PLOS | ONE

RESEARCH ARTICLE

Prevalence of chronic kidney disease and risk factors for its progression: A cross-sectional comparison of Indians living in Indian versus U.S. cities

Shuchi Anand[1,2,3]*, Dimple Kondal[1,2], Maria Montez-Rath[3], Yuanchao Zheng[3], Roopa Shivashankar[1,2], Kalpana Singh[1,2], Priti Gupta[1,2], Ruby Gupta[1,2], Vamadevan S. Ajay[1,2], Viswanathan Mohan[4], Rajendra Pradeepa[4], Nikhil Tandon[1,5], Mohammed K. Ali[1,6], K. M. Venkat Narayan[1,6], Glenn M. Chertow[3], Namratha Kandula[7], Dorairaj Prabhakaran[1,2], Alka M. Kanaya[8]

1 Centre for Chronic Conditions and Injuries, Public Health Foundation of India, New Delhi, India, **2** Centre for Chronic Disease Control, New Delhi, India, **3** Division of Nephrology, Stanford University School of Medicine, Palo Alto, CA, United States of America, **4** Madras Diabetes Research Foundation & Dr. Mohan's Diabetes Specialties Centre, Chennai, India, **5** Department of Endocrinology, All India Institute of Medical Sciences, New Delhi, India, **6** Rollins School of Public Health, Emory University, Atlanta, GA, United States of America, **7** Division of General Internal Medicine and Department of Preventive Medicine, Northwestern University, Chicago, IL, United States of America, **8** Division of General Internal Medicine, University of California San Francisco, San Francisco, CA, United States of America

* sanand2@stanford.edu

Check for updates

OPEN ACCESS

Citation: Anand S, Kondal D, Montez-Rath M, Zheng Y, Shivashankar R, Singh K, et al. (2017) Prevalence of chronic kidney disease and risk factors for its progression: A cross-sectional comparison of Indians living in Indian versus U.S. cities. PLoS ONE 12(3): e0173554. https://doi.org/10.1371/journal.pone.0173554

Editor: Xu-jie Zhou, Peking University First Hospital, CHINA

Received: November 4, 2016

Accepted: February 23, 2017

Published: March 15, 2017

Copyright: © 2017 Anand et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: Since both CARRS and MASALA are funded by NIH, data are publically available. MASALA data access decided upon by MASALA project committee; interested parties can apply via http://www.masalastudy.org/for-researchers/. CARRS data used in our analyses have been submitted to the NHLBI; more information available at http://www.nhlbi.nih.gov/about/org/globalhealth/centers/.

Abstract

Background

While data from the latter part of the twentieth century consistently showed that immigrants to high-income countries faced higher cardio-metabolic risk than their counterparts in low- and middle-income countries, urbanization and associated lifestyle changes may be changing these patterns, even for conditions considered to be advanced manifestations of cardio-metabolic disease (e.g., chronic kidney disease [CKD]).

Methods and findings

Using cross-sectional data from the Center for cArdiometabolic Risk Reduction in South Asia (CARRS, n = 5294) and Mediators of Atherosclerosis in South Asians Living in America (MASALA, n = 748) studies, we investigated whether prevalence of CKD is similar among Indians living in Indian and U.S. cities. We compared crude, age-, waist-to-height ratio-, and diabetes- adjusted CKD prevalence difference. Among participants identified to have CKD, we compared management of risk factors for its progression. Overall age-adjusted prevalence of CKD was similar in MASALA (14.0% [95% CI 11.8–16.3]) compared with CARRS (10.8% [95% CI 10.0–11.6]). Among men the prevalence difference was low (prevalence difference 1.8 [95% CI -1.6,5.3]) and remained low after adjustment for age, waist-to-height ratio, and diabetes status (-0.4 [-3.2,2.5]). Adjusted prevalence difference was higher among women (prevalence difference 8.9 [4.8,12.9]), but driven entirely by a higher prevalence of albuminuria among women in MASALA. Severity of CKD—-i.e., degree of

Funding: This work was supported by federal funds from the National Heart, Lung, and Blood Institute, at National Institutes of Health [Contract #HHSN2682009900026C, CARRS study; # R01HL093009, MASALA study]. Data collection at University of California San Francisco was also supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, at National Institutes of Health [grant # UL1 RR024131]. Dr. Anand is supported by National Institute for Diabetes and Digestive and Kidney Health [grant # K23 DK101826]. Dr. Chertow is supported by National Institute for Diabetes and Digestive and Kidney Health [grant # K24 DK 085446]. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, And Blood Institute, National Institute for Diabetes and Digestive and Kidney Health, or the National Institutes of Health.

Competing interests: The authors have declared that no competing interests exist.

albuminuria and proportion of participants with reduced glomerular filtration fraction-—was higher in CARRS for both men and women. Fewer participants with CKD in CARRS were effectively treated. 4% of CARRS versus 51% of MASALA participants with CKD had A1c < 7%; and 7% of CARRS versus 59% of MASALA participants blood pressure < 140/90 mmHg. Our analysis applies only to urban populations. Demographic—-particularly educational attainment—-differences among participants in the two studies are a potential source of bias.

Conclusions

Prevalence of CKD among Indians living in Indian and U.S. cities is similar. Persons with CKD living in Indian cities face higher likelihood of experiencing end-stage renal disease since they have more severe kidney disease and little evidence of risk factor management.

Introduction

Historically, migration from low- and middle-income countries (LMIC) to high-income countries (HIC) has conferred higher cardio-metabolic risk among the immigrant groups. For example, three West African populations studied along "the migration ladder"—living in Nigeria, Jamaica, and the U.S.—demonstrated higher body mass indices in a stepwise fashion [1]. Indian immigrants to London in the 1990s had higher body mass index, systolic blood pressure, and fasting blood glucose compared with their siblings living in Punjab, India[2]. Japanese immigrants to Hawaii and California in the 1970s experienced a doubling in the incidence of myocardial infarction compared with contemporaries living in Japan[3].

However, as many LMIC experience rapid urbanization—accompanied by a rise in consumption of energy-dense foods and declines in physical activity—it is conceivable that the burden of cardio-metabolic diseases in urban residents of LMIC now approaches that of immigrants to HIC. In fact, recent data suggest that prevalence of diabetes mellitus is *higher* in Indians living in Indian rather U.S. cities [4]. Whether this trend holds true for other cardio-metabolic diseases, particularly ones that are considered late manifestations, is not known.

