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Very High Prevalence of Albuminuria among Adults in Northern India, Not Explained by Traditional Risk Factors: A Cause for Concern

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ABSTRACT

Objectives: India is witnessing a disturbing growth in non-communicable diseases (NCDs), including chronic kidney disease (CKD). Recently, a WHO STEPS survey was conducted in the state of Punjab, India to collect data from the adult population on NCD risk factors. We sought to compare the prevalence of CKD and its risk factors between this large state in northern India and the United States.

Setting: Samples were drawn from both locations, Punjab, India and the US, using multi-stage stratified sampling designs to collect data representative of the general population.

Participants: Data from 2,002 participants in the Punjab survey (2014-2015) and 5,057 in the US (National Health and Nutrition Examination Survey (NHANES; 2013-2014), between the ages of 18-69 years were examined.

Primary and secondary outcome measures: Modified Poisson regression was employed to compare prevalence rates between the two countries for markers of CKD and its risk factors. All analyses used sampling weights.

Results: The average age in the Punjab sample was significantly lower than the US (38.3 vs. 42.5 years, $p<0.0001$). While smoking and obesity were higher in the US, hypertension was much more common in Punjab (48.2% vs. 33.4%, $p<0.0001$). Significant differences were seen in the prevalence of CKD, with lower prevalence of eGFR < 60 ml/min/1.73m^2 (2.0% vs. 3.8%, $p<0.0001$), but markedly higher prevalence of albuminuria (46.7% vs. 8.9%, $p<0.0001$) in Punjab. These differences could not be explained by traditional risk factors such as diabetes and hypertension.

Conclusions: We report a strikingly high prevalence of albuminuria in Punjab, India, compared with the United States. This requires further study and may have enormous public

health implications for future burden of progressive CKD, end stage renal disease, morbidity, mortality, and specifically for elevated risk or presence of cardiovascular disease in the northern state of Punjab, India.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

Strengths:

- Representative Samples from both the State of Punjab, India and the United States
- Uniform laboratory testing for identification of kidney disease
- Comprehensive data collection on anthropomorphic measurements, laboratory measurements, comorbid conditions, and health behaviors

Limitations:

- Cross-sectional study design cannot establish causality
- Because the sample from India was only from one state, the Punjab, we cannot generalize our findings to all of India

INTRODUCTION

The state of Punjab - indeed all of India, similar to other low and middle income countries (LMICs), is witnessing a disturbing growth in NCDs.[1] The country faces this epidemiologic transition while continuing to grapple with the problem of communicable diseases, which still remain a significant burden.[2] With this knowledge, the Department of Health and Family Welfare in Punjab, India, worked closely with the Post Graduate Institute of Medical Education and Research, Chandigarh, India, and medical colleges in the state to conduct the first representative survey of NCDs in the state of Punjab in 2014 and 2015.

The goal of this survey was to collect critical and up to date data on risk factors for NCDs in Punjab, with the hope of improving health planning and implementation of state initiatives, such as the National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular disease and Stroke (NPCDCS).[3] This survey provides a wealth of data on both risk factors for kidney disease and kidney disease itself, comparable to data collected in the United States from the National Health and Nutrition Examination Survey (NHANES).

Previous work utilizing data from this source have shown an alarmingly high prevalence of hypertension (40.1%) and pre-hypertension (40.8%) in the region, with approximately 70% of these individuals being unaware of their condition.[4] Similarly, although less prevalent, diabetes was found in 8.3% (6.3% with pre-diabetes) participants, with only 18% of individuals being aware of their disease.[5] Since diabetes and hypertension are two of the key risk factors for kidney disease, we hypothesized that the state of Punjab may be experiencing or on the verge of experiencing a significant burden of kidney disease.

Therefore, in the current study we sought to examine the prevalence of CKD (both low glomerular filtration rate and albuminuria) and risk factors for CKD, comparing the Punjab to a

representative sample of individuals from the US National Health and Nutrition Examination Survey (NHANES). In addition, we also sought to compare the magnitude of the associations between risk factors and CKD in the two countries.

