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ORIGINAL ARTICLE

Relationship between hypertension, diabetes and proteinuria in rural and urban households in Yemen

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Little information is available on the meanings of proteinuria in low-resource settings. A population-based, cross-sectional survey was performed in Yemen on 10 242 subjects aged 15–69 years, stratified by age, gender and urban/rural residency. Hypertension is defined as systolic blood pressure (BP) of $\geqslant$140 mm Hg and/or diastolic BP of $\geqslant$90 mm Hg, and/or self-reported use of antihypertensive drugs; diabetes is diagnosed as fasting glucose of $\geqslant$126 mg dl^{-1} or self-reported use of hypoglycaemic medications; proteinuria is defined as $\geqslant +1$ at dipstick urinalysis. Odds ratios (ORs) for associations were determined by multivariable logistic regression models. Prevalence (weighted to the Yemen population aged 15–69 years) of hypertension, diabetes and proteinuria were 7.5, 3.7 and 5.1% in urban, and 7.8, 2.6 and 7.3% in rural locations, respectively. Proteinuria and hypertension were more prevalent among rural dwellers (adjusted ORs 1.56; 95% confidence limit (CI) 1.31–1.86, and 1.23; 1.08–1.41, respectively), diabetes being less prevalent in rural areas (0.70; 0.58–0.85). Differently from hypertension and diabetes, proteinuria was inversely related with age. Most importantly, 4.6 and 6.1% of urban and rural dwellers, respectively, had proteinuria in the absence of hypertension and diabetes. The approach of considering kidney damage as a consequence of hypertension and diabetes might limit the effectiveness of prevention strategies in low-income countries.

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INTRODUCTION

The major causes of death and disability in developing countries are now shifting from a predominance of nutritional deficiencies and infectious diseases to cardiovascular disease.[1] Changes in lifestyle and diet habits following urbanization are indeed greatly contributing to increased obesity, diabetes and dyslipidemia.[2] Likewise, increased salt and alcohol intake in urban areas are the major risk factors for high blood pressure (BP).[3,4] These global changes are now expected to increase also the potential health burden of kidney damage.[5] The common risk factors shared by kidney damage and cardiovascular diseases support the focus on diabetes and hypertension as an adequate strategy to deal with kidney damage also in the developing countries.[5] In low-income countries, infectious diseases may however add substantial burden to non-communicable risk factors in enhancing the global prevalence of chronic kidney disease.[6–10] Proteinuria is a recognized early marker of kidney damage and a risk factor to develop chronic kidney disease, and eventually end-stage renal disease (ESRD).[11] In a meta-analysis of more than 1.1 million individuals aged 42–81 years,[12] dipstick proteinuria of 1+ or greater conferred also an increased risk for all-cause mortality, independently of age and estimated glomerular filtration rate. The evaluation of the different meanings of proteinuria in urban and rural settings is however rarely addressed in scientific literature. This information may have relevant clinical implications, because in low-income countries the possibility to treat ESRD may be limited, although early detection and treatment of subjects with proteinuria using readily available, inexpensive therapies can slow down or prevent progression to ESRD.[13] Furthermore, the possibility to focus antihypertensive treatment on high-risk subjects might thus have potential implications for health-care resource allocation in low-resource settings.[14]

Yemen is characterized by a highly traditional lifestyle and a low prevalence of hypertension, as observed in two limited surveys conducted in the capital area.[15,16] The country may thus represent an ideal scenario to investigate the interaction between urbanization, non-communicable disease (hypertension and diabetes) and proteinuria. Hypertension and Diabetes in Yemen (HYDY) project was thus designed to investigate, with a door-to-door approach, the prevalence of diabetes, hypertension, proteinuria and their relationships, both in rural and urban residents of Yemen.

MATERIALS AND METHODS

Study sites and study population

A multistage stratified sampling method was used as previously reported.[14] Briefly in the first stage, Yemen was stratified into three regions, the capital area, the inland and the coastal area. The governorate of Sana'a (capital area), the governorate of Taizz (inland) and the governorates of Al Hudaydah and Hadramaut (coast) were selected to be representatives of the geographic, economic and climatic characteristics of the three regions. In the second stage, rural and urban regions were identified from each study area. In the third stage, districts were arbitrarily identified within each urban and rural region, boundaries being defined using local maps or in consultation with the local health workers. The total number of districts within each study area (20 in the

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capital area, 12 in the inland and 8 in the coastal area) was proportional to the estimated population size of the area. In the final stage, due to the lack of a national population register,[17] 250 adult participants from each district were allocated to a cluster stratified by gender and age decades (15–24 years; 25–34; 35–44; 45–54; 55–69) to a total of 10 000 individuals allocated into 10 strata. The study was approved by the Ethical Committee of the University of Science and Technology, Sana'a, Yemen. Informed verbal consent was obtained from every participant before data collection.

Data collection

The survey was performed following the three different levels, which included questionnaire, physical measurements and biochemical measurements, as previously reported.[14] Briefly, the burden of hypertension and diabetes in the population was assessed by taking BP and fasting glucose (FG) measurements on two visits, separated by a median interval of 5.36 days (95% confidence limit (CI) 5.30–5.42; range 1–13 days).[14] Data collection was conducted at home by centrally trained survey teams composed of two investigators of the opposite gender.