We therefore compared data from the Center for cArdiometabolic Risk Reduction in South Asia (CARRS) and Mediators of Atherosclerosis in South Asians Living in America (MASALA) studies to: 1. compare the prevalence of chronic kidney disease (CKD) among Indians living in Indian cities (CARRS) with Indians who have immigrated to U.S. cities (MASALA); 2. assess whether differences in body size or diabetes prevalence explain any CKD prevalence difference; and 3. among participants identified to have CKD in the two studies, describe the management of parameters associated with progression to end-stage renal disease (ESRD).

Methods

The methodologies of the CARRS[5] and MASALA[6] studies have been previously described in detail. Briefly, the CARRS Study is a community-based prospective study that employed a multistage cluster sampling technique to capture the prevalence and incidence of cardio-metabolic diseases in three major cities of South Asia—Chennai and Delhi, India, and Karachi, Pakistan. The study received approval for human subjects research from the Ethics Committees of the Public Health Foundation of India and All India Institute of Medical Sciences (Delhi), Madras Diabetes Research Foundation (Chennai), and Emory University (Atlanta). We restricted this analysis to Delhi and Chennai (n = 12 271) as the laboratory in Karachi used

different laboratory kits and equipment for serum and urine creatinine assays. To match MASALA study entry criteria, we further restricted the analysis to participants aged ≥ 40 years old without self-reported heart disease or stroke (n = 6537) **(See Figure A in S1 File for study flowchart)**. Of these, 5294 participants had complete data on albuminuria and serum creatinine, and comprise the analytical group. **Table A in S2 File** demonstrates that while men were more likely to have missing data, participants with and without data on markers of CKD were similar in their age distribution and educational status.

The MASALA study is a prospective study investigating the prevalence and outcomes of subclinical cardiovascular disease in 906 South Asian adults, aged ≥ 40 years and free of physician-diagnosed cardiovascular disease. **(Figure B in S1 File).** This study invited random samples of South Asians (identified as such from census tracts or surrounding counties using surname identification techniques) living in the San Francisco Bay Area and greater Chicago area to participate via mail. Study participants had been living in the U.S. for a mean of 27 ± 11 years. Institutional Review Boards at the University of California, San Francisco and Northwestern University approved the study. In this analysis, we included persons who were born in India (n = 757) and had complete data on albuminuria and serum creatinine (n = 748).

Correlates of CKD

Both the CARRS and MASALA studies obtained data on age, sex, household income, years of schooling and highest level of education achieved, tobacco use, and use of medications using standardized questionnaires. Both studies also obtained weight, height, waist circumference, and hip circumference measurements using protocols similar to those employed for the U.S. National Health and Nutrition Examination Survey (NHANES). For other demographic and clinical risk factors for CKD and/or progression of CKD, we attempted to harmonize the correlate definitions across the two studies (**Table 1**).

Laboratory measures

Accredited site laboratories processed participants' fasting blood and urine samples. Both studies employed the same assay methodology for: fasting plasma glucose (hexokinase/kinetic method), glycosylated hemoglobin (high performance liquid chromatography standardized to the National Glycohemoglobin Standardization Program), lipid panel (enzymatic), and urine albumin (immunoturbidimetric). To measure urine and serum creatinine, CARRS used the rate-blanked and compensated kinetic Jaffe assay whereas MASALA used the enzymatic colorometric assay, both traceable to isotope dilution mass spectrometry (IDMS) at the National Institute of Standards[7]. The two assays have been shown to have a nearly identical reference range [8–10].

Definitions of disease status

With the 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines[11] as a reference, we defined a participant as having CKD with albuminuria (albumin-to-creatinine ratio ≥ 3.4 mg/mmol [30 mg/g]) and/or CKD-EPI[12] estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2. We defined diabetes as fasting glucose ≥ 7 mmol/L (126 mg/dL) and/or use of medications for diabetes; and hypertension as systolic BP ≥ 140 or diastolic ≥ 90 mmHg and/or use of medications for hypertension.

Statistical analyses

Using means and standard deviations for continuous, or counts and percentages for categorical variables, we described baseline characteristics stratified by sex and study type. We report

Table 1. Harmonizing measures from the CARRS and MASALA studies.

Measure	Methodology in CARRS	Methodology in MASALA	Harmonized measure
Income	Monthly household income (categories)	Annual household income (categories)	Compare individuals in top tertile of income versus not
Physical activity	International Physical Activity Questionnaire (IPAQ)[37]	Typical Week's Physical Activity Questionnaire [38]	Weekly vigorous physical activity (yes/no), since both surveys described vigorous physical activity similarly
Diet	Frequency of consumption of major food groups for the past year (including typical foods consumed in India)	Study of Health Assessment and Risk in Ethnic Groups (SHARE) questionnaire[39]	Fruit and vegetable intake (number of times/day), since both surveys described these food groups similarly
Blood pressure	After 5 minutes of rest, Seated blood pressure at rest at least two times, using an oscillometric device (Omron Dailan Co., Ltd, Dalian, Liaoning, China). A third measurement was obtained if the difference between the first two systolic or diastolic measurements was more than 10 mmHg and 5 mmHg, with at least 30 seconds in between each.	After 5 minutes of rest, seated blood pressure at rest three times with at one minute in between each reading, using an oscillometric device (V100 Vital Signs Monitor, GE Healthcare, Fairfield, CT. U.S.)	Average of last two readings
Medications	Obtained 1 year after baseline; individual medication names	Obtained at baseline; individual medication names	Categorized by study investigators into broader categories (yes/no): 1.Blood pressure medications, 2. ACEI/ARB therapy, 3. Anti-glycemic therapy, including insulin, and 4. Lipid therapy, including statins, fibrates and ezetimibe
Chronic kidney disease	Spot urine albumin measured via immunoturbidimetric assaySerum and urine creatinine measured via rate-blanked compensated kinetic Jaffe method	Spot urine albumin measured via immunoturbidimetric assay Serum and urine creatinine measured via enzymatic colorometric method	Creatinine assays in both laboratories traceable to IDMS. CKD defined in both studies as: 1. Single urine albumin to creatinine ratio $\geq$ 3.4 mg/mmol [30 mg/g], or 2. Single calculation of CKD-EPI eGFR < 60 ml/min/1.73m^2

Abbreviations: IDMS- isotope dilution mass spectrometry; CKD-chronic kidney disease; eGFR-estimated glomerular filtration rate.

https://doi.org/10.1371/journal.pone.0173554.t001

raw, age-adjusted, and sex-stratified prevalence of overall CKD, eGFR $<$ 60 ml/min/1.73m^2, and albuminuria in each study. We also examined prevalence of CKD according to the following demographic and behavioral categories: income, education, physical activity, and fruit and vegetable intake.