MATERIALS AND METHODS

Study Sample

The STEPS survey of non-communicable disease (NCD) risk factors was carried out from June 2014 to August 2015 in Punjab.[3] A multi-stage stratified sampling design was used to generate representative data for two age-groups (18-44, 45-69), sex, and area of residence in the state. A total of 5,127 adults, ages 18-69 years, participated in the survey. The overall response rate for STEP1/2 and STEP 3 was 95% and 93% respectively. Data were collected in three steps: Socio-demographic and behavioral information was collected in Step 1, physical measurements such as height, weight and blood pressure were done in Step 2, and biochemical measurements were undertaken to assess salt intake, blood glucose, triglycerides and cholesterol levels in Step 3. This analysis included individuals from STEP 3 of the survey, which was carried out in a subset of 2700 participants. A total of 2,002 individuals who had complete data on both albuminuria and serum creatinine were analyzed. Specific sample weights were available for the individuals included in STEP 3.

The US data for comparison were from the 2013-2014 National Health and Nutrition Examination Survey (NHANES), included 5,057 individuals. Multi-stage stratified sampling design was used to collect data representative of the US general population.[6] The NHANES is supported by the National Center for Health Statistics and was designed to assess the health and nutritional status of adults and children in the United States. The study combines interviews,

physical examinations, laboratory tests, and participant lifestyle surveys. Individuals between the ages of 18 and 69 years, with complete information on estimated glomerular filtration rate and albuminuria, were examined to match with the Punjab sample.

Patient and Public Involvement

The research question was assessed using existing data taken from large, representative surveys, which contained more health questions and health measures than those presented in this work. The aim of the larger studies were to assess the overall health of each region, focused on diseases of global health impact, rather than individual patient priorities. The NHANES program began in the early 1960s, as a series of surveys focusing on different population groups or health topics over time. Participants were not involved in the design of the study, recruitment, or conduct of the study. NHANES participants receive their results from their examination as a preliminary report when leaving the exam center. A final report of findings is sent to each participant through the mail 12-16 weeks after their exam. Patients are free to discuss their results with their doctor and to keep for their own medical records.

Similarly, the Punjab STEPS survey was a state-level public health effort undertaken to estimate the burden of many non-communicable diseases in that region. The government funded study, similar to NHANES did not enlist patient opinion during study design, but did have a plan to provide results to patients if abnormal and warranting medical follow-up.

Measures

Kidney function was assessed by estimated glomerular filtration rate (eGFR), calculated with using the CKD-Epi formula in both samples, employing the coefficients for White race in India.[7] Albuminuria was defined as a urine albumin to creatinine ratio (UACR) > 30 mg/g. Kidney disease was also assessed using the KDIGO risk categories, which places individuals into four risk groups for mortality based on their eGFR and UACR levels (low risk: eGFR > 60 and UACR < 30; moderately high risk: eGFR 45-59 with UACR < 30 or eGFR > 60 with UACR 30-300; high risk: eGFR 30-44 with UACR < 30, eGFR 45-59 with UACR 30-300, or eGFR > 60 with UACR > 300; or very high risk: eGFR < 30, eGFR 30-44 with UACR > 30, or eGFR 45-59 with UACR > 300.[8]

Risk factors for kidney disease were defined similarly between the two samples. Diabetes was defined by presence of any of the following: being told by a doctor they had diabetes or taking medication for diabetes (including medication from traditional healers in India). Hypertension was defined as any of the following: being told by a doctor they had hypertension, taking medications for hypertension, or having systolic blood pressure (SBP) > 140mmHg or diastolic blood pressure (DBP) > 90mmHg.

Different cut-points for identifying obesity were used between countries to account for the differences in stature. In the US, the WHO definition was employed where underweight was defined as BMI < 18.5, normal weight as BMI 18.5 – 24.99, overweight as BMI 25 – 29.99, and obese as BMI ≥ 30 kg/m^2. In Punjab obesity was defined using the same criteria as other published papers using this survey data with underweight being defined as BMI < 18.5, normal weight as BMI 18.5 – 22.99, overweight as BMI 23 – 26.99, and obese as BMI ≥ 27 kg/m^2.[1-3]

Statistical Analysis

Demographic, socio-economic, anthropometric, health status, and markers of kidney disease were compared between counties using sample weighted t-tests or Chi-square tests. Associations between patient characteristics and risk factors for kidney disease with laboratory markers of kidney disease were modeled using modified Poisson regression with robust errors. This modeling approach was chosen, as opposed to logistic regression, because it yields estimates of prevalence ratios (PRs), rather than odds ratios.[9,10] PR estimates were determined for the kidney disease risk factors within each country using interactions between a country indicator variable and each measure.

