, especially non-communicable diseases. In a prospective, cohort study done in Indonesia, rural to urban migration, was associated

with a disproportionately higher increase in BMI and leptin :adiponectin ratio compared to urban-to-urban migration.[35] Migration and urbanization may lead to unhealthy lifestyle modifications such as consumption of more processed food and physical inactivity, which ultimately lead to obesity and significantly impact one's health.[24,25] More recently, another link between migration and obesity with its ensuing complication has been established.[26,27] Migration and urbanization with their inevitable dietary changes and gene-environmental interaction (through epigenetics) have been strongly linked to changes in the gut microbiome of migrants. Both epigenetics and the gut microbiome are independently associated with CMD and obesity, predisposing migrants to obesity and CMD driven by epigenetic changes and changes in their gut microbiome.[26,27] Migration and urbanization thus may exert their effect on adiponectin and leptin through other mediators, however, the exact mechanism by which migration and urbanization affect adiponectin and leptin independent of obesity remains unknown requiring further studies. Further studies can potentially look at other mediators besides obesity such as epigenetics and gut microbiome or discrimination and stress associated with migration and urbanization. Some researchers, however, have investigated the possibility of migration and urbanization directly affecting serum adiponectin and leptin.

Conflicting data, however, exist on the effect of migration and urbanization on adiponectin and leptin in various populations. In addition, information on the effect of migration and urbanization on leptin and adiponectin levels is limited, with notable studies carried out in the Solomon Islands and Papua New Guinea. Furusawa et al[28] reported no association between urbanization and serum leptin levels in a population located in the Solomon Islands. Similarly, Tanaka et al[29] reported no association between migration on serum leptin levels in Austronesians and Non-Austronesians in Papua New Guinea. These contrasting results from these studies compared to this current study can largely be explained by the differences in context between the studies carried out in Papua New Guinea and the Solomon Islands, and this current study. Firstly, in these 2 studies, migration was from a peri-urban to an urban location compared to this study where migration was from rural to urban or rural/urban to a high-income country, with the largest differences seen when comparing rural participants with urban or migrant participants. Secondly, several studies also suggest significant ethnic differences in serum adiponectin and leptin levels,[30,31] thus the ethnic differences may explain in part the contrasting findings. Finally, in these 2 studies, the populations studied were not homogenous in terms of a common ancestral origin, ethnicity, and culture. In the Papua New Guinea study, the populations were classified based on the language they spoke, whilst the study in the Solomon Islands classified the participants based on their geographic location of origin.

This current study suggests that there are significant variations in serum adiponectin and leptin levels explained by sex, a finding comparable to 2 separate studies carried out in Northern America.[32,33] From the literature, the higher leptin levels in women could be fully explained by the higher total body fat percentage in women compared to men.[34] Again, the higher adiponectin levels seen in women can also be partially explained by the differences in visceral adipose tissue (VAT) between men and women.[34] Obesity and fat distribution are thus invariably the most relevant explanatory variable of variations in serum adiponectin and leptin between sexes; however, other factors like migration and urbanization have been shown to affect serum adiponectin and leptin levels differently between males and females as shown in this current study.

Strengths and limitations

A key strength of the RODAM study was the use of well-standardized approaches to data collection across the various study sites. Secondly, the use of an ethnically homogenous Ghanaian population of predominantly Akan ancestral heritage living in different geographical locations in West Africa and Europe gave the study a unique strength in that it provided an unparalleled opportunity to assess the impact of migration and urbanization-related factors on serum adiponectin and leptin. Using an ethnically homogenous population attenuated the effect of ethnic variations believed to be associated with variations in serum adiponectin and leptin levels.

A key limitation of this study was its cross-sectional nature, and therefore conclusions on causality between migration and urbanization, and deranged serum adipokines should be drawn with caution. In addition, the lack of standard cut-offs for low adiponectin and high leptin levels limits the ability to extrapolate these findings to other populations, as the cut-offs used were specific to this homogeneous Ghanaian population. Large population-based studies focused on specific ethnic groups in specific geographic locations may provide insight for developing cut-offs specific to these ethnic groups providing insight to clinicians for interventions and predictions.

Conclusion

Compared to their rural counterparts, urban and migrant Ghanaians have low serum adiponectin, high serum leptin and high leptin: adiponectin ratios. However, the geographical differences in serum adiponectin could be fully explained by the differences in conventional risk factors, whiles the differences in serum leptin in women living in urban Ghana and men living in Amsterdam and urban Ghana could only partly be explained by the differences in conventional risk factors. Urbanization is independently associated with a high leptin: adiponectin ratio in men living in urban Ghana. Our findings thus suggest that other migration and urbanization related factors are key determinants of variations in serum leptin levels and the leptin: adiponectin ratio in this Ghanaian population. These findings serve as a backdrop for further research to unravel the role adipokines play in CMD epidemiology

amongst Africans and to understand the mechanism by which migration and urbanization affect adipokines.

Declarations

Author Contributions

Yaw A Kusi-Mensah: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Visualization; Writing—original draft; Writing—review & editing. **Charles Hayfron-Benjamin:** Supervision. **Sean Chetty:** Supervision. **Eva L. van der Linden:** Writing—review & editing. **Karlijn A.C. Meeks:** Writing—review & editing. **Erik Beune:** Writing—review & editing. **Frederick Anokye-Danso:** Writing—review & editing. **Rexford S. Ahima:** Writing—review & editing. **Bert-Jan van den Born:** Supervision. **Charles Agyemang:** Conceptualization; Supervision.

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Availability of Data and Materials

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

ORCID iD

Yaw A Kusi-Mensah https://orcid.org/0000-0002-0578-0654

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