We adjusted the between-study prevalence difference in overall CKD, eGFR $<$ 60 ml/min/1.73m^2, and albuminuria for age, waist-to-hip ratio, and diabetes, using a generalized linear model with a log link and Binomial distribution (log-Binomial), or Poisson with robust standard errors (modified Poisson model) if the log-Binomial model failed to converge[13]. While persons with vascular disease can manifest hypertension and CKD, hypertension is also often a consequence of CKD. We therefore did *not* adjust the prevalence difference in CKD for prevalence of hypertension in the two studies.

Since overall missingness in the CARRS analytic study was approximately 20%, we performed multiple imputation for missing covariates[14]. We assumed data to be missing at random and used the Fully Conditioning Specification[15] approach to impute 20 full datasets, stratified by sex. The MASALA study had only two missing observations; we thus performed a complete case analysis for this study.

In the participants with CKD in the two studies, we describe differences in prevalence of risk factors associated with progression to ESRD and/or cardiovascular events in the two studies. Further, we estimate the relative likelihood of an important clinical outcome—i.e., ESRD or death due to kidney disease—among participants with diabetes and CKD in CARRS versus MASALA. We used recently described five-year event rates from the standard arm of the multi-country Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study[16]. We obtained these event rates stratified according to A1c category (<8 versus ≥ 8%), and multiplied the proportion of CKD participants falling in the these two A1c categories with the respective events rates to estimate a relative risk in CARRS versus MASALA. We used SAS, version 9.4 (SAS Institute, Inc., Cary, NC) or Stata version 13.1 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.) to perform all analyses.

Results

Table 2 provides details of participant characteristics in the CARRS and MASALA studies, stratified by sex. In general, CARRS participants were younger, with substantially fewer men and women in the ≥ 55 years of age categories. Educational attainment was strikingly different between the two studies: more than 85% of men and women in the MASALA study had attained a college degree, whereas fewer than 20% in CARRS had done so. Close to a quarter of participants had diabetes, with the exception of women in the MASALA study in whom the prevalence was 15%. More women in both studies had abnormal waist-to-height ratio; more men in both studies reported smoking and performing vigorous physical activity.

Prevalence of CKD

Raw and age-adjusted prevalence of overall CKD was similar among men in CARRS and MASALA, but substantially higher among women in MASALA compared with women in CARRS (**Table 3**). Prevalence increased with age in both studies, and for both sexes (**See Table B in S2 File for age- and sex- stratified CKD prevalence**). Overall, there was a modestly higher prevalence of CKD in MASALA (14.0% [95% CI 11.8–16.3]) than in CARRS (10.8% [95% CI 10.0–11.6]).

Investigating albuminuria further we found that while the *prevalence* of albuminuria was higher in MASALA than in CARRS, the *severity* of albuminuria was higher in CARRS: log-mean albuminuria value was 4.5 ± 1.0 versus 4.1 ± 0.8 (p value = 0.01) among women in CARRS and MASALA respectively, and 4.6 ± 1.2 versus 4.2 ± 0.7 (p value < 0.001) among men in CARRS and MASALA (**See Figures C-E in S1 File for albuminuria distribution and Table C in S2 File for albuminuria categories**). Odds of albuminuria did not differ by meat intake status in either study (data not shown).

For both men and women, prevalence of CKD was higher in the highest tertile of income in CARRS, but lower in MASALA when compared with participants in the lower tertiles of income (**Fig 1A and 1B**). For other potential correlates such as physical activity, diabetes, and hypertension, CARRS and MASALA study participants had similar directions of associations with CKD. Women in MASALA had higher prevalence of CKD than women in CARRS across all correlates.

Adjusted prevalence difference in CKD

We examined the prevalence difference in CKD after adjusting for diabetes, waist-to-height ratio, and the residual effects of age (**Fig 2A and 2B**). Adjustment for these covariates led to a slight attenuation in the magnitude of the CKD prevalence difference between MASALA and

Table 2. Demographic, anthropometric, laboratory and disease status in the CARRS and MASALA studies, 2010–2013.

	Men		Women	
	CARRSN = 2563	MASALA N = 402	CARRS N = 2731	MASALA N = 346
Demographics				
Mean age, years	51.9 ± 9.8	56.2 ± 9.9	50.9 ± 8.9	54.6 ± 8.6
40 to 54	1705 (66.5)	191 (47.5)	1878 (68.8)	186 (53.8)
55 to 69	681 (26.6)	164 (40.8)	732 (26.8)	142 (41.0)
≥70	177 (6.9)	47 (11.7)	121 (4.4)	18 (5.2)
Less than college degree	2045 (79.8)	30 (7.5)	2367 (86.7)	44 (12.7)
Current tobacco user*	772 (30.1)	24 (6.0)	21 (0.8)	4 (1.2)
Missing	-	1 (0.2)	-	-
Fruits and Vegetable Intake (# of times/day)				
<2	1063 (41.5)	11 (2.7)	1383 (50.6)	2 (0.6)
2 to 4	1244 (48.5)	68 (16.9)	1173 (43.0)	28 (8.1)
>4	256 (10.0)	322 (80.1)	175 (6.4)	316 (91.3)
Missing	-	1 (0.2)	-	-
Any vigorous physical activity in the week	450 (17.6)	120 (29.9)	271 (9.9)	54 (15.6)
Missing	17 (0.7)	13 (3.2)	21 (0.8)	3 (0.9)
BP and anthropometry				
Mean waist-to-height ratio	0.55 ± 0.07	0.57 ± 0.06	0.57 ± 0.08	0.57 ± 0.06
Abnormal waist-to-height ratio[¶]	1541 (60.1)	353 (87.8)	1871 (68.5)	299 (86.4)
Missing	560 (21.8)	2 (0.5)	491 (18.0)	-
BP(mmHg): Sys &/or Dias[†]				
<120 & <80	535 (20.9)	141 (35.1)	769 (28.2)	169 (48.8)
120–139 or 80–89	958 (37.4)	189 (47.0)	1029 (37.7)	117 (33.8)
≥140 or ≥90	910 (35.5)	72 (17.9)	859 (31.5)	60 (17.3)
Missing	160 (6.2)	-	74 (2.7)	-
Laboratories[†]				
Fasting glucose (mmol/L)				
< 5.6	1196 (46.7)	200 (49.8)	1149 (42.1)	235 (67.9)
5.6 to <7	798 (31.1)	138 (34.3)	1026 (37.6)	92 (26.6)
≥7	568 (22.2)	58 (14.4)	555 (20.3)	18 (5.2)
Missing	1 (0.0)	6 (1.5)	1 (0.0)	1 (0.3)
Hemoglobin A1c (%)				
<5.7	649 (25.3)	115 (28.6)	578 (21.2)	98 (28.3)
5.7 - <6.5	993 (38.7)	202 (50.2)	1126 (41.2)	206 (59.5)
≥6.5	908 (35.4)	83 (20.6)	1006 (36.8)	40 (11.6)
Missing	13 (0.5)	2 (0.5)	21 (0.8)	2 (0.6)
Diabetes[#]	624 (24.3)	97 (24.1)	631 (23.1)	52 (15.0)
Missing	1 (0.0)	-	1 (0.0)	-
Hypertension[‖]	987 (38.5)	181 (45.0)	971 (35.6)	126 (36.4)
Missing	154 (6.0)	-	63 (2.3)	-

Data are expressed as mean (standard deviation), or number (percent in each group).