Analysis of de-identified data received from the Punjab WHO Steps Survey for this study was deemed IRB exempt by the University of Michigan IRB. NHANES data is publically available for use by researchers and does not require an IRB approval.

RESULTS

Many differences exist between individuals in Punjab and the US, as shown in Table 1. The mean age was approximately four years younger in Punjab ($p<0.0001$), with a higher proportion of men (58.2% vs. 48.9%, $p<0.0001$) compared with the US. The US had a much higher percentage of both high school or higher education and private health insurance coverage ($p<0.0001$). Overall body size was very different, with Punjab residents being 6 cm shorter, weighing 18 kilograms less, having 10 cm smaller waist circumference, and BMI lower by 4.6 kg/m^2 (all $p<0.0001$). Comparison of obesity by categories showed a higher percentage of individuals in Punjab as underweight (11.3% vs. 1.5% in the US) and a higher proportion of obese individuals in the US (37.9% vs. 28.9%, $p<0.0001$), while proportions of those in the normal or overweight categories were very similar. While smoking was higher in the US,

hypertension was much more common in Punjab (48.2% vs. 33.4%, p<0.0001). No differences were seen in the prevalence of diabetes, cardiovascular disease, or triglyceride levels, although the US had higher total cholesterol levels (4.9 vs. 3.9 mmol/L [189 vs. 150 mg/dL] in Punjab, p<0.0001).

Table 1: Comparison of Weighted Survey Sample Participant Characteristics between the Adult Populations in the State of Punjab, India and the United States

Measure	Punjab (2014-2015)		US (2013-2014)		P value
	N	Mean (SE) or %	N	Mean (SE) or %	
Age (years)	2,002	38.3 (0.60)	5,057	42.5 (0.38)	<0.0001
Male (%)	2,002	58.2%	5,057	48.9%	0.0001
Education to high school or above (%)	2,002	43.4%	4,718	85.3%	<0.0001
Health Insurance (%)	2,002	6.2%	5,052	79.8%	<0.0001
Height (cm)	1,986	163.0 (0.37)	5,008	169.0 (0.31)	<0.0001
Weight (Kg)	1,993	65.4 (0.6)	5,006	83.5 (0.54)	<0.0001
BMI (kg/m^2) *	1,982	24.6 (0.23)	5,000	29.2 (0.20)	<0.0001
Underweight	1,982	11.3	5,000	1.5	<0.0001
Normal		29.5		29.1	
Overweight		30.3		31.5	
Obese		28.9		37.9	
Waist (cm)	1,995	89.0 (0.62)	4,836	98.8 (0.38)	<0.0001
Current smoker (%)	2,002	7.5%	5,057	21.6%	<0.0001
Diabetes (%)	1,043	7.7%	5,057	8.9%	0.42
Hypertension (%)	2,000	48.2%	5,057	33.4%	<0.0001
CVD (%)	1,989	4.6%	5,057	3.4%	0.08
Triglyceride (mmol/L)	2,001	1.4 (0.04)	2,294	1.4 (0.04)	0.35
Total cholesterol (mmol/L)	2,002	3.9 (0.06)	4,812	4.9 (0.02)	<0.0001
Creatinine (µmol/L)	2,002	0.70 (0.01)	4,798	0.88 (0.01)	<0.0001
eGFR (mL/min/1.73m^2)	2,002	114.8 (1.1)	4,798	97.8 (0.6)	<0.0001
ACR (mg/mmol; median)	1,928	2.5 (0.25)	4,971	0.66 (0.07)	<0.0001
eGFR < 60 ml/min/1.73m^2	2,002	2.0%	4,798	3.8%	<0.0001
ACR > 3 mg/mmol	1,928	46.7%	4,971	8.9%	<0.0001

Although Punjab had a lower prevalence of eGFR < 60 ml/min/1.73m^2 (2.0% vs. 3.8%, p<0.0001), the prevalence of albuminuria was five times higher (46.7% vs. 8.9%, p<0.0001). When assessing kidney function using the KDIGO risk categories (Table 2), the high prevalence of high UACR lead to 46.2% of participants in Punjab being classified as "moderately high risk", compared to only 9.1% in the US. In contrast, Punjab had only 1.4% in the "high risk" or "extremely high risk" groups compared to 2.1% in the US (Figure 1).

