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Cardiovascular risk factors among the inhabitants of an urban Congolese community: results of the VITARAA Study

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ABSTRACT

Objective: The objective is to assess cardiovascular risk profile in an urban Congolese population.
Design and Methods: From July 2007 to March 2008, we investigated 1824 inhabitants (≥10 year old) randomly recruited from the Adoula quarter (Kinshasa, Congo). Measurements included: anthropometry, medical history and lifestyle habits via questionnaire, blood pressure and pulse rate (Omron M6, HEM 7001E), blood glucose, plasma lipids, and semi-quantitative proteinuria tests. We used stepwise logistic regression to model the odds for hypertension and diabetes.
Results: In 1292 adult participants ≥20 years (56.6% women, mean age 37 ± 15 years), the prevalence of hypertension and known diabetes was 30.9% and 4.2%, respectively. Among participants with hypertension respectively 46.6%, 29.3% and 18.3% were aware, on treatment and controlled. Control was better among women and subjects below age 55, but lower in overweight/obese subjects. The odds for hypertension independently increased with age ($P < 0.0001$), overweight/obesity ($P < 0.0001$), pulse rate ($P = 0.0249$) and high legumes consumption ($P = 0.0453$). The odds for diabetes increased with age ($P = 0.0009$) and overweight/obesity ($P = 0.0016$). The prevalence of other risk factors was 5.5%, 42.2%, 42.8% and 30.9%, for smoking, overweight/obesity, abdominal adiposity and hypercholesterolemia; 4.6% of participants had proteinuria. Smoking predominated in men (10.8% vs. 1.4%), obesity (8.6% vs. 21.5%) and hypercholesterolemia (23.2% vs. 37.4%) in women. Hypertension clustered with three or more risk factors including diabetes or proteinuria in 68.7%.
Conclusion: Our findings highlight the staggering rates of cardiovascular risk factors in sub-Saharan Africa and underscore the pressing need to move their prevention and control higher on the political agenda.

1. Introduction

Hypertension related in-hospital mortality was reported to be elevated among Congolese patients [1] and more recently among Nigerians [2]. In these two reports [1,2] like in earlier observation among South African hypertensive Blacks, mortality occurred frequently from cerebral hemorrhage, congestive heart failure, or uremia [3]. Already recognized as the number one single risk factor for death worldwide [4], hypertension also appears as the main driver [3,5] of the emerging epidemics of cardiovascular disease in sub-Saharan Africa [3,6,7]. However, a major concern dealing with this epidemics of cardiovascular disease in sub-Saharan Africa is the scarcity of reliable statistics on the prevalence of its risk factors at the population level. Accurate and representative data are required in order to recommend the most appropriate preventive measures. We, therefore, designed the 'Visite de la Tension Artérielle et des Facteurs de Risque Associés en Afrique subsaharienne', the VITARAA Study, to assess the burden of cardiovascular risk factors. We assumed that global trade and urbanization do expose sub-Sahara African populations to unhealthy lifestyles

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that contribute to the observed epidemiological transition from pestilential era to that of non-communicable diseases. In this paper we investigated the determinants of hypertension and diabetes mellitus and the magnitude of other risk factors in a random sample of the population of Adoula, a quarter of Kinshasa, in the Democratic Republic of the Congo (DRC).

2. Methods

2.1. Study population

The Adoula Quarter is located north west of Kinshasa, DRC. Its population of 27,860 inhabitants (14,820 females, 53.2%) resides in 3,486 households (nearly 8 members/household). The people aged 10 years or over represent about 64% of the whole population (n = 17,830). To identify a 10% representative sample of the latter people, we randomly selected 350 households. We expected a total of 1,790 subjects to constitute the target population for the VITARAA Study. The teams of trained observers visited the selected households at home where they approached 1,914 subjects (107% of the expected total) of whom 1,888 people were examined whereas 26 individuals declined to participate in the study. Therefore the participation rate was 98.6%. However, the files of 64 participants got lost during the transfer from the quarter to our office, leaving data of 1,824 subjects available for analysis. Since age (average: 30 ± 17 years) and gender distribution (49 females; 54.4%) of these 90 subjects not included in the study were similar to those of the whole study group, we felt that the incidents would not seriously impact the study outcomes.