During the first visit (visit 1), study questionnaire was administered after obtaining consent. Study questionnaire included questions about demographics, lifestyle and medical history.[14] Three measurements of systolic (SBP) and diastolic (DBP) pressure and pulse rate were taken 2 min apart on dominant arm after a rest of at least 15 min in the seated position.[18] Readings were obtained with a clinically validated semiautomatic sphygmomanometer (HEM 705 IT; Omron Matsusaka Co, Ltd, Matsusaka, Japan) using appropriate cuff size. The averages of the last two readings for SBP and DBP were defined as SBP1 and DBP1, respectively. Anthropometric measurements were taken on standing participants wearing light clothing and without shoes by using standard techniques.[18] Body weight was measured to the nearest 0.1 kg using a spring balance, and height to the nearest 0.5 cm using a stadiometer. Waist and hip circumference was measured to the nearest 0.1 cm. Finger-prick blood samples were then obtained from fasting (>8 h) subjects to measure FG (Accutrend system, Roche Diagnostics, Mannheim, Germany), cholesterol and triglyceride blood values (MultiCare-in, Biochemical System International, Arezzo, Italy).[19] A urine sample was collected and a dipstick test (Auction sticks, A Menarini Diagnostics, Florence, Italy)[20] was immediately performed, results being decided by careful visual comparison of the test strip with a color chart provided on the bottle label. A new appointment was taken for non-fasting participants.

All subjects were then visited again within the next 10 days by the same survey team, using the same measurement devices and procedures for the second session of BP (SBP2 and DBP2) and fasting glucose (FG2) measurements.

Diagnostic criteria and definition of variables

Measures have been taken to attain complete reliability and to reduce the variation to reasonable limits. All the study personnel successfully completed the specific 1-week training program organized in Sana'a (December 2007) on the aims of the study and the specific methods used to standardize the procedure for sampling and contacting individuals, questionnaire administration and form filling, BP measurements using electronic devices, performing blood biochemical assay, performing urine assay and data entry into computerized database. The training program included a pilot testing performed on a population sample of 400 individuals in urban and rural areas of Sana'a.

Arterial hypertension was defined as (1) SBP1 and SBP2 $\geqslant$140 mm Hg and/or DBP1 and DBP2 $\geqslant$90 mm Hg and/or, (2) self-reported use of antihypertensive drugs at the time of the interview.[18] Diabetes was defined as (1) FG $\geqslant$126 mg dl^{-1} at both the visits or, (2) self-reported use of hypoglycaemic medications at the time of the interview.[21] Overweight and obesity were defined as a body mass index of 25.0–29.9 kg m^{-2}, and $\geqslant$30 kg m^{-2}, respectively. Abdominal obesity was defined as waist circumference >102 cm in men and >88 cm in women. On the basis of cholesterol and triglycerides assessments, subjects were classified as high cholesterol (>190 mg dl^{-1}) or high triglycerides (>150 mg dl^{-1}).[18] Results of dipstick urinalysis were recorded as follows: (1) urinary proteins: negative (0), trace (+/−) or proteinuria (1+, 2+, 3+ or 4+). Reliability of measurements performed by visual inspection of strips was previously assessed.[20] On the basis of education level, subjects were classified into six categories: (1) illiterate; (2) can read and write; (3) primary school; (4) secondary school; (5) high school and (6) college or post. Daily smokers and daily khat users were defined as those who smoked tobacco or chewed khat on a daily basis. Fruit and vegetable consumption were classified as (1) $\leqslant$1 day per week; (2) 2–4 days per week; (3) $\geqslant$5 days per week. Participants were categorized as sedentary when self-reporting vigorous physical exercise (job, sport or recreational activities) for <10 min daily.

Statistical methods

Description and validation of the database can be found elsewhere.[22] Prevalence estimates were calculated for the five age groups in the overall population and by gender. All calculations were weighted to represent the total Yemen population aged 15–69 years. Weights were calculated on the basis of age- and gender-stratified data from the year 2008-estimated Yemen population.[17] Additionally, to allow a direct comparison with prevalence data obtained in other countries, prevalence was also age standardized to the World Health Organization's World Standard Population for age ranges 15–69 and 35–69 years.[23] Data are expressed as mean with 95% CI for continuous variables, and as rates with 95% CI for categorical variables.

Unadjusted odds ratios (ORs) between exposure variables and urban/rural location were determined by using univariate logistic regression analysis.

Factors associated with hypertension awareness or pharmacologic treatment were investigated by logistic regression analysis in the subgroup of subjects diagnosed with hypertension. Factors associated with BP drug control were investigated in the subgroup of 528 hypertensive subjects treated with antihypertensive drugs. Age, gender, urban/rural location, education categories and proteinuria were included as independent variables.

Factors independently associated with proteinuria were investigated at multivariate logistic regression analysis to evaluate the simultaneous effect of the various exposure variables, with adjustment for any confounding variables. Variables included in the model were age, gender, location, level of education, self-reported sedentary lifestyle, daily smoking, daily khat use, categories of vegetable and fruit consumption, hypertension, diabetes, high cholesterol, high triglycerides, obesity and abdominal obesity.

Differences between urban and rural dwellers were investigated at logistic regression analysis with urban/rural residency as dependent variable, and age, gender, level of education, self-reported sedentary lifestyle, daily smoking, daily khat use, categories of fruit and vegetable consumption, hypertension, diabetes, high cholesterol, high triglycerides, obesity, abdominal obesity and proteinuria as independent variables.