Table 2: Prevalence of Albuminuria and eGFR KDIGO Risk Categories among Adults in Punjab and United States

Punjab, India				Albuminuria categories			Total
				A1	A2	A3	
				Normal to mildly increased	Moderately increased	Severely increased	
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol	
GFR categories ($ml/min/1.73\ m^2$)	G1	Normal to high	≥90	46.7	42.0	0.2	88.9
	G2	Mildly decreased	60-89	5.7	3.5	0	9.2
	G3a	Mildly to mod decreased	45-59	0.7	0.5	0	1.2
	G3b	Mod to severe decreased	30-44	0.3	0.5	0	0.8
	G4	Severely decreased	15-29	0.03	0.01	0	0.04
	G5	Kidney failure	<15	0	0	0	0
Total				53.4	46.5	0.2	100

United States				Albuminuria categories			Total
				A1	A2	A3	
				Normal to mildly increased	Moderately increased	Severely increased	
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol	
GFR categories ($ml/min/1.73\ m^2$)	G1	Normal to high	≥90	60.7	4.8	0.5	66.0
	G2	Mildly decreased	60-89	28.1	2.2	0.1	30.4
	G3a	Mildly to mod decreased	45-59	2.1	0.4	0.2	2.7
	G3b	Mod to severe decreased	30-44	0.3	0.2	0.1	0.6
	G4	Severely decreased	15-29	0.05	0.05	0.09	0.2
	G5	Kidney failure	<15	0	0.06	0.07	0.1
Total				91.2	7.7	1.1	91.3

To compare the magnitude of association between traditional risk factors for CKD between the two countries, we modeled prevalence ratios in each country within one model to allow for the associations to be compared statistically (Table 3). When examining low eGFR (< 60 ml/min/1.73m^2) as the outcome, male participants in Punjab showed a much lower prevalence compared with females (prevalence ratio: PR=0.22, p=0.007); while no association was seen in the US between sex and low eGFR (PR=1.09, p=0.56). These associations were significantly different from each other with p=0.006. Another difference between the associations and outcome was seen for hypertension (p=0.008), where a non-significant lower prevalence ratio was observed in Punjab (PR=0.75, p=0.43) and a strong positive association was seen in the US (PR=2.24, p<0.0001). Similar positive associations were seen in both countries for older age, higher education level, CVD, and DM on the prevalence of low eGFR.

Table 3b displays the associations between patient factors and the prevalence of albuminuria. Significant differences between the countries was again seen with sex and the outcome (p=0.02). No association between sex and albuminuria was seen in Punjab, where in the US males had a lower prevalence of albuminuria (PR=0.77, p=0.004). While in both countries hypertension and DM were associated with a higher prevalence of albuminuria, the magnitude of association was much stronger in the US (PR=1.19 in Punjab vs. PR=1.93 in the US for hypertension and PR=1.32 in Punjab vs. PR=2.54 in the US for DM). Current smoking was associated with albuminuria only in the US (PR=1.34, p=0.002), while higher total cholesterol was associated with albuminuria in the Punjab (PR=1.11 per 0.5 mmol/L higher total cholesterol).

When combining low eGFR and albuminuria into a composite (CKD) outcome (Table 3c) more differences were found between the countries in certain associations. Significantly larger associations were found in the US for the relationship between older age, hypertension, DM, and BMI; while a larger association was seen between total cholesterol and the composite CKD measure in the Punjab.

Table 3: Prevalence Ratios for Markers of CKD by Risk Factors

A. Low eGFR (eGFR < 60 ml/min/1.73m^2)

Measure	Punjab			US			P-value for interaction
	PR	95% CI	P	PR	95% CI	P	
Age (per 10 years)	1.73	1.29 – 2.31	0.0002	2.14	1.82 – 2.52	<0.0001	0.20
Male (vs. Female)	0.22	0.07 – 0.66	0.007	1.09	0.81 – 1.47	0.56	***0.006***
Education high school + (vs. no)	1.86	0.84 – 4.10	0.13	1.53	1.06 – 2.20	0.02	0.66
Current smoker (vs. no)	2.32	0.31 – 1.74	0.41	0.92	0.63 – 1.34	0.66	0.38
Hypertension (vs. no)	0.75	0.37 – 1.52	0.43	2.24	1.51 – 3.33	<0.0001	***0.008***
DM (vs. no)	2.75	1.17 – 6.48	0.02	1.76	1.27 – 2.44	0.0007	0.34
CVD (vs. no)	1.11	0.34 – 3.60	0.87	1.98	1.20 – 1.38	0.0002	0.35
Total Cholesterol (per 20 mg/dl, per 0.5 mmol/L)	1.09	0.73 – 1.64	0.67	0.92	0.76 – 1.11	0.36	0.44
BMI (per 5 Kg/m^2)	0.82	0.59 – 1.15	0.25	1.13	1.04 – 1.23	0.006	0.07
Obesity:							
Underweight	1.24	0.26 – 5.95	0.79	1.45	0.36 – 5.89	0.60	0.88
Healthy weight	1.00	-	ref	1.00	-	ref	
Overweight	2.63	1.09 – 6.34	0.03	1.31	0.83 – 2.07	0.25	0.17
Obese	0.73	0.27 – 1.95	0.53	1.40	0.91 – 2.14	0.13	0.23