*Current tobacco use is defined as any cigarette use in the past 12 months.

[¶]Waist-to-height ratio > 0.5 is defined as abnormal

[†]Blood pressure and laboratory values report measured results regardless of self-reported disease status.

[#]Diabetes is defined as fasting glucose ≥ 7 mmol/L (126 mg/dL) and/or use of medications for diabetes.

[‖]Hypertension is defined as systolic BP ≥ 140 or diastolic ≥ 90 mmHg and/or use of medications for hypertension.

https://doi.org/10.1371/journal.pone.0173554.t002

Table 3. Prevalence of chronic kidney disease in the CARRS and MASALA studies.

	Overall		Men		Women	
	CARRS	MASALA	CARRS	MASALA	CARRS	MASALA
	N = 5294	N = 748	N = 2563	N = 402	N = 2731	N = 346
Raw Prevalence						
CKD	10.5 (9.7–11.4)	16.3 (13.7–19.0)$^{+}$	10.5 (9.3–11.7)	12.2 (9.0–15.4)	10.6 (9.4–11.7)	21.1 (16.8–25.4)$^{+}$
Albuminuria	8.6 (7.9–9.4)	15.1 (12.5–17.7)$^{+}$	8.5 (7.4–9.5)	10.9 (7.9–14.0)	8.8 (7.7–9.8)	19.9 (15.7–24.2)$^{+}$
eGFR<60	3.1 (2.6–3.6)	2.0 (1.0–3.0)	3.0 (2.3–3.7)	2.2 (0.8–3.7)	3.2 (2.5–3.8)	1.7 (0.4–3.1)
Age-adjusted Prevalence						
CKD	10.8 (10.0–11.6)	14.0 (11.8–16.3)$^{+}$	10.8 (9.6–12.0)	10.3 (7.6–13.0)	10.8 (9.6–11.9)	18.6 (14.9–22.4)$^{+}$
Albuminuria	8.7 (8.0–9.5)	13.8 (11.4–16.1)$^{+}$	8.6 (7.5–9.7)	9.8 (7.1–12.6)	8.8 (7.7–9.9)	18.5 (14.5–22.4)$^{+}$
eGFR<60	3.2 (2.8–3.7)	1.6 (0.8–2.3) $^{+}$	3.1 (2.5–3.8)	1.7 (0.6–2.8)$^{+}$	3.2 (2.6–3.9)	1.4 (0.3–2.5)$^{+}$

Values in table are prevalence % (95% confidence interval).

$^{+}$p value for prevalence difference from CARRS < 0.05

https://doi.org/10.1371/journal.pone.0173554.t003

CARRS for both men and women. Nonetheless, the main findings remained unchanged. Men in the two studies had similar prevalence of CKD, with albuminuria prevalence higher in MASALA and eGFR < 60 ml/min/1.73m^2 prevalence higher in CARRS. Women in MASALA had a substantially higher prevalence of overall CKD and albuminuria than women in CARRS, but the prevalence of eGFR < 60 ml/min/1.73m^2 was slightly higher in women in CARRS.

In sensitivity analyses adjustment for hypertension status led to a further slight attenuation of the prevalence difference between women (**Table D in S2 File**). Since income had a differential relationship with CKD in the two studies, we performed stratified analyses further adjusting for income and education. Among participants in the top tertile of income, men in MASALA seemed to have slightly *lower* CKD prevalence, whereas women in MASALA continued to demonstrate a higher CKD prevalence compared with counterparts in CARRS.

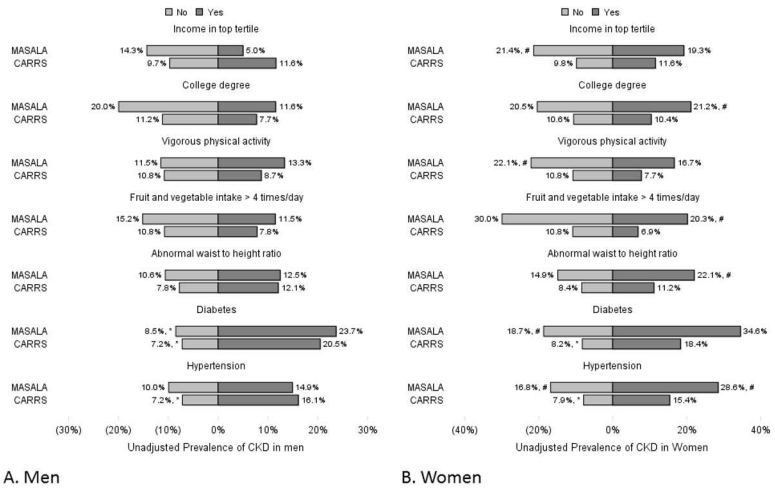

Fig 1. Prevalence of CKD according to demographic correlates in (A) men and (B) women In MASALA, men with income in the lower tertiles had higher CKD prevalence than men with income in the top tertile. In CARRS, men with no college education had higher CKD prevalence than men with college education. Across studies, men with income in the lower tertiles in CARRS had higher CKD prevalence than men with income in the lower tertiles in the MASALA. Women in the MASALA study had significantly higher prevalence of CKD across nearly all demographic correlates compared with women in CARRS. * denotes statistically significant difference within each study, # denotes statistically significant difference between studies.