2.2. Procedures

A month before the field work started, the authorities of the quarter mobilized the selected households highlighting the benefits of screening for chronic diseases as implemented in the current study. A calendar for household visits was elaborated taking into account the availability of heads of families. The day before scheduled visit, households were reminded and asked to refrain from caffeinated beverages and tobacco consumption the next evening. From July 2007 to March 2008, two working days per week, the teams of observers visited the households between 6.00 and 9.00 pm. By mean of WHO STEPS adapted questionnaire [8], they obtained demographic data and information on current smoking, alcohol intake, leisure time physical activity, weekly consumption of vegetables and fruits, medical history including awareness of hypertension and diabetes mellitus, and current use of medication for chronic diseases. Smokers and drinkers were participants who reported the use of tobacco or alcoholic beverages at least once per week. People whose physical activity was less than 30 minutes for at least three days per week were categorized as not engaging in sport. Consumption of at least one vegetable serving five days per week or one fruit three days per week was considered as high.

After the subject had relaxed five minutes or more in the sitting position, the observers measured blood pressure two times consecutively using a validated electronic device (OMRON M6, HEM 7001E) with an appropriately sized cuff secured at the upper right arm. A third measurement was required if the first two differed by at least 10 mmHg. The brachial pulse rate was automatically recorded along with blood pressure. For analysis, we averaged these blood pressure and pulse rate readings. The calibration of blood pressure monitors was checked every four weeks against a standard mercury sphygmomanometer using a T-tube and applying static pressures ranging from 0 to 200 mmHg at 50 mmHg intervals. Devices that deviated by 4 mmHg or more were replaced by new machines.

With the subject in loose clothing without shoes, the observers obtained measurements of body weight to the nearest 100 grams using an electronic scale (Terraillon;TT100, Terraillon SAV MGF Logistique, Gennevilliers, France), and, to the nearest centimeter, body height, waist and hip circumferences using a tape measure. Body mass index was weight in kilograms divided by the square of height in meters. We applied a dipstick test (Medi Test Combi 9, Düren, Germany) on a freshly voided urine sample. Proteinuria was a score of + or higher. A random glycemia was determined on a capillary blood drop (Accu-Chek Aviva, Roche, Mannheim, Germany). A five milliliter blood sample drawn from an antecubital vein was centrifuged during five minutes at 3000 rounds/min. The buffy coat was immediately discarded. The plasma was stored at −70 degrees for later determination of lipid concentrations at the laboratory of biochemistry, Erasme Hospital, Brussels, Belgium.

We assessed cardiovascular risk factors according to the 2007 ESH/ESC guidelines [9] in the adults ≥20 years. Hypertension was a blood pressure of at least 140 mmHg systolic or 90 mmHg diastolic, or use of antihypertensive drugs. Overweight/Obesity was a body mass index of 25 kg/m^2 or higher [10]. Abdominal adiposity was a waist circumference of at least 80 cm or 94 cm in women and men, respectively [11]. Diabetes mellitus was a self-reported diagnosis or use of diabetic medication [12]. Hypercholesterolemia was a total cholesterol greater than 190 mg/dL.

2.3. Statistical methods

For database management and statistical analysis, we used SAS software, version 9.3 (SAS Institute, Cary, NC). We compared means and proportions by Student's t-test and the χ^2-statistic, respectively. In multivariable adjusted analyses, we modeled the odds of hypertension and diabetes using stepwise logistic regression with the *P*-value for independent variables to enter and stay in the model set at 0.10. The independent covariables considered for entry into the model were sex, age, body mass index, waist circumference, pulse rate, and classification variables (0,1) coding for current smoking, alcohol intake, physical activity, vegetable and fruit consumption, hypercholesterolemia, proteinuria, and diabetes mellitus. Statistical significance was a *P*-value of 0.05 or less on two-sided tests.