The independent association of proteinuria with hypertension and diabetes was separately tested among urban and rural residents. Comparisons were performed using two models of logistic regression including proteinuria as dependent variable, with hypertension, diabetes, urban/rural location, age, gender, education categories included as independent variables (model 1). Model 2 included also high cholesterol, obesity and abdominal obesity as independent variables.

Results are expressed as OR with 95% CI. Test of hypothesis was done at a significance level of 0.05 (two-sided). Statistical Package for the Social Sciences software version 19.0 (SPSS, Chicago, IL, USA), was used for statistical analyses.

RESULTS

The survey was completed within 16 months, with an overall response rate of 92 and 94% in urban and rural locations, respectively. Response rate did not differ by age or gender. The numbers of included participants stratified by age, gender and urban/rural location are reported as Supplementary Data Table 1S. Main characteristics of the 10 242 participants (5063 male and 5179 female participants) are reported in Table 1. Overall, 51.5% of the women and 19.5% of the men were illiterate, differences being higher in rural than in urban settings (see Supplementary Data Table S2).

Prevalence and urban/rural distribution of risk factors

Age-weighted prevalence of the main risk factors in the overall population, and in rural and urban householders is reported in Table 2. For prevalence of age standardized to the World Health Organization's World Standard Population for age ranges of 15–69 and 35–69 years, see Supplementary Table S3. Obesity, abdominal obesity and high cholesterol were more prevalent in women than

Table 1. Characteristics of participants

Variables	All		Urban		Rural	
	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)
All						
Education (years)	10 235	7.7 (7.5–7.9)	5106	8.3 (8.0–8.6)	5129	7.1 (6.8–7.4)
BMI (kg m^{-2})	10 205	22.9 (22.7–23.1)	5089	23.3 (23.1–23.6)	5116	22.4 (22.2–22.7)
Hip (cm)	10 202	88.6 (88.1–89.2)	5079	90.2 (89.4–91.0)	5123	87.1 (86.4–87.9)
W/H ratio	10 202	0.864 (0.868–0.861)	5079	0.861 (0.866–0.855)	5123	0.868 (0.873–0.863)
SBP (mm Hg)	10 232	118.9 (118.3–119.4)	5104	119.0 (118.2–119.8)	5128	118.8 (118.0–119.6)
DBP (mm Hg)	10 227	74.7 (74.3–75.1)	5099	74.9 (74.4–75.4)	5128	74.5 (74.0–75.0)
FG (mg dl^{-1})	10 181	85.4 (84.5–86.3)	5083	85.9 (84.5–87.2)	5098	85.0 (83.6–86.5)
TC (mg dl^{-1})	10 138	79.3 (75.8–82.7)	5064	91.3 (86.2–96.3)	5074	67.3 (62.6–71.9)
TG (mg dl^{-1})	10 127	139.1 (136.4–142.6)	5058	145.3 (140.8–149.7)	5069	133.7 (129.3–140.8)
Men						
Education (years)	5058	9.4 (9.1–9.6)	2516	9.6 (9.3–10.0)	2542	9.1 (8.7–9.5)
BMI (kg m^{-2})	5041	22.3 (22.0–22.5)	2506	22.7 (22.3–23.1)	2535	21.9 (21.5–22.2)
Hip (cm)	5041	86.6 (85.8–87.3)	2503	87.8 (86.7–89.0)	2538	85.3 (84.4–86.3)
W/H ratio	5041	0.879 (0.884–0.874)	2503	0.882 (0.890–0.874)	2538	0.877 (0.884–0.870)
SBP (mm Hg)	5056	119.3 (118.5–120.1)	2515	120.1 (119.0–121.2)	2541	118.5 (117.5–119.5)
DBP (mm Hg)	5053	74.5 (74.0–75.0)	2512	75.2 (74.5–75.8)	2541	73.8 (73.1–74.5)
FG (mg dl^{-1})	5028	84.1 (82.8–85.4)	2498	84.5(82.7–86.1)	2530	83.9 (82.1–85.7)
TC (mg dl^{-1})	5014	71.5 (66.9–76.2)	2493	83.9 (76.9–90.5)	2521	59.5 (53.4–66.1)
TG (mg dl^{-1})	5009	141.7 (136.0–147.0)	2488	148.8 (143.5–155.0)	2521	135.5 (129.3–140.8)
Women						
Education (years)	5177	6.1 (5.8–6.4)	2590	7.1 (6.7–7.5)	2587	5.2 (4.8–5.6)
BMI (kg m^{-2})	5164	23.4 (23.2–23.7)	2583	24.0 (23.5–24.4)	2581	22.9 (22.6–23.3)
Hip (cm)	5161	90.7 (89.9–91.5)	2576	92.5 (91.3–93.7)	2585	88.9 (87.9–90.0)
W/H ratio	5161	0.850 (0.856–0.845)	2576	0.841 (0.849–0.833)	2585	0.859 (0.867–0.852)
SBP (mm Hg)	5176	118.5 (117.8–119.3)	2589	118.0 (116.9–119.1)	2587	119.1 (118.0–120.2)
DBP (mm Hg)	5174	74.9 (74.4–75.4)	2587	74.7 (74.0–75.4)	2587	75.1 (74.4–75.9)
FG (mg dl^{-1})	5153	86.6 (85.2–88.1)	2585	87.4 (85.4–89.2)	2568	85.9 (83.8–88.3)
TC (mg dl^{-1})	5124	86.6 (81.6–91.6)	2571	98.2 (91.3–105.6)	2553	74.6 (68.1–81.6)
TG (mg dl^{-1})	5118	137.3 (132.9–140.8)	2570	141.7 (136.4–147.03)	2548	132.0 (126.7–137.3)