B. Albuminuria (ACR > 30 mg/g, 3 mg/mmol)

Measure	Punjab			US			P-value for interaction
	PR	95% CI	P	PR	95% CI	P	
Age (per 10 years)	1.03	0.99 – 1.08	0.16	1.06	0.98 – 1.14	0.15	0.60
Male (vs. Female)	0.99	0.88 – 1.12	0.93	0.77	0.65 – 0.92	0.004	***0.02***
Education high school + (vs. no)	0.99	0.88 – 1.11	0.80	0.81	0.67 – 0.98	0.03	0.09
Current smoker (vs. no)	1.09	0.85 – 1.40	0.48	1.35	1.11 – 1.63	0.002	0.20
Hypertension (vs. no)	1.19	1.06 – 1.34	0.005	1.93	1.59 – 2.36	<0.0001	***<0.0001***
DM (vs. no)	1.32	1.12 – 1.56	0.0008	2.54	2.07 – 3.13	<0.0001	***<0.0001***
CVD (vs. no)	1.14	0.92 – 1.37	0.24	1.32	1.16 – 0.99	0.06	0.37
Total Cholesterol (per 20 mg/dl, per 0.5 mmol/L)	1.11	1.04 – 1.17	0.001	0.99	0.90 – 1.09	0.81	***0.05***
BMI (per 5 Kg/m^2)	0.99	0.94 – 1.03	0.54	1.04	0.98 – 1.10	0.19	0.16
Obesity:							
Underweight	0.90	0.72 – 1.11	0.32	1.20	0.56 – 2.56	0.64	0.47
Healthy weight	1.00	-	ref	1.00	-	ref	-
Overweight	0.95	0.82 – 1.10	0.48	0.93	0.72 – 1.18	0.53	0.85
Obese	0.95	0.83 – 1.09	0.48	1.01	0.80 – 1.27	0.96	0.68

C. CKD (low eGFR or Albuminuria)

Measure	Punjab			US			P-value for interaction
	PR	95% CI	P	PR	95% CI	P	
Age (per 10 years)	1.04	1.00 – 1.09	0.06	1.20	1.12 – 1.29	<0.0001	***0.0007***
Male (vs. Female)	0.97	0.86 – 1.09	0.58	0.81	0.70 – 0.94	0.007	0.0686
Education high school + (vs. no)	1.00	0.90 – 1.12	0.96	0.91	0.77 – 1.09	0.31	0.379
Current smoker (vs. no)	1.09	0.85 – 1.40	0.49	1.26	1.06 – 1.49	0.008	0.3526
Hypertension (vs. no)	1.18	1.05 – 1.33	0.006	1.87	1.57 – 2.23	<0.0001	***<0.0001***
DM (vs. no)	1.35	1.16 – 1.58	0.0002	2.11	1.77 – 2.53	<0.0001	***0.0002***
CVD (vs. no)	1.13	0.94 – 1.37	0.19	1.49	1.12 – 1.18	0.0006	0.072
Total Cholesterol (per 20 mg/dl, per 0.5 mmol/L)	1.09	1.04 – 1.16	0.002	0.97	0.88 – 1.05	0.41	***0.02***
BMI (per 5 Kg/m^2)	0.98	0.94 – 1.03	0.48	1.06	1.01 – 1.12	0.017	***0.025***
Obesity:							
Underweight	0.89	0.72 – 1.10	0.28	1.31	0.67 – 2.54	0.43	0.28
Healthy weight	1.00	-	ref	1.00	-	ref	-
Overweight	0.98	0.86 – 1.13	0.81	0.98	0.79 – 1.22	0.84	0.97
Obese	0.95	0.83 – 1.09	0.48	1.06	0.86 – 1.29	0.60	0.41