3. Results

3.1. Characteristics of the study population

The study population age averaged 30.6 ± 16.4 years and included 999 women (54.7%). Table 1 lists the characteristics of the participants and illustrates the sex related differences for teenagers and adult participants. Women and men had similar weight, but women were smaller and therefore had substantially higher body mass index. Waist and hip circumferences, total, LDL and HDL-cholesterol levels were higher ($P < 0.05$ or less) in women ($P < 0.0001$ or less) than men whereas their systolic pressure was lower ($P < 0.0001$). There were no sex difference in diastolic pressure and plasma glucose, and triglycerides level. Compared with boys, girls had higher ($P < 0.05$ or less) average values of body mass index, waist and hip circumferences, total and LDL-cholesterol. Pulse rate was faster ($P < 0.0001$) in teenager and women than in men of the corresponding age group.

3.2. Prevalence of cardiovascular risk factors

Table 2 contrasts the prevalence of hypertension, diabetes mellitus, proteinuria, and other cardiovascular risk factors in the 1292 adults, 52 of whom (4%, all women) were free of risk factors. In the remaining 1240 adults (96%), the number of risk factors amounted to one in 137 (10.6%), two in 339 (26.2%), three in 320 (24.8%), four in 207 (16%), and five up to seven in 120 (9.3%).

3.2.1. Hypertension

The prevalence of hypertension was 30.9% (Table 2) with no significant difference between women (31.7%) and men (29.8%).

Table 1
Characteristics of the youths and adult subjects.

	Youths <20 years				Adults ≥20 years			
Gender	All	Girls	Boys	*P*	All	Women	Men	*P*
n (%)	532	268 (50.4)	264 (49.6)		1292	731 (56.6)	561 (43.4)	
Age, years:	15 ± 3	15 ± 3	15 ± 3	0.145	37 ± 15	38 ± 15	37 ± 15	0.331
Height, cm:	158 ± 12	157 ± 10	158 ± 14	0.144	166 ± 10	162 ± 8	171 ± 9	< 0.0001
Weight, kg:	50 ± 12	51 ± 11	50 ± 15	0.176	69 ± 15	69 ± 17	70 ± 13	0.443
Body mass index, kg/m^2:	20.1 ± 4.1	20.7 ± 4.2	19.5 ± 4.4	0.0014	25.2 ± 5.6	26.2 ± 6.1	23.8 ± 4.5	< 0.0001
Waist, cm:	70 ± 8	72 ± 9	68 ± 8	<0.0001	85 ± 14	87 ± 14	82 ± 13	< 0.0001
Hip, cm:	83 ± 11	85 ± 10	81 ± 11	<0.0001	97 ± 13	100 ± 13	94 ± 11	< 0.0001
Systolic pressure, mmHg;	110 ± 13	110 ± 12	111 ± 14	0.306	126 ± 22	124 ± 22	129 ± 22	< 0.0001
Diastolic pressure, mmHg;	69 ± 11	69 ± 11	69 ± 11	0.651	80 ± 16	80 ± 14	80 ± 16	0.492
Pulse rate, beats/min;	83 ± 13	85 ± 12	80 ± 12	<0.0001	78 ± 12	81 ± 11	74 ± 13	< 0.0001
Plasma glucose, mg/dL;	100 ± 30	99 ± 20	101 ± 37	0,446	109 ± 46	110 ± 48	107 ± 43	0.274
Total cholesterol, mg/dL;	154 ± 38	160 ± 40	147 ± 33	0.0071	172 ± 43	177 ± 45	166 ± 39	0.001
HDL cholesterol, mg/dL;	43 ± 12	44 ± 13	42 ± 11	0.482	44 ± 14	45 ± 15	43 ± 13	0.032
LDL cholesterol, mg/dL;	92 ± 31	98 ± 33	84 ± 27	0.0004	103 ± 35	107 ± 36	99 ± 34	0.003
Triglycerides, mg/dL;	100 ± 57	94 ± 57	105 ± 57	0.149	126 ± 86	128 ± 92	125 ± 79	0.598

Lipid measurements were obtained in 1013 subjects: 227 youths (124 girls and 103 boys) and 786 adult subjects (428 women and 358 men).