Abbreviations: BMI, body mass index; CI, confidence limits; DBP, diastolic blood pressure (mean of the two visits); FG, fasting plasma glucose (mean of the two visits); SBP, systolic blood pressure (mean of the two visits); TC, Total cholesterol; TG, Triglycerides; W/H, waist-to-hip ratio. Data (education, anthropometric parameters, blood pressure and laboratory values) are reported as the number of subjects who gave a response to the specific item(s), and mean value with 95% confidence limits. All values are weighted to the Yemen population aged 15–69 years in 2008.

in men, no differences being observed for diabetes. Overall, 1307 participants fulfilled the criteria of hypertension, prevalence being higher among women than men (OR 1.22; 95% CI 1.01–1.37). Hypertension awareness, allocation to treatment and achievement of drug control were more prevalent in women than in men (Table 3). After adjustment for age and level of education, women gender was no more associated with hypertension diagnosis (adjusted OR 1.09; 0.96–1.24), whereas prevalence of obesity (adjusted OR 2.13; 1.86–2.44), abdominal obesity (adjusted OR 11.45; 9.69–13.54) and high cholesterol (adjusted OR 1.41; 1.25–1.58) remained higher in women than in men.

Obesity, abdominal obesity, high cholesterol and diabetes were less prevalent in rural than in urban residents in the overall population, and by gender (Table 2). After adjustment for age, gender, education categories, diabetes, high cholesterol, obesity and abdominal obesity, hypertension was more prevalent in rural than in urban locations (Table 2). Hypertension awareness and allocation to antihypertensive treatment were also more prevalent among urban residents (Table 3).

Prevalence and urban/rural distribution of indicators of chronic kidney damage

The presence of urinary protein (trace or more) at dipstick test was more prevalent among rural (1366 out of 4925) than among urban dwellers (895 out of 5100) (χ^2 33.12; $P<0.001$). More precisely, 654, 179, 44, 1 and 4 urban dwellers had protein trace, 1+, 2+, 3+ and 4+, respectively. Conversely, 998, 263, 71, 27 and 7 rural dwellers had protein trace, 1+, 2+, 3+ and 4+ at dipstick test, respectively. Overall, 6.2% of Yemen population aged 15–69 years had proteinuria ($\geqslant$1+) at dipstick test (Table 2), proteinuria being more prevalent in rural (7.3%) than in urban residents (5.1%) (OR 1.63; 1.38–1.93) (Table 2). Conversely, the presence of glucose (trace or more) in urinary samples was more prevalent among urban (490 out of 5097) than among rural dwellers (417 out of 5120; χ^2 6.81, $P<0.01$). The amount of overlap between hypertension, diabetes and proteinuria among urban and rural dwellers is shown in Figure 1.

The independent association of proteinuria with rural setting was confirmed after further adjustment for diet habits (vegetable and fruit consumption), self-reported sedentary lifestyle, daily smoking, obesity, abdominal obesity, high cholesterol, hypertension and diabetes (logistic regression analysis including 9384 participants) (Figure 2). More precisely, on performing adjusted logistic regression, proteinuria, divided into six categories (none, trace, +1, +2, +3 and +4), remained the only investigated risk condition more prevalent in rural than in urban areas (Figure 3).

To further investigate the interaction of proteinuria with hypertension and diabetes, logistic regression was separately performed in urban and rural residents (Table 4). After adjustment with different models, proteinuria was associated with hypertension both in urban and rural locations, whereas diabetes was

Table 2. Prevalence estimates of main investigated clinical conditions in all subjects and stratified by gender, and urban/rural locations