Figure 2 displays the changes in prevalence ratios comparing US to Punjab for each marker of CKD with different levels of adjustment for traditional risk factors examined in Table 3. Before accounting for any differences in participants in the two studies, the prevalence of low eGFR was much higher in the US (PR=2.16), but after accounting for demographics and other health measures, the US has a much lower prevalence of low eGFR compared to Punjab (PR=0.13, and 0.05, respectively), suggesting that if the US had the same patient make up as Punjab, the prevalence of low eGFR would be much lower. The findings for albuminuria and any CKD

were very similar in showing that before adjustment the prevalence of either marker was much lower in the US (PR=0.24 and 0.29, respectively) and accounting for difference in demographics and health measures between the countries changed these estimates very little. These results suggest that traditional risk factors do not entirely explain the difference in prevalence seen among markers of kidney disease between the US and Punjab.

DISCUSSION

In comparing two representative samples of patients from the adult population of Punjab, India and the United States, we found a very high prevalence of albuminuria in the Punjab, with almost half of the residents with urine ACR > 3 mg/mmol (30 mg/g). This is in contrast to the prevalence of albuminuria in the US of approximately 9%. When examining glomerular filtration rate, the Punjab had much higher average eGFR and a lower prevalence of eGFR < 60 ml/min/1.73m^2 (2.0% vs. 3.8%). Because of the high prevalence of albuminuria in the Punjab, almost half the population falls into the "moderately high risk" CKD risk category per KDIGO risk stratification criteria. Even more striking is the fact that the between country differences in the prevalence estimates of albuminuria could not be explained by traditional risk factors for CKD, such as age, hypertension, and diabetes.

If true, these findings have enormous public health and resource implications for a low-middle income country such as India, specifically in the realm of CKD, cardiovascular disease and other NCDs. Currently there are no definitive estimates of prevalence of chronic kidney disease in India, as there is no ongoing national kidney registry/surveillance system. Recent publications have suggested that 220,000 patients are diagnosed with ESRD every year.[11] It is estimated that this will result in demand for an additional 34 million dialysis sessions in India

each year. Besides the growing population of patients with kidneys disease, the country is faced with a shortage of nephrologists, late referral of patients, inadequate health awareness about preventive measures, and a lack of more cost-effective alternatives like renal transplantation or peritoneal dialysis (PD).[11] It has been estimated that 70% of those who start dialysis in India eventually give up dialysis due to financial constraints or death.[12] The health care system, with most out-of-pocket expenditures borne by the households pose significant barriers to accessing health services with approximately 60 million households pushed below the poverty line in India as a result each year.[13]

Although not to the same degree, we reported similar findings in a recent study comparing CKD between China in the US.[14] China, another country which has gone through great economic and population growth in recent years, displayed a low prevalence of advanced kidney disease (eGFR < 60 ml/min/1.73m^2), but a higher prevalence of albuminuria than the US. The strength of association between traditional risk factors, such as hypertension and diabetes, were also weaker among the Chinese sample, although the association between age and CKD prevalence was much stronger.

One explanation for these findings in India may be that nontraditional factors are driving this very high rate of early stage kidney disease. The evidence linking kidney disease to environmental factors continues to grow. Air pollution is one area that has been examined in depth recently in terms of its potential role in kidney disease. In the US, PM2.5 levels have been linked to the prevalence of CKD, risk of incident CKD, and its progression.[15,16] This association is also being explored outside the US with findings published from Taiwan and Korea showing similar results.[17-19] India currently has some of the highest levels of air pollution in the world. It is estimated that 1.5 million people died from the effects of air pollution

in 2012.[20,21] While less studied, it is also plausible that kidney disease may be influenced by pollutants in both the water and soil as well, similar to the factors potentially underlying the epidemic of CKD of unknown etiology.[22]

Unless actions are undertaken now to further investigate and reduce the high rate of albuminuria (albeit based on single cross-sectional estimates) reported in this study, the infrastructure and economy in India will likely not be able to optimally care for an increasing burden of those who may progress to ESRD in the not too distant future. Further, since albuminuria is also a marker of endothelial dysfunction and has been linked to cardiovascular outcomes, even at low levels, the higher risk of premature cardiovascular disease needs to be kept in mind in relation to albuminuria.[23-25]