Hypertensive participants were older (47 ± 16 vs. 33 ± 12 years; $P < 0.0001$) with greater body mass index (27.5 ± 5.8 vs. 24.1 ± 5.2 kg/m^2; $P < 0.0001$) than subjects with normal blood pressure. Fig. 1 depicts average systolic and diastolic pressures (left upper panel) and age related prevalence of hypertension by sex and decennia (left lower panel). Of the hypertensive patients, 186 (46.6%) were aware of their condition, 117 (29.3%) reported use of antihypertensive medication, and 73 (18.3%) had their blood pressure controlled below 140 mmHg (systolic) and 90 mmHg (diastolic). The control was observed in 56 (24.1%) women and 17 (10.2%) men with hypertension ($P < 0.001$). Using stepwise logistic regression analysis (Table 3), the odds of hypertension increased with age (odds ratio [95% confidence interval] for age ≥55 years (6.99 [4.56–10.71]; $P < 0.0001$), overweight/obesity (2.26 [1.70–3.00]; $P < 0.0001$), pulse rate (1.013 [1.00–1.03]; $P = 0.0249$) and high vegetables consumption (1.15 [1.00–1.32]; $P = 0.045$). The probability of hypertension control decreased with male sex (0.57 [0.42–0.79]; $P = 0.0031$), age (≥55 years, 0.12 [0.10–0.24]; $P = 0.0001$), overweight/obesity (0.40 [0.30–0.55]; $P < 0.0001$) and faster pulse rate (0.98 [0.97–0.996]; $P = 0.0116$).

3.2.2. Diabetes mellitus

Diabetes mellitus was reported by 54 (4.2%; Table 2), 51 of whom (94.4%) were currently treated. Fig. 1 shows the prevalence of diabetes mellitus by sex and age group. In the logistic model (Table 3), the odds for diabetes mellitus increased with age (age ≥55 years, 2.86 [1.53–5.31]; $P = 0.0009$) and overweight/obesity (2.69 [1.46–4.95]; $P = 0.0016$).

Table 2
The prevalence of hypertension, diabetes mellitus, and other risk factors among adult participants.

	All subjects	Women	Men	*P*
Number of participants	1292	731	561	
No risk factor	52 (4.0)	52 (7.1)	0 (0.0)	
Hypertension	399 (30.9)	232 (31.7)	167 (29.8)	0.202
Diabetes mellitus	54 (4.2)	31 (4.2)	23 (4.1)	0. 900
Overweight	340 (26.3)	215(29.4)	125(22.3)	0.002
Obesity	205 (15.9)	157 (21.5)	48 (8.6)	< 0.0001
Abdominal adiposity	553 (42.8)	452 (61.8)	101 (18)	< 0.0001
Smokers	68 (5.5)	10 (1.4)	58 (10.8)	< 0.0001
Drinking alcohol	673 (52.1)	350 (47.9)	323 (57.6)	0.0005
Physical inactivity	1083 (83.8)	675 (92.3)	408 (72.7)	< 0.0001
Hypercholesterolemia[a]	243 (30.9)	160 (37.4)	83 (23.2)	< 0.0001
Proteinuria	59 (4.6)	30 (4.1)	29 (5.2)	0.363
Low fruits consumption	722 (55.9)	387 (52.9)	335 (59.7)	0.0151
Low vegetables consumption	469 (36.3)	259 (35.4)	210 (37.4)	0.458

Abdominal adiposity was waist circumference of at least 80 cm or 94 cm in women and in men, respectively; hypercholesterolemia.
Total cholesterol concentration 190 mg/dL.
[a] Cholesterol was obtained in 786 subjects (428 women and 358 men).

3.2.3. Other risk factors

While tobacco and alcohol use were more prevalent among men, overweight/obesity, abdominal adiposity, physical inactivity and hypercholesterolemia were commonest among women (Table 2). Fig. 2 shows average body mass index and LDL cholesterol of the participants (upper panels) and the prevalence of overweight/obesity and hypercholesterolemia (lower panels) by sex and age group.