Variables	*All*	*Urban*	*Rural*	*Odd ratio rural vs urban (95% CI)*	
				Unadjusted	*Adjusted*
All					
Hypertension	7.7 (7.2–8.1)	7.5 (6.8–8.1)	7.8 (7.2–8.5)	1.08 (0.96–1.21)	1.23 (1.08–1.41)
Diabetes	3.2 (2.9–3.5)	3.7 (3.3–4.2)	2.6 (2.2–3.0)	0.67 (0.56–0.80)	0.70 (0.58–0.85)
High cholesterol	10.8 (10.1–11.4)	14.0 (12.9–15.0)	7.6 (6.8–8.4)	0.47 (0.42–0.53)	0.46 (0.41–0.52)
Obesity	8.0 (7.4–8.5)	9.5 (8.7–10.4)	6.5 (5.8–7.1)	0.66 (0.58–0.75)	0.77 (0.66–0.89)
Abdominal obesity	10.9 (10.2–11.5)	12.6 (11.7–13.6)	9.1 (8.3–9.9)	0.66 (0.59–0.74)	0.72 (0.62–0.82)
Proteinuria	6.2 (5.6–6.8)	5.1 (4.4–5.9)	7.3 (6.4–8.1)	1.63 (1.38–1.93)	1.56 (1.31–1.86)
Men					
Hypertension	6.7 (6.1–7.3)	7.0 (6.0–7.9)	6.5 (5.6–7.3)	1.01 (0.85–1.20)	1.06 (0.87–1.29)
Diabetes	2.9 (2.5–3.3)	3.5 (2.8–4.1)	2.4 (1.9–2.9)	0.70 (0.55–0.91)	0.77 (0.59–1.01)
High cholesterol	8.5 (7.7–9.4)	11.2 (9.9–12.5)	5.9 (4.9–6.8)	0.46 (0.38–0.55)	0.46 (0.38–0.55)
Obesity	5.4 (4.7–6.1)	6.0 (5.0–7.1)	4.8 (4.0–5.7)	0.86 (0.69–1.06)	1.07 (0.83–1.38)
Abdominal obesity	2.2 (1.8–2.6)	2.8 (2.2–3.4)	1.6 (1.1–2.0)	0.52 (0.38–0.72)	0.51 (0.35–0.75)
Proteinuria	7.0 (6.2–7.9)	5.6 (4.5–6.8)	8.5 (7.1–9.8)	1.79 (1.42–2.25)	1.76 (1.39–2.23)
Women					
Hypertension	8.6 (7.9–9.3)	8.1 (7.1–9.0)	9.2 (8.2–10.2)	1.14 (0.97–1.34)	1.37 (1.14–1.65)
Diabetes	3.4 (3.0–3.9)	4.0 (3.4–4.7)	2.8 (2.2–3.4)	0.64 (0.50–0.82)	0.62 (0.48–0.81)
High cholesterol	13.0 (11.9–14.0)	16.6 (15.0–18.3)	9.3 (8.0–10.5)	0.48 (0.41–0.56)	0.46 (0.39–0.55)
Obesity	10.5 (9.7–11.4)	13.0 (11.6–14.4)	8.1 (7.0–9.1)	0.57 (0.49–0.67)	0.65 (0.54–0.79)
Abdominal obesity	19.5 (18.4–20.7)	22.5 (20.7–24.2)	16.6 (15.1–18.1)	0.65 (0.58–0.74)	0.73 (0.63–0.85)
Proteinuria	5.3 (4.6–6.1)	4.6 (3.7–5.6)	6.1 (5.0–7.2)	1.45 (1.13–1.86)	1.33 (1.03–1.73)

Abbreviation: CI, confidence limits. Hypertension, systolic blood pressure ⩾140 mm Hg or diastolic blood pressure ⩾90 mm Hg at the two visits and/or self-reported use of antihypertensive drugs at the time of the interview; diabetes, fasting blood glucose ⩾126 mg dl^{-1} at both the visits or self-reported use of insulin or oral hypoglycaemic medications at the time of the interview; high cholesterol, total cholesterol >190 mg dl^{-1}; obesity, body mass index ⩾30 kg m^{-2}; abdominal obesity, waist circumference >102 cm in men and >88 cm in women; Proteinuria, ⩾+1 at dipstick urinalysis. Age-weighted rates to the 15–69-year-old Yemen population 2008 (mean, 95% CI). Odds ratio (with 95% CI) for the differences between rural and urban householders, unadjusted and adjusted for age, gender, education categories, hypertension, diabetes, high cholesterol, obesity and abdominal obesity.

Table 3. Logistic regression[a] of factors for the association with hypertension awareness, pharmacologic treatment (including all the 1307 subjects with hypertension) and blood pressure (BP) drug control (including the 528 subjects treated with hypertension on antihypertensive treatment)

Factors	*Awareness OR (95% CI)*	*Treatment OR (95% CI)*	*BP drug control OR (95% CI)*
Age (per decade)	1.19 (1.04–1.35)	1.23 (1.08–1.41)	0.71 (0.56–0.88)
Gender (women vs men)	1.29 (1.01–1.64)	1.31 (1.03–1.68)	1.75 (1.15–2.67)
Location (rural vs urban)	0.56 (0.45–0.71)	0.61 (0.48–0.76)	1.13 (0.77–1.65)
Education (per category)	0.92 (0.84–1.01)	0.91 (0.83–1.00)	1.06 (0.91–1.23)
Proteinuria (yes vs no)	1.20 (0.82–1.76)	1.34 (0.91–1.97)	0.57 (0.29–1.11)

Abbreviation: CI, confidence limits. [a]Adjusted variables are age (decades), gender, urban/rural location, education categories (illiterate, able to read and write, primary school, secondary school, high school, college or more) and proteinuria (⩾+1 at dipstick urinalysis).

associated with proteinuria only in urban areas (Table 4). The presence of proteinuria, however, did not affect hypertension awareness, allocation to antihypertensive treatment or achievement of BP control (Table 3).

DISCUSSION

The common risk factors shared by kidney damage and cardiovascular diseases support the focus on diabetes and hypertension as an adequate strategy to deal with kidney damage also in the developing countries. It is however intriguing to see that in Yemen the prevalence of proteinuria is higher in the rural areas compared with the urban areas.

According to the 2010 US Renal Data System Annual Data Report,[24] diabetes is the leading cause of ESRD in the United States. The increasing number of people with diabetes in developing countries due to population growth, aging, urbanization,[25] and increased prevalence of diabetes, obesity and physical inactivity is expected to have profound negative effects on global health. The broad package of prevention and screening strategies implemented by the main Scientific Societies is thus mainly focused to cope with the effects of globalization (urbanization) on hypertension, diabetes and metabolic disease.[5,26]