https://doi.org/10.1371/journal.pone.0173554.g001

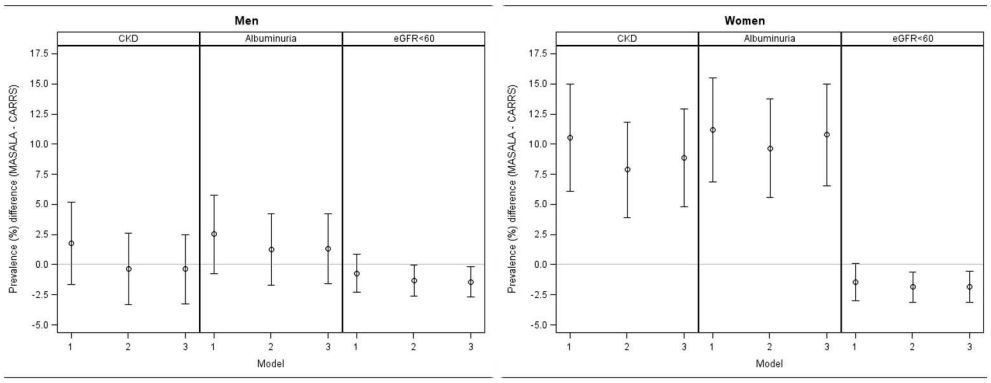

Fig 2. Prevalence difference in CKD in the MASALA study from the CARRS study (A) men and (B) women. We present prevalence difference in CKD 1. Unadjusted, 2. Adjusted for age, and 3. Adjusted for age, waist-to-height ratio, and diabetes. Prevalence difference in overall CKD and albuminuria among men in CARRS and MASALA was negligible in all three models; prevalence of eGFR < 60 ml/min/1.73m^2 was slightly higher in men in CARRS. Unadjusted prevalence in overall CKD and albuminuria among women in MASALA was 11.1% and 11.8% higher respectively compared with CARRS; adjusting for diabetes and waist-to-height ratio did not attenuate this prevalence difference.

https://doi.org/10.1371/journal.pone.0173554.g002

Risk factor management in participants with CKD

Among participants identified to have CKD in the two studies, the prevalence of hypertension was similar and the prevalence of diabetes was lower in the MASALA than in the CARRS study (Fig 3). Fewer participants in CARRS with these conditions were treated with medications and fewer had evidence of meeting targets such as hemoglobin A1c < 7.0 among those with diabetes (4% in CARRS versus 51% in MASALA) or blood pressure $< 140/90$ mmHg (7% in CARRS versus 59% in MASALA) among those with hypertension. In sensitivity analyses, we restricted this comparison to patients with a college degree or more, or to patients in the top tertile of income and found that while the likelihood of meeting targets went up in both groups, the gap between CARRS and MASALA participants in meeting targets remained large. For example, among those with diabetes and CKD in the top income tertile, 9% of CARRS participants had A1c < 7.0 compared with 63% in MASALA.

Since event rates for ESRD and/or death due to kidney disease are more than two-times higher among those with poor glycemic control ($\geq$ 8%) and CKD[17], CARRS participants with diabetes and CKD are estimated to have 40% higher risk for experiencing this combined outcome (relative risk 1.4, 95% CI: 0.8–2.6).

Behavioral characteristics known to attenuate risk for progression of CKD (e.g., physical activity and abstaining from tobacco use) and/or associated cardiovascular events (e.g., fruit and vegetable intake) were also more likely to be suboptimal in the CARRS than in MASALA study. Awareness of presence of CKD was low in both studies.

Discussion

Our study finds that the overall age-adjusted prevalence of CKD in Indians living in Indian cities approaches that of Indians living in U.S. cities. Men in particular provided the strongest evidence for a change in the trend that migration to HIC results in a dramatic increase in risk for cardio-metabolic diseases. Furthermore, compared with counterparts living in the U.S., those with CKD living in urban India have more severe CKD and worse risk factor profiles—e.g., higher likelihood of uncontrolled A1c or untreated hypertension—rendering them vulnerable to experiencing more cardiovascular events and rapid kidney disease progression.