A body mass index below 18.5 kg/m^2 (underweight) was found in 97 (7.5%) subjects, 43 women (5.9%) and 54 men (9.6%) while 650 subjects (50.3%), 316 women (43.2%) and 334 men (59.5%) had a body mass index within the normal range. High fruit consumption was more (P = 0.015) reported among women (n = 344; 47.1%) than men (n = 226; 40.3%) whereas the proportion of high vegetable consumers was similar [472 women (64.6%) vs. 351 men (62.6%) P = 0.458].

3.2.4. Clustering of risk factors

Hypertension, diabetes mellitus, abdominal adiposity and hypercholesterolemia predominated among overweight and obese participants; their prevalence did not significantly differ between underweight and normal weight subjects (Fig. 3). Among those with hypertension, 159 subjects (39.8%) had either normal weight (149; 37.3%) or were underweight (10 subjects; 2.5%). The respective proportions for diabetes mellitus were 16 subjects (29.6%), 12 with normal weight (22.2%) and 4 underweight (7.4%).

Hypertension was an isolated condition in 5 subjects (1.3%) only. It was associated to one or two additional risk factors in 120 patients (30.1%), to three or more in 219 (54,9%), to three or more risk factors, diabetes and/or proteinuria in 274 participants (68.7%). Hypertension was significantly prominent among participants with than without diabetes mellitus [n = 28 (51.9%) vs. n = 371 (30%); P = 0.0007]. Likewise proteinuria tended to be more detected among diabetics (n = 4; 7.4%) than non-diabetic (n = 55; 4.4%) participants (P = 0.307).

4. Discussion

Elevated rates of cardiovascular risk factors that strikingly clustered among participants with high blood pressure characterize this urban adult Congolese population. Nearly 70% of participants with hypertension had three or more risk factors, proteinuria and/or diabetes mellitus in addition. Such a constellation of risk factors characterizes a population that is likely to develop acute cardiovascular events.