Only minor attention is however paid to three aspects of kidney damage, which might be relevant to the context of low-income countries. First, the presence of proteinuria is a recognized marker of cardiovascular risk.[18] Proteinuria of trace or 1+ at dipstick test was indeed found to be associated with an adjusted HR of 2.1 for all-cause mortality, 2.7 for doubling of the serum creatinine level and 1.7 for ESRD among individuals with initially normal estimated glomerular-filtration rate.[12] Proteinuria is a risk factor to develop chronic kidney disease and eventually ESRD; the higher the proteinuria the higher the risk.[11] Recent evidence is also revealing that kidney damage hazards (death, cardiovascular death and ESRD) are independent of diabetes and hypertension.[27,28] Second, in China, where the prevalence of proteinuria is high,[29] glomerulonephritis, mainly post-infectious, is the main cause of end-stage kidney disease.[30] In those communities, the dualism of communicable and non-communicable disease is indeed deprived of content, rheumatic heart disease being also a not negligible cause of atrial fibrillation and stroke.[31,32] Third, although in low-income countries the possibility to treat ESRD may be limited, early detection and treatment of kidney damage using readily available, inexpensive therapies might slow down or prevent the progression of renal disease.[13] Therefore, the importance of

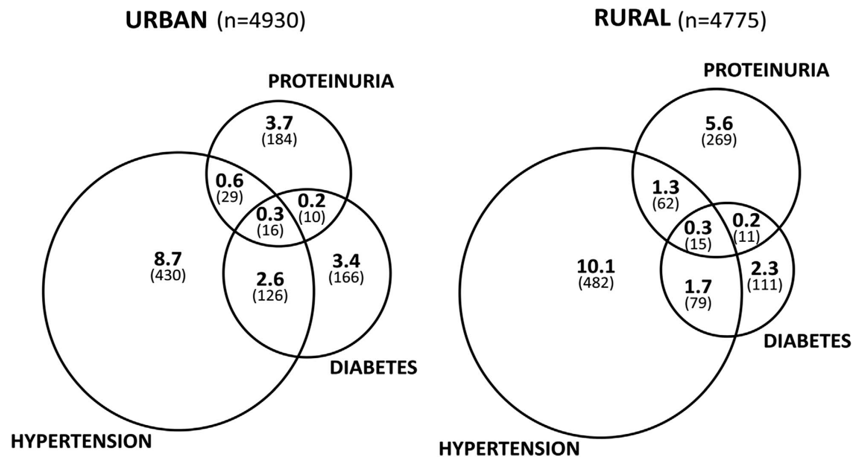

Figure 1. Venn diagram showing the amount of overlap between hypertension, diabetes and proteinuria, separate for the subjects from the urban and rural area. Data are expressed as percent of urban or rural subjects, the absolute number being reported in brackets.

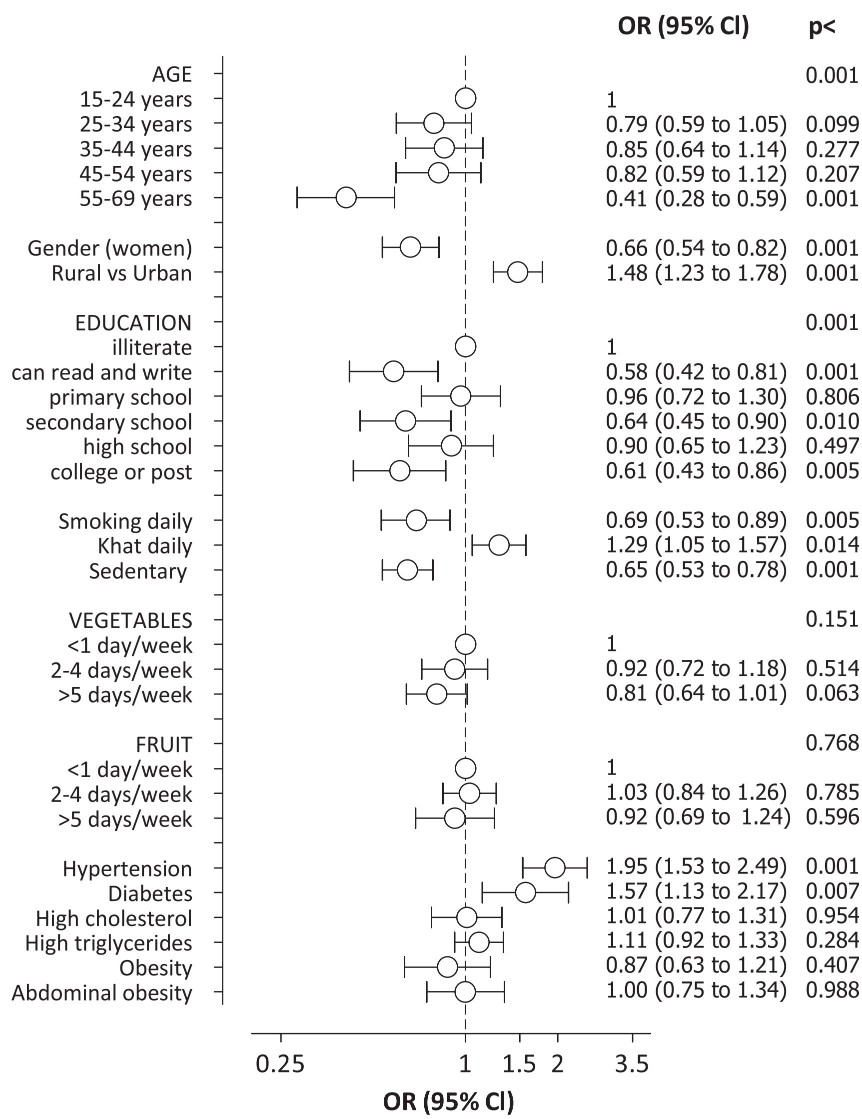

Figure 2. Factors independently associated with proteinuria at logistic regression analysis including 9385 participants. Results are expressed as OR with 95% Cl.