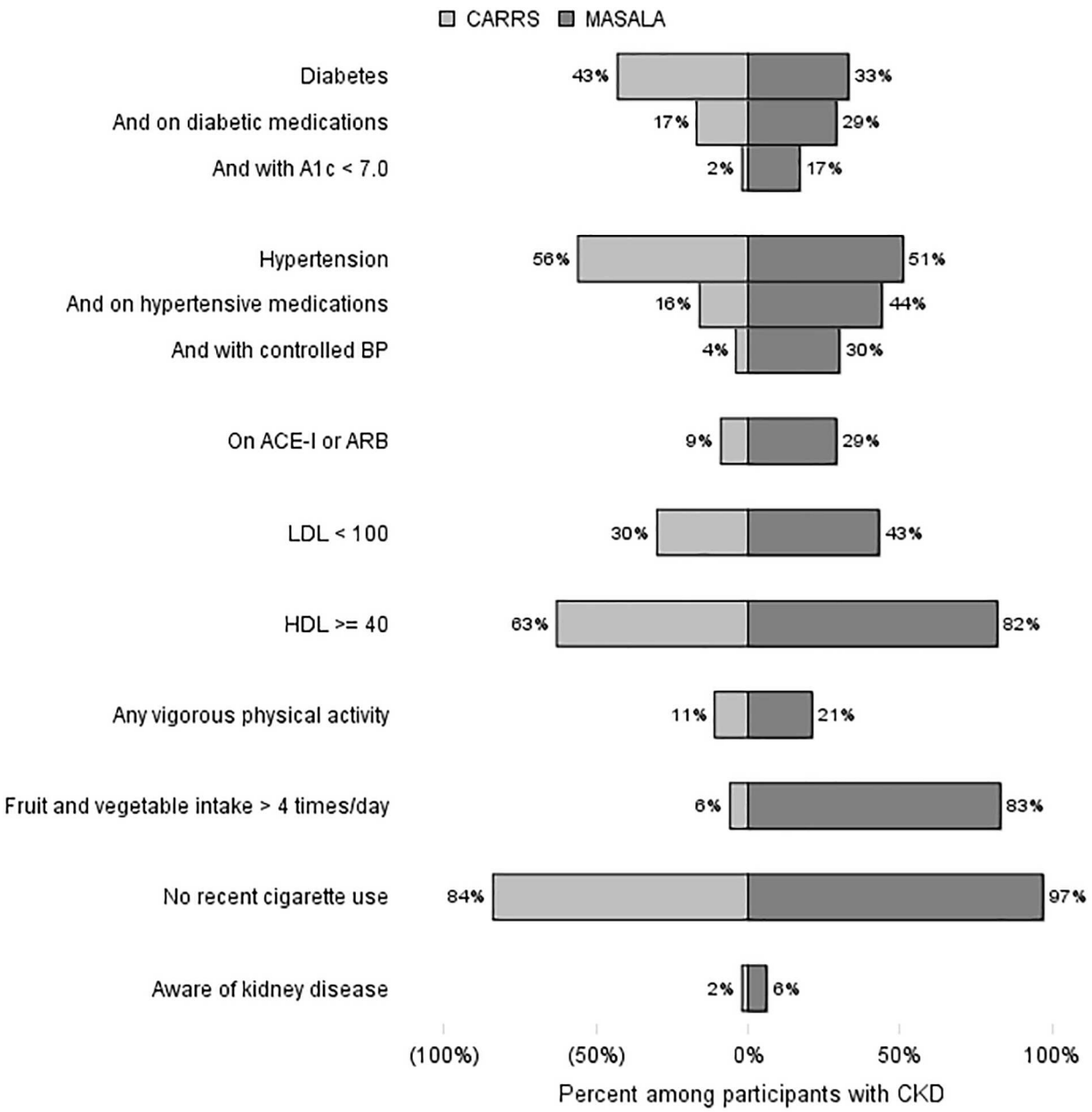

Fig 3. Prevalence of risk factors for adverse events, and evidence of their management among participants with CKD. Of the 558 and 122 participants with CKD in CARRS and MASALA respectively, 430 (77%) and 119 (98%) had complete data on prevalence of risk factors for progression of CKD and/or cardiovascular events. While 43% of participants with CKD in CARRS had diabetes, only 17% were on medications and only 2% (i.e., 4% of those with CKD and diabetes) had A1c < 7.0.

https://doi.org/10.1371/journal.pone.0173554.g003

Women participating in the MASALA study had a substantially higher prevalence of albuminuria without reduction in eGFR than women participating in CARRS. The small prevalence difference in overall CKD between the two studies was driven in its entirety by a substantially higher prevalence of albuminuria without a reduction in eGFR among women participating in MASALA. Counter-intuitively, women in MASALA had similar prevalence of hypertension, and lower prevalence of diabetes. They also attained higher educational status, performed more physical activity, and consumed more fruits and vegetables than women in

CARRS. Odds of albuminuria did not vary by meat intake status in the two studies. Women in MASALA did have higher prevalence of abnormal waist-to-height ratio compared with women in CARRS. Studies have linked central obesity to the presence[18] and severity[19] of albuminuria. In 205 South Asian adults without diabetes, the odds of albuminuria were 4-fold higher in the group with highest waist-to-hip ratios, despite accounting for age, smoking status, and blood pressure[20]. However, in our study, the albuminuria prevalence difference among women persisted even after adjusting for age, diabetes, and waist-to-height ratio. Since a single measure indicating presence of albuminuria strongly predicts 24 hour urine collection results[21], as well as future cardiovascular[22] and renal[23] outcomes, this finding deserves further exploration.

Demographic correlates had a similar direction of association with prevalence of CKD in CARRS and MASALA, with the notable exception of income. Compared with participants in the highest income tertile, those with lower incomes were more likely to have CKD in MASALA; the reverse was true for CARRS. A majority of studies in the U.S. and other HIC have shown that higher income and educational status are associated with lower likelihood of chronic diseases[24]. This pattern has not yet emerged in LMIC, where higher socioeconomic groups experience higher metabolic risk. Lower socioeconomic groups are more likely facing restricted caloric intake and/or physically active in their jobs, thereby counterbalancing other high risk behaviors such as tobacco use and low fruit and vegetable intake[25, 26].

Participants with CKD in the CARRS study demonstrated more severe kidney disease, and most were not effectively managing risk factors. When restricting to participants with CKD who also had a college degree or were in the top tertile of income–so a cohort more similar to the MASALA participants–the proportion of patients on medications increased but a vast majority (90% or more with diabetes or hypertension) were not meeting targets. Clearly a lack of awareness of their condition[27, 28] is a major reason, but even among those with a diagnosis of diabetes or hypertension, there is little understanding of the need for regular medical care[29]. In a large survey performed in Chennai, only 40% of patients with diabetes knew that their disease could lead to any organ complications[30]. Many experts also point to 'clinical inertia' in initiating and titrating medications[31, 32]. In an international comparison of physicians practices in managing diabetes, Indian physicians were among the most likely to delay insulin therapy[33].

The lack of glycemic and blood pressure control has important implications for consequent ESRD. Follow up data from the ADVANCE trial—which recruited participants from India, China, and Eastern European countries in addition to HIC—demonstrate that hemoglobin A1c can serve as a universal and significant predictor of ESRD[17]. If we apply the event rates from the standard arm follow up of this trial, CARRS participants with diabetes and CKD are at 40% higher risk of experiencing ESRD or death due to kidney disease, since a much larger proportion of them currently have hemoglobin A1c $\geq$ 8%. On the other hand, the ADVANCE trial also proves that aggressively treating these risk factors can mitigate the most serious risks associated with CKD in persons from a range of ethnicities, living in settings with a range of healthcare resources [34].

Even among highly educated participants of the MASALA study (nearly all of whom avoid smoking and eat fruits and vegetables regularly), we identified significant gaps in meeting targets for diabetes or hypertension management in the participants with CKD. Similar gaps are noted in the rest of the U.S. Using data from the 2005–2010 NHANES, the United States Renal Data System reports that 48% of participants with CKD and diabetes had A1c $<$ 7.0%; 51% meet this target in MASALA[35]. About a third of participants with CKD in our study and in NHANES 2005–2010 [36] have been prescribed angiotensin converting enzyme inhibitors or angiotensin II receptor blockers.

Our study has several strengths. First, since a majority of participants in the MASALA study were born in India, we were able to test the impact of "residence" (i.e., U.S. metropolitan versus Indian metropolitan areas) in genetically similar populations. Second, both studies used standardized and comparable methodologies for laboratory, blood pressure, and anthropometric ascertainment. Because both albuminuria and IDMS-standardized serum creatinine were measured in the studies, we were able to use the most widely-accepted definition of CKD. Detailed ascertainment of medication use allowed us to compare management of risk factors among participants with CKD.

Limitations of our study include the different eligibility criteria and sampling techniques used in CARRS and MASALA, and while we attempted to select a subset of CARRS cohort to match MASALA entry criteria, important demographic differences in the two studies' participants remain a source of bias. Most strikingly and as reflective of South Asian immigrants to the U.S., the MASALA participants attained a much higher level of education than CARRS participants. Serum creatinine was also measured via two different assays in the two studies, but the two have been shown to have excellent agreement[10] and were calibrated against the same standard (IDMS)[7], further minimizing inter-assay variation. Both studies only assessed serum creatinine and urine albumin to creatinine at a single time point, and both may therefore be over-estimating the prevalence of CKD since we cannot assess for persistence of abnormal results. Since we studied only urban populations, we cannot generalize to the entire populations of Indians living in either region. Finally, the overall nature of our cross-sectional analyses is descriptive, without ability to draw causal inferences.