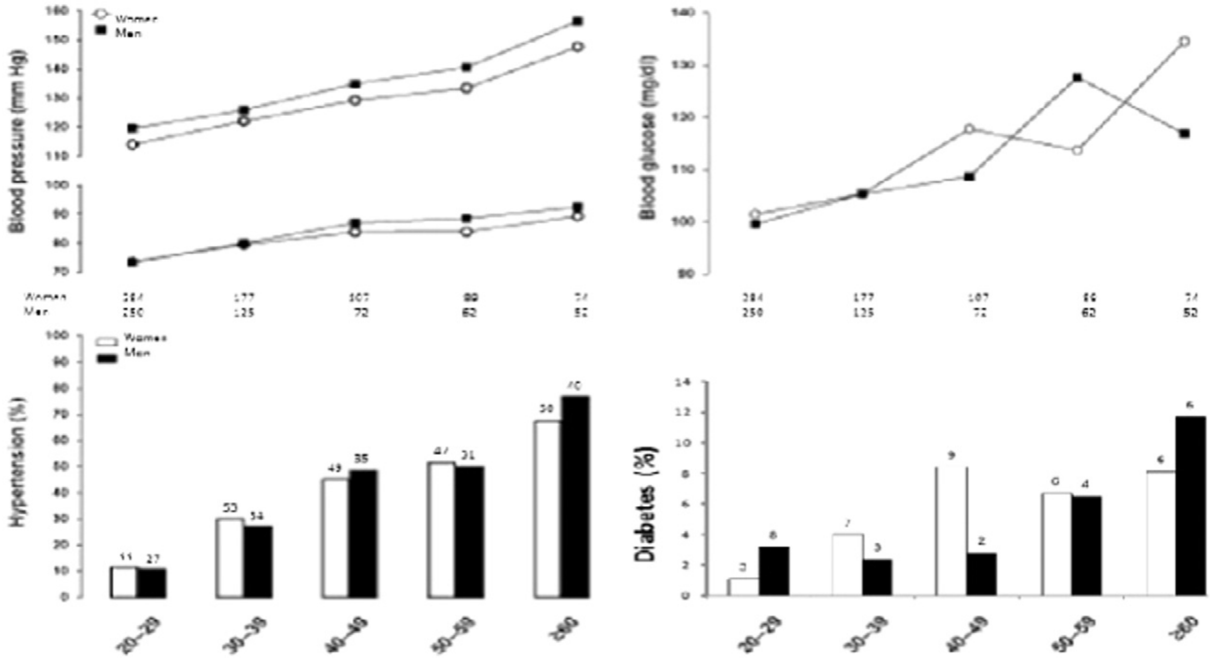

Fig. 1. Average systolic and diastolic blood pressures (left upper panel), and age specific prevalence of hypertension (left lower panel), and random blood glucose (right upper panel) and age specific prevalence of diabetes mellitus (right lower panel) for women (O) and men (Δ) in various age groups. Numbers of participants with characteristics are given for each sex–age category.

The observed 30.9% prevalence of hypertension is consistent with other data in urban Africans [13,14] and shows a sizeable increase compared to 16.7% we previously found in the same community some 23 years before [15]. For both women and men the prevalence of hypertension consistently increased with age. Most hypertensive individuals were undiagnosed, undertreated and uncontrolled. The rate of hypertension control was higher among women and younger people than in men and older subjects, probably because of more difficult access to treatment for the elderly. The low level of detection, awareness, management and control of hypertension is characteristic of sub-Saharan Africa [16]. It bears the potential of premature target organ damages and looming complications with pejorative outcomes [1] in view of the clustering of high blood pressure with diabetes, proteinuria and several other additional risk factors. Moreover, a huge proportion of hypertensive people might require pharmacological treatment which surely runs out of national resources.

The prevalence of diabetes mellitus is also in line with the findings in the Africans [17–19]. It is however lower than recently reported from a sample of the inhabitants of Kinshasa, probably not randomly selected [20]. The prevalence of diabetes mellitus increased with age with no difference between women and men. Unlike hypertension, awareness of diabetes mellitus was greater among the patients most of whom reported current use of diabetic medication and/or dietary measures.

The odds for both hypertension and diabetes mellitus increased with overweight/obesity suggesting that total obesity and visceral adiposity do contribute to concurrent rates of hypertension and diabetes mellitus [21,22]. Indeed, the prevalence of hypertension and diabetes increased throughout the categories of body mass index. While underweight accounted for 7.5% of adult participants, overweight, obesity and abdominal adiposity affected 26.3%, 15.9% and 43.6% of subjects, respectively. Overweight/Obesity and abdominal adiposity have thus reached staggering proportions with rates increasing with age and being greater especially among women. Obesity currently exceeds the 2005 world adult population prevalence estimate of 9.8% (95% confidence interval 9.6–10.0%); [23] it is higher than the rate of 14% we previously reported in the same community at body mass index cut-point of 28 kg/m^2) [15]. Our results agree with the 2005 estimated prevalence of overweight (23.2% [22.8–23.5%]) [23] and concur with a recent report in the Africans of 13% and 35% for total obesity among men and women, and 11% and 58% respectively, for abdominal adiposity [24]. We used the IDF criteria to define visceral obesity [16]. Applying other thresholds has been the subject of controversy [25]. Thus, in accordance with other studies [26], the impact of excess weight on the burden of hypertension and diabetes appears to be evident. As stressed by others [27], two feasible lifestyle changes to stem the epidemic of hypertension in Africa might include a decrease in salt intake and measures to reduce obesity, especially in women. It is worth noting however, that a sizeable proportion of those with hypertension or diabetes had normal or even lower body mass indices in line with other reports in the Africans [28]. Such an observation could suggest that among the Africans, insulin resistance is not an obliged feature underlying these conditions [28,29]. Atypical type 2 diabetes mellitus is often encountered in the Africans with no overweight or insulin resistance, but genetic, metabolic and/or infectious factors among incriminated causes [30].

The prevalence of hypercholesterolemia was higher in women than in men and increased in parallel to categories of body mass index.

Table 3
Multivariable-adjusted odds ratios for hypertension, hypertension control and diabetes mellitus.