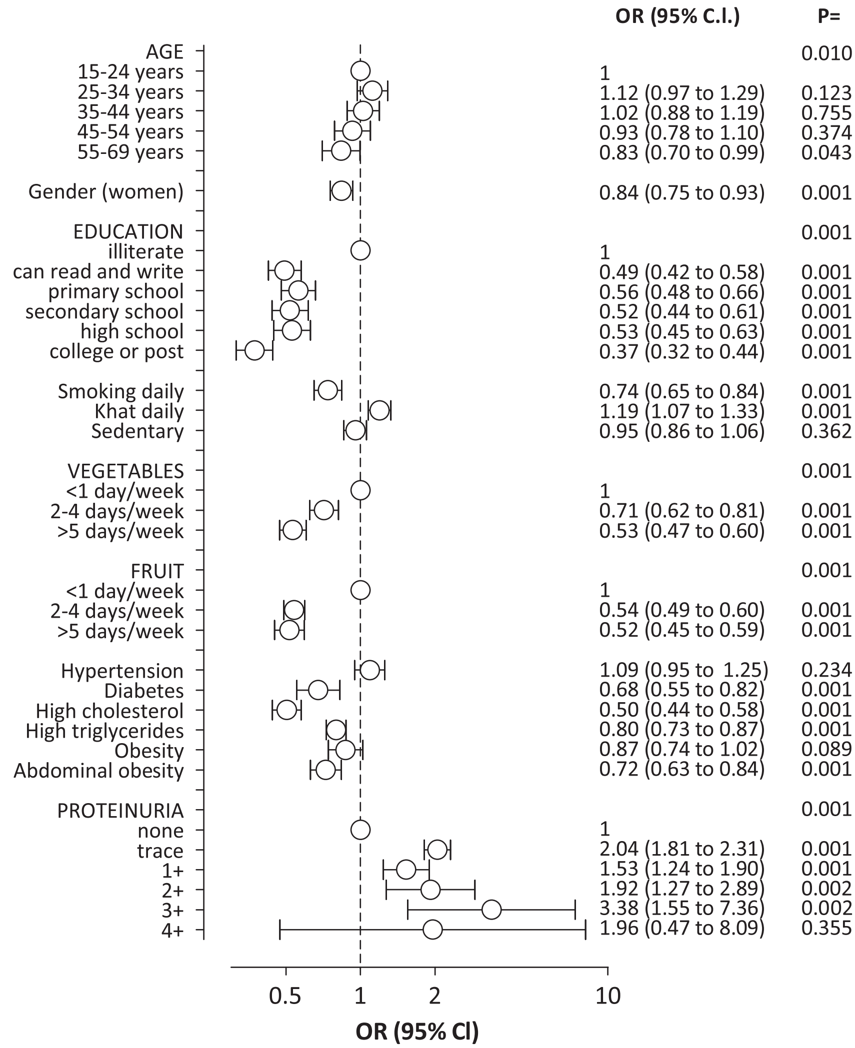

Figure 3. Factors independently associated with rural setting at logistic regression analysis including 9385 participants. Results are expressed as OR with 95% CI.

Table 4. Unadjusted and adjusted (logistic regressions[a,b]) odds ratios (OR) of factors associated with proteinuria among all participants (including 10 242 subjects), and among urban (including 5109 subjects) or rural dwellers (including 5133 subjects)

Factors	*Unadjusted OR (95% CI)*	*Adjusted[a] OR (95% CI)*	*Adjusted[b] OR (95% CI)*
All participants			
Hypertension (yes vs no)	1.78 (1.45–2.19)	1.97 (1.56–2.48)	1.95 (1.54–2.47)
Diabetes (yes vs no)	1.71 (1.27–2.31)	1.60 (1.17–2.20)	1.62 (1.18–2.23)
Location (rural vs urban)	1.63 (1.38–1.93)	1.57 (1.32–1.86)	1.56 (1.31–1.86)
Age (per decade)	0.95 (0.90–1.01)	0.85 (0.79–0.91)	0.84 (0.78–0.91)
Urban			
Hypertension (yes vs no)	1.68 (1.20–2.35)	1.95 (1.33–2.84)	1.95 (1.33–2.87)
Diabetes (yes vs no)	1.84 (1.20–2.81)	1.82 (1.15–2.88)	1.80 (1.13–2.87)
Age (per decade)	0.87 (0.79–0.95)	0.77 (0.68–0.86)	0.76 (0.68–0.86)
Rural			
Hypertension (yes vs no)	1.82 (1.39–2.37)	1.95 (1.45–2.63)	1.91 (1.41–2.58)
Diabetes (yes vs no)	1.75 (1.14–2.67)	1.47 (0.95–2.30)	1.49 (0.96–2.33)
Age (per decade)	1.01 (0.94–1.09)	0.90 (0.82–0.99)	0.90 (0.82–0.99)

Abbreviation: CI, confidence limits. [a]Adjusted variables are hypertension, diabetes, urban/rural location, age, gender and education categories. [b]Adjusted variables are hypertension, diabetes, urban/rural location, age, gender, education categories, high cholesterol, obesity and abdominal obesity.