To the best of our knowledge, this is the first study to estimate kidney disease prevalence at state level in India based on a random sample of the adult population living in a large, populous, northern Indian state. Further, it is also the first to compare prevalence of CKD between India and the US (after adjusting for patient characteristics around the same time period in the two nations). However, it is not without limitations. Because the sample from India was only from one state, the Punjab, we cannot generalize our findings to all of India. Although this is a large state, the risk factor distribution and prevalence could be different in other areas of the country.[26] In addition, the people, land and environment in India are diverse and of a highly variegated nature with significant urban-rural differences. It should also be acknowledged that the Punjab STEPS survey is cross-sectional in design and while appropriately sampled to be representative of the state, may be limited by its sample size. Lastly, both NHANES and the Punjab STEPS survey checked albuminuria and serum creatinine at a single point in time, whereas the KDIGO definition of CKD requires demonstration of persistence of these

abnormalities. We believe however, that repeat sampling of blood and urine in public health surveys, while highly desirable, is often difficult to achieve in the real world.

Future research examining the association between environmental factors and kidney disease in India is urgently warranted. Such studies would benefit from having population samples from multiple states, preferably be longitudinal in nature, and have the potential to examine multiple environmental factors, while accounting for the traditional risk factors for kidney disease.

In summary, we report very high prevalence of albuminuria in a large state (the Punjab) in northern India. Albuminuria is considered an early sign of kidney damage as well as may reflect endothelial dysfunction, a harbinger of atherosclerosis-related cardiovascular disease. Progression of this early stage kidney and cardiovascular disease elevates the potential for an epidemic of ESRD and higher rates of cardiovascular disease in a country undergoing rapid epidemiologic and economic transition. Urgent action and further research is needed to determine the underlying cause(s) of these findings, in the hopes of stemming the tide of rising rates of kidney failure and cardiovascular disease. India must clearly prepare for an inevitable increase in the need for renal replacement therapy in the coming years.

COMPETING INTERESTS:

Jennifer L. Bragg-Gresham: None

JS Thakur: None

Gursimer Jeet: None

Sanjay Jain: None

Arnab Pal: None

Rajendra Prasad: None

Subramaniam Pennathur: None

Rajiv Saran: None

CONTRIBUTION STATEMENT:

Jennifer L. Bragg-Gresham: Data analysis, manuscript writing, tables/figures creation

JS Thakur: Study design (India), data collection, manuscript planning, manuscript review and editing

Gursimer Jeet: Study design, data collection and programming, manuscript review and editing

Sanjay Jain: Study design, manuscript review and editing

Arnab Pal: Study design, manuscript review and editing

Rajendra Prasad: Study design, manuscript review and editing

Subramaniam Pennathur: Manuscript review and editing

Rajiv Saran: Manuscript planning, manuscript writing, manuscript review and editing

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DATA SHARING STATEMENT

All US data from the National Health and Nutrition Examination Survey (NHANES) is publically available at https://www.cdc.gov/nchs/nhanes/index.htm. The Punjab data is available by request and approval through collaborative agreements with the sponsors. Professor JS Thakur is the Principal Investigator and can be contacted at jsthakur64@gmail.com.

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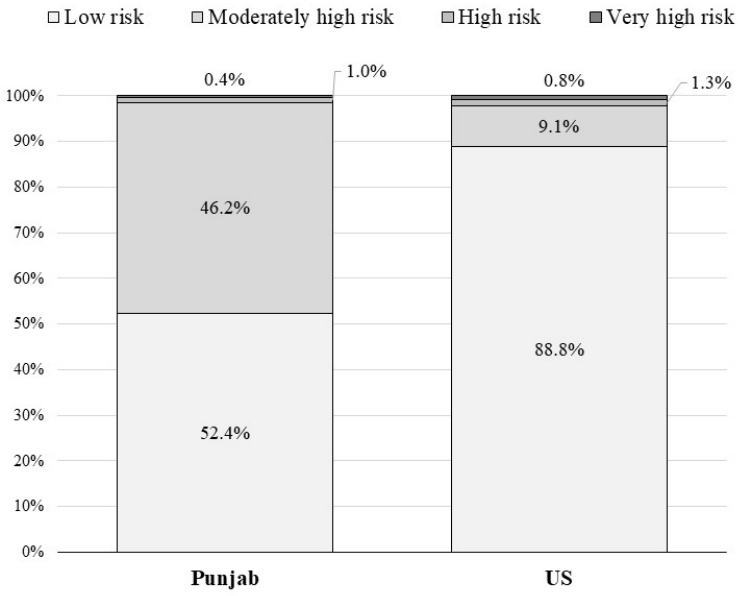