Variable	Odds ratio (95% CI) for hypertension	P	Odds ratio (95% CI) for hypertension control	P	Odds ratio (95% CI) for diabetes mellitus	P
Sex, male	–	–	0.57 (0.42 – 0.79)	0.0006	–	–
Age ≥ 55 years	6.99 (4.561–10.71)	<0.0001	0.12 (0.10–0.24)	<0.0001	2.855 (1.534–5.313)	0.0009
Overweight/Obesity	2.26 (1.704–3.004)	<0.0001	0.40 (0.30–0.55)	<0.0001	2.685 (1.456–4.949)	0.0016
Pulse rate	1.01 (1.002–1.025)	0.0249	0.98 (0.97–0.996)	0.0116	1.019 (0.998–1.040)	0.0781
High vegetable intake	1.15 (1.003–1.324)	0.0453	–	–	–	–

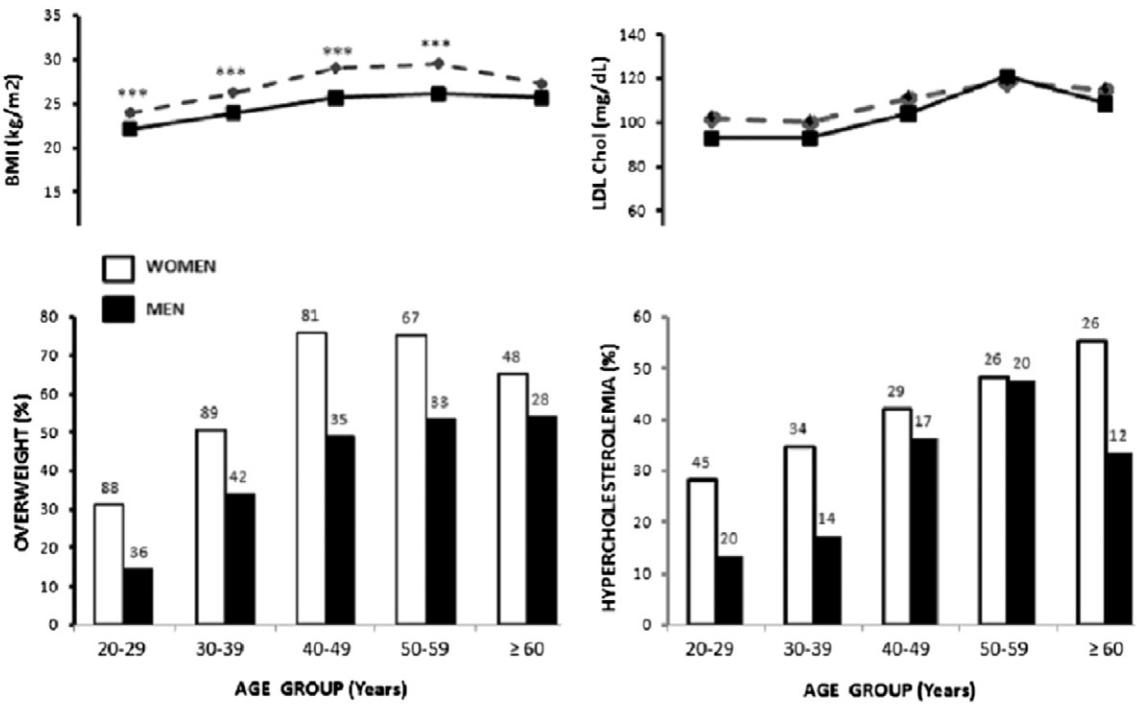

Fig. 2. Average body mass index (left upper panel) and age specific prevalence of overweight/obesity (left lower panel), and average plasma LDL cholesterol (right upper panel) and age specific prevalence of hypercholesterolemia (right lower panel) for women and men in various age groups. Numbers of participants with characteristic are given for each sex–age category. ***$P < 0.001$ for comparison between women and men.

Traditionally, favorable lipid profiles are reported in populations of African descent which, together with less exposure to smoking, explain lower risk of coronary artery disease in comparison to Caucasians [31]. Unhealthy diet and changes in culinary usages in the urban environment tend to alter the lipid profile towards less safer patterns. Such patterns could account for the observed relationship between high vegetable intake and hypertension. Indeed, consumption of rough vegetables is rather exceptional in our dietary habits. The manner which vegetables are processed in urban settings consists of excessive fat seasoning, use of salty cubes and fatty nut pastes that, at least partly, might account for their apparent detrimental property. In this population, smoking habit represented a marginal cardiovascular threat, especially among women.