focusing treatments on subjects at high risk is now recognized to have potential implications for health-care resource allocation in low-resource settings.[13,14] Screening strategies based on BP readings only were reported to overestimate the population at risk. Hypertension prevalence based on BP readings obtained after two visits is indeed 35% lower than the estimation based on the first visit.[14] The inclusion of urine dipstick test might be of help, as only 1.9% of the subjects classified at high or very high cardiovascular risk at visit 1 on the basis of BP readings and urine dipstick test moved to average, low or moderate cardiovascular risk categories after two visits.[14] The results of the present study add important information revealing that in developing countries, a large number of subjects have proteinuria in the absence of hypertension and diabetes in agreement with observations performed in Nepal and Bolivia.[10] Furthermore, in Yemen the prevalence of proteinuria is higher in the rural areas compared with the urban areas. According to the present findings obtained at the population level, the association with rural location was present for proteinuria categories trace, 1+, 2+ and 3+, the lack of significant association for the highest category (4+) being probably due to low numbers (seven among rural and four among urban dwellers). In addition, diabetes is associated with kidney injury only in urban areas, whereas the association between hypertension and proteinuria is present among both urban and rural residents. The relationship between hypertension and proteinuria is however bidirectional, renal disease being either a form of target organ damage or a secondary cause of hypertension, and a condition frequently associated with pre-existing primary kidney disease. After adjustment, only proteinuria remained the single risk condition that was more prevalent among rural residents. It is thus conceivable that hypertension among rural residents might be linked with pre-existing kidney disease. Difference between rural and urban areas might also be caused by the disparity in health care between the different areas of Yemen.[33] According to the present findings, awareness and treatment of hypertension were substantially lower in rural areas than in urban areas, consistent with previous results obtained in other countries.[34] However, the possibility to achieve hypertension control in Yemen, as also in Iran,[35] did not differ between urban and rural residents. Most importantly, the absence of educational influence on hypertension awareness, treatment and BP control (Table 3) indicates that knowledge on cardiovascular prevention among Yemen population is limited.

Our study had several limitations. First, the true rate of kidney damage assessed by the presence of proteinuria might be lower than that estimated, as proteinuria is to be confirmed with repeated assessment, a procedure which was not adopted in the present survey strategy. However, a similar reduction is expected to occur independently in the urban or rural residency, so that this methodological bias should not modify the main observation. Furthermore, the same higher prevalence in rural than in urban dwellers was observed for all proteinuria scores, high values being less affected by test variability than trace levels. Second, the use of dry chemistry for laboratory investigations could also be considered a limitation in our study. However, the possibility to have investigations carried out during a home visit could turn into a great advantage when operating in developing countries. The long distance to get to a service laboratory requires shipments under special conditions, often resulting in deterioration and spoilage of the specimen. In addition, all investigators completed a certification program before the study, and quality-control procedures were used during the study. Third, we did not collect information regarding outdoor activity of participants, therefore, we cannot exclude that urine of the rural dwellers could be more concentrated. Measuring the urinary proteins/creatinine ratio could have solved this problem.

Fourth, the definition of diabetes was based on FG measured at the two visits, and oral glucose-tolerance test was not done. However, the number of subjects with urinary glucose at dipstick test was also higher among urban than rural dwellers. In addition, measuring HbA1c, which could be done even in the field, could perhaps have solved the underestimation of diabetes by only measuring fasting samples. Finally, the cross-sectional design of the study makes inference of a causal relationship between indicators of kidney damage and associated factors impossible. We recognize that in the absence of prospective studies performed in low-resource settings, it is impossible to infer that proteinuria, on a completely different background in rural settings like this, should carry the same risk found in studies performed in industrialized societies.

In conclusion, proteinuria is related to hypertension and diabetes in the developed countries but not in Yemen, particularly in the rural setting. The amount of overlap between hypertension, diabetes and proteinuria indeed clearly indicates that the majority of proteinuria is neither related to hypertension nor diabetes as recently reported for other low-income countries.[10] The inverse relationship between proteinuria and age compared with other complications/risk factors also suggests a completely different background. Notwithstanding these limitations, our results clearly show that the approach of considering kidney damage only as a consequence of cardiovascular diseases (including hypertension) and diabetes might limit the effectiveness of secondary prevention strategies, as well as of health-promoting interventions, especially in low-income countries.

What is known about the topic

- Changes in lifestyle and diet habits following urbanization are greatly contributing to increase in the prevalence of cardiovascular disease in developing countries.
- The common risk factors shared by kidney damage and cardiovascular diseases support the focus on diabetes and hypertension as an adequate strategy to deal with kidney damage also in the developing countries.
- However, in countries at the earliest stages of epidemiological transition, where the prevalence of post-infectious glomerulonephritis is still high, little information is available on the different meanings of proteinuria among urban and rural dwellers.

What this study adds

- The prevalence of proteinuria is higher in the rural areas of Yemen compared with the urban areas. Proteinuria is independently associated with diabetes only among urban dwellers, whereas the association with hypertension was present in either urban or rural dwellers. A prescreening phase including clinical history, BP and biochemical measurements might be insufficient to identify and treat those at risk for progressive renal disease.
- The approach of considering kidney damage as a consequence of hypertension and diabetes might thus limit the effectiveness of secondary prevention strategies, as well as of health-promoting interventions in low-income countries.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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DISCLAIMER

The sponsor had no role in study design; collection, analysis and interpretation of data; writing the report and the decision to submit the report for publication.

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