In conclusion, the prevalence of CKD in Indians living in Indian and U.S. cities is similar. When we compare the risk profile of individuals with CKD, it is evident that those living in Indian cities are substantially more likely to face worse outcomes. As more and more people living in LMIC move to urban settings, their likelihood of disease may be similar, but likelihood of receiving effective treatment is much lower than counterparts living in HIC. Focused and contextually-appropriate programs targeting aggressive metabolic control can help close these gaps.

Supporting information

S1 File. Figures A-B: Study flowcharts demonstrating creation of analytic group. Figures C-E: Distribution of log-albumin to creatinine ratio in CARRS versus MASALA participants with albuminuria.
(DOCX)

S2 File. Table A. Age and education in participants with and without available information on albuminuria and serum creatinine in the CARRS* study. Table B. Age-stratified CKD prevalence in CARRS and MASALA studies. Table C: Albuminuria in the CARRS and MASALA studies. Table D: CKD prevalence (%) difference, after adjustment.
(DOCX)

Author Contributions

Conceptualization: SA AK MA VN DP GMC.

Data curation: DK KS PG.

Formal analysis: MMR YZ.

Funding acquisition: SA AK NK DP NT MA VN.

Investigation: RS RG AV RP VM.

Methodology: RG RS DK MMR.

Project administration: RS AK NK.

Resources: RG.

Software: YZ PG KS.

Supervision: AK NK DP NT MA VN GMC.

Validation: MMR YZ.

Visualization: MMR YZ SA.

Writing – original draft: SA.

Writing – review & editing: SA MA VN GMC.

References

1. Luke A, Durazo-Arvizu R, Rotimi C, Prewitt TE, Forrester T, Wilks R, et al. Relation between body mass index and body fat in black population samples from Nigeria, Jamaica, and the United States. American journal of epidemiology. 1997; 145(7):620–8. PMID: 9098179
2. Bhatnagar D, Anand IS, Durrington PN, Patel DJ, Wander GS, Mackness MI, et al. Coronary risk factors in people from the Indian subcontinent living in west London and their siblings in India. Lancet. 1995; 345(8947):405–9. PMID: 7853948
3. Robertson TL, Kato H, Rhoads GG, Kagan A, Marmot M, Syme SL, et al. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California. Incidence of myocardial infarction and death from coronary heart disease. The American journal of cardiology. 1977; 39 (2):239–43. PMID: 835482
4. Gujral UP, Narayan KM, Pradeepa RG, Deepa M, Ali MK, Anjana RM, et al. Comparing Type 2 Diabetes, Prediabetes, and Their Associated Risk Factors in Asian Indians in India and in the U.S.: The CARRS and MASALA Studies. Diabetes care. 2015; 38(7):1312–8. PubMed Central PMCID: PMC4477335. https://doi.org/10.2337/dc15-0032 PMID: 25877810
5. Nair M, Ali MK, Ajay VS, Shivashankar R, Mohan V, Pradeepa R, et al. CARRS Surveillance study: design and methods to assess burdens from multiple perspectives. BMC public health. 2012; 12:701. PubMed Central PMCID: PMC3491014. https://doi.org/10.1186/1471-2458-12-701 PMID: 22928740
6. Kanaya AM, Kandula N, Herrington D, Budoff MJ, Hulley S, Vittinghoff E, et al. Mediators of Atherosclerosis in South Asians Living in America (MASALA) study: objectives, methods, and cohort description. Clinical cardiology. 2013; 36(12):713–20. PubMed Central PMCID: PMC3947423. https://doi.org/10.1002/clc.22219 PMID: 24194499
7. Myers GL, Miller WG, Coresh J, Fleming J, Greenberg N, Greene T, et al. Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. Clin Chem. 2006; 52(1):5–18. https://doi.org/10.1373/clinchem.2005.0525144 PMID: 16332993
8. Mazzachi BC, Peake MJ, Ehrhardt V. Reference range and method comparison studies for enzymatic and Jaffe creatinine assays in plasma and serum and early morning urine. Clin Lab. 2000; 46(1–2):53–5. PMID: 10745982
9. Junge W, Wilke B, Halabi A, Klein G. Determination of reference intervals for serum creatinine, creatinine excretion and creatinine clearance with an enzymatic and a modified Jaffe method. Clin Chim Acta. 2004; 344(1–2):137–48. https://doi.org/10.1016/j.cccn.2004.02.007 PMID: 15149882
10. Peake M, Whiting M. Measurement of serum creatinine—current status and future goals. Clin Biochem Rev. 2006; 27(4):173–84. PubMed Central PMCID: PMCPMC1784008. PMID: 17581641
11. Stevens PE, Levin A, Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group M. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Annals of internal medicine. 2013; 158(11):825–30. https://doi.org/10.7326/0003-4819-158-11-201306040-00007 PMID: 23732715
12. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Annals of internal medicine. 2009; 150(9):604–12. PubMed Central PMCID: PMC2763564. PMID: 19414839

13. Zou G. A modified poisson regression approach to prospective studies with binary data. American journal of epidemiology. 2004; 159(7):702–6. PMID: 15033648

14. Montez-Rath ME, Winkelmayer WC, Desai M. Addressing missing data in clinical studies of kidney diseases. Clinical journal of the American Society of Nephrology: CJASN. 2014; 9(7):1328–35. PubMed Central PMCID: PMC4078963. https://doi.org/10.2215/CJN.10141013 PMID: 24509298

15. Lee KJ, Carlin JB. Multiple imputation for missing data: fully conditional specification versus multivariate normal imputation. American journal of epidemiology. 2010; 171(5):624–32. https://doi.org/10.1093/aje/kwp425 PMID: 20106935

16. Perkovic V, Joshi R, Patel A, Bompoint S, Chalmers J, Group AC. ADVANCE: lessons from the run-in phase of a large study in type 2 diabetes. Blood Press. 2006; 15(6):340–6. PMID: 17472024

17. Wong MG, Perkovic V, Chalmers J, Woodward M, Li Q, Cooper ME, et al. Long-term Benefits of Intensive Glucose Control for Preventing End-Stage Kidney Disease: ADVANCE-ON. Diabetes care. 2016; 39(5):694–700. https://doi.org/10.2337/dc15-2322 PMID: 27006512