Our survey has limitations. The reported burden of hypertension relies on two measurements of blood pressure obtained at one single home visit. Repeated blood pressure measurements at various occasions through regression towards the mean would have improved the reliability of the results. The prevalence of diabetes mellitus was surely underestimated. Only subjects already aware of their disease were considered as diabetics. The casual capillary blood glycemia could not reliably be used to diagnose the condition. The survey was restricted to an urban community. We are therefore not certain that our results would apply to the whole Congolese adult population. Nonetheless, our findings highlight the staggering elevated prevalence of cardiovascular risk factors and underscore the pressing need for preventive measures in sub-Saharan Africa, where cardiovascular

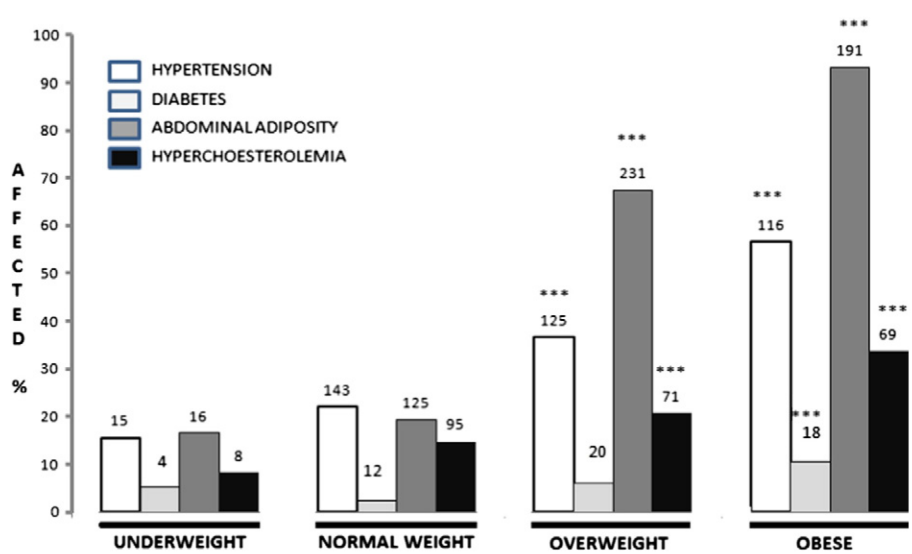

Fig. 3. The figure depicts the rates of hypertension, diabetes, abdominal adiposity and hypercholesterolemia among underweight, normal weight, overweight and obese participants. The number of participants with characteristic in the various body weight categories is given. ***$P < 0.001$ in comparison to normal weight.

complications due to limited curative resources run at a high death rate. For management of risk factors in the low resources African context, contribution of nurses [31] and or non-physician clinicians [32] should be highly encouraged. In line with the EUROASPIRE findings [33] prevention by informing the population about a healthy lifestyle, at this stage, is the mostly feasible way forward, because information and health education can be provided at little cost.

Contributors

JR M'Buyamba-Kabangu, D Lemogoum and JP Degaute planned the study. JR M'Buyamba-Kabangu coordinated while PM Bayauli and JRJr M'Buyamba-Kayamba supervised and implemented the field work in Kinshasa, DR Congo. D Lemogoum and JR M'Buyamba-Kabangu constructed the database in Brussels, Belgium, and L Thijs and JR M'Buyamba-Kabangu did the statistical analysis at the Studies Coordinating Centre in Leuven, Belgium. PM Bayauli, JR M'Buyamba-Kabangu and JA Staessen wrote the first draft of the manuscript. All authors interpreted the results and approved the final version of the article.

Disclaimer

The funding sources had no role in the design of the study, data collection, database management, statistical analysis, or writing of this report. DL and JRM-K had full access to all of the data and carry the final responsibility for the decision to submit this manuscript for publication.

Conflict of interest

The authors declare no conflict of interest

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