18. Liese AD, Hense HW, Doring A, Stieber J, Keil U. Microalbuminuria, central adiposity and hypertension in the non-diabetic urban population of the MONICA Augsburg survey 1994/95. J Hum Hypertens. 2001; 15(11):799–804. https://doi.org/10.1038/sj.jhh.1001266 PMID: 11687925

19. Bello AK, de Zeeuw D, El Nahas M, Brantsma AH, Bakker SJ, de Jong PE, et al. Impact of weight change on albuminuria in the general population. Nephrol Dial Transplant. 2007; 22(6):1619–27. https://doi.org/10.1093/ndt/gfm091 PMID: 17360767

20. Chandie Shaw PK, Berger SP, Mallat M, Frolich M, Dekker FW, Rabelink TJ. Central obesity is an independent risk factor for albuminuria in nondiabetic South Asian subjects. Diabetes care. 2007; 30(7):1840–4. https://doi.org/10.2337/dc07-0028 PMID: 17456841

21. Gansevoort RT, Verhave JC, Hillege HL, Burgerhof JG, Bakker SJ, de Zeeuw D, et al. The validity of screening based on spot morning urine samples to detect subjects with microalbuminuria in the general population. Kidney Int Suppl. 2005;(94):S28–35. https://doi.org/10.1111/j.1523-1755.2005.09408.x PMID: 15752236

22. Chronic Kidney Disease Prognosis C, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010; 375(9731):2073–81. PubMed Central PMCID: PMCPMC3993088. https://doi.org/10.1016/S0140-6736(10)60674-5 PMID: 20483451

23. Fox CS, Matsushita K, Woodward M, Bilo HJ, Chalmers J, Heerspink HJ, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. Lancet. 2012; 380(9854):1662–73. PubMed Central PMCID: PMCPMC3771350. https://doi.org/10.1016/S0140-6736(12)61350-6 PMID: 23013602

24. Adler NE, Boyce T, Chesney MA, Cohen S, Folkman S, Kahn RL, et al. Socioeconomic status and health. The challenge of the gradient. Am Psychol. 1994; 49(1):15–24. PMID: 8122813

25. Rosero-Bixby L, Dow WH. Surprising SES Gradients in mortality, health, and biomarkers in a Latin American population of adults. J Gerontol B Psychol Sci Soc Sci. 2009; 64(1):105–17. PubMed Central PMCID: PMCPMC2654981. https://doi.org/10.1093/geronb/gbn004 PMID: 19196695

26. Ali MK, Bhaskarapillai B, Shivashankar R, Mohan D, Fatmi ZA, Pradeepa R, et al. Socioeconomic status and cardiovascular risk in urban South Asia: The CARRS Study. Eur J Prev Cardiol. 2016; 23(4):408–19. https://doi.org/10.1177/2047487315580891 PMID: 25917221

27. Anchala R, Kannuri NK, Pant H, Khan H, Franco OH, Di Angelantonio E, et al. Hypertension in India: a systematic review and meta-analysis of prevalence, awareness, and control of hypertension. J Hypertens. 2014; 32(6):1170–7. PubMed Central PMCID: PMCPMC4011565. https://doi.org/10.1097/HJH.0000000000000146 PMID: 24621804

28. Deepa M, Grace M, Binukumar B, Pradeepa R, Roopa S, Khan HM, et al. High burden of prediabetes and diabetes in three large cities in South Asia: The Center for cArdio-metabolic Risk Reduction in South Asia (CARRS) Study. Diabetes Res Clin Pract. 2015; 110(2):172–82. PubMed Central PMCID: PMCPMC4752677. https://doi.org/10.1016/j.diabres.2015.09.005 PMID: 26432412

29. Bjork S, Kapur A, King H, Nair J, Ramachandran A. Global policy: aspects of diabetes in India. Health Policy. 2003; 66(1):61–72. PMID: 14499166

30. Mohan D, Raj D, Shanthirani CS, Datta M, Unwin NC, Kapur A, et al. Awareness and knowledge of diabetes in Chennai—the Chennai Urban Rural Epidemiology Study [CURES-9]. J Assoc Physicians India. 2005; 53:283–7. PMID: 15987011

31. Wangnoo SK, Maji D, Das AK, Rao PV, Moses A, Sethi B, et al. Barriers and solutions to diabetes management: An Indian perspective. Indian J Endocrinol Metab. 2013; 17(4):594–601. PubMed Central PMCID: PMCPMC3743358. https://doi.org/10.4103/2230-8210.113749 PMID: 23961474

32. Hasan H, Zodpey S, Saraf A. Diabetologist's perspective on practice of evidence based diabetes management in India. Diabetes Res Clin Pract. 2012; 95(2):189–93. https://doi.org/10.1016/j.diabres.2011.09.021 PMID: 22001282

33. Peyrot M, Rubin RR, Lauritzen T, Skovlund SE, Snoek FJ, Matthews DR, et al. Resistance to insulin therapy among patients and providers: results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study. Diabetes care. 2005; 28(11):2673–9. PMID: 16249538

34. Zoungas S, de Galan BE, Ninomiya T, Grobbee D, Hamet P, Heller S, et al. Combined effects of routine blood pressure lowering and intensive glucose control on macrovascular and microvascular outcomes in patients with type 2 diabetes: New results from the ADVANCE trial. Diabetes care. 2009; 32(11):2068–74. PubMed Central PMCID: PMCPMC2768202. https://doi.org/10.2337/dc09-0959 PMID: 19651921

35. USRDS Atlas of CKD [Internet]. National Institute of Diabetes and Digestive and Kidney Diseases. 2012.

36. Sonawane KB, Qian J, Hansen RA. Utilization patterns of antihypertensive drugs among the chronic kidney disease population in the United States: a cross-sectional analysis of the national health and nutrition examination survey. Clin Ther. 2015; 37(1):188–96. https://doi.org/10.1016/j.clinthera.2014.11.011 PMID: 25524390

37. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 2003; 35(8):1381–95. https://doi.org/10.1249/01.MSS.0000078924.61453.FB PMID: 12900694

38. Ainsworth BE, Irwin ML, Addy CL, Whitt MC, Stolarczyk LM. Moderate physical activity patterns of minority women: the Cross-Cultural Activity Participation Study. J Womens Health Gend Based Med. 1999; 8(6):805–13. https://doi.org/10.1089/152460999319129 PMID: 10495261

39. Kelemen LE, Anand SS, Vuksan V, Yi Q, Teo KK, Devanesen S, et al. Development and evaluation of cultural food frequency questionnaires for South Asians, Chinese, and Europeans in North America. J Am Diet Assoc. 2003; 103(9):1178–84. https://doi.org/10.1053/jada.2003.50578 PMID: 12963948