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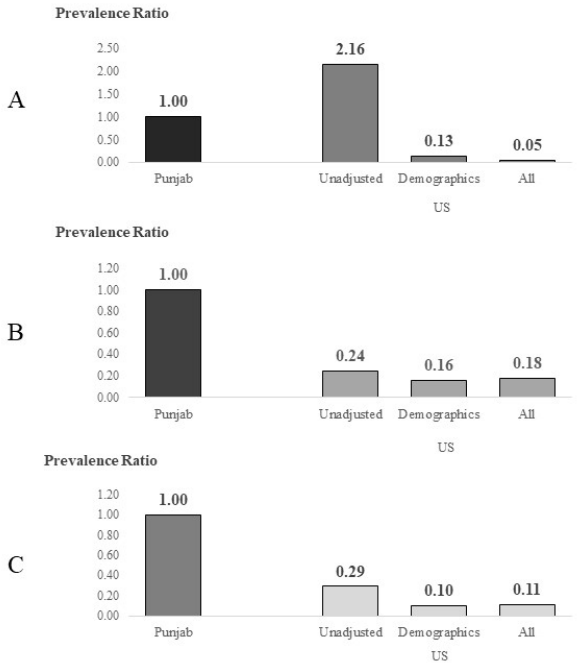

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	8
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-10
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-15

		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20-21

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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High Prevalence of Chronic Kidney Disease and its Risk Factors in the Punjab, Northern India: A Comparison with the United States

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High Prevalence of Chronic Kidney Disease and its Risk Factors in the Punjab, Northern India: A Comparison with the United States

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Running Headline: CKD Prevalence in Punjab, India

ABSTRACT

Objectives: India is witnessing a disturbing growth in non-communicable diseases (NCDs), including chronic kidney disease (CKD). Recently, a WHO STEPS survey was conducted in the state of Punjab, India to collect data from the adult population on NCD risk factors. We sought to compare the prevalence of CKD and its risk factors between this large state in northern India and the United States.

Setting: Samples were drawn from both locations, Punjab, India and the US, using multi-stage stratified sampling designs to collect data representative of the general population.

Participants: Data from 2,002 participants in the Punjab survey (2014-2015) and 5,057 in the US (National Health and Nutrition Examination Survey (NHANES; 2013-2014), between the ages of 18-69 years were examined.

Primary and secondary outcome measures: Modified Poisson regression was employed to compare prevalence rates between the two samples for markers of CKD and its risk factors. All analyses used sampling weights.

Results: The average age in the Punjab sample was significantly lower than the US (38.3 vs. 42.5 years, $p<0.0001$). While smoking and obesity were higher in the US, hypertension was much more common in Punjab (48.2% vs. 33.4%, $p<0.0001$). Significant differences were seen in the prevalence of CKD, with lower prevalence of eGFR < 60 ml/min/1.73m^2 (2.0% vs. 3.8%, $p<0.0001$), but markedly higher prevalence of albuminuria (46.7% vs. 8.9%, $p<0.0001$) in Punjab. These differences could not be explained by traditional risk factors such as diabetes and hypertension.

Conclusions: We report a strikingly high prevalence of albuminuria in Punjab, India, compared with the United States. This requires further study and may have enormous public

health implications for future burden of progressive CKD, end stage kidney disease, morbidity, mortality, and specifically for elevated risk or presence of cardiovascular disease in the northern state of Punjab, India.

Funding came from the National Health Mission, Punjab, India, JST and the Centers for Disease Control and Prevention, Atlanta, GA, USA.

STRENGTHS AND LIMITATIONS OF THIS STUDY

Strengths:

- Representative Samples from both the State of Punjab, India and the United States
- Uniform laboratory testing for identification of kidney disease
- Comprehensive data collection on anthropomorphic measurements, laboratory measurements, comorbid conditions, and health behaviors

Limitations:

- Cross-sectional study design cannot establish causality
- Because the sample from India was only from one state, the Punjab, we cannot generalize our findings to all of India

INTRODUCTION

The state of Punjab - indeed all of India, similar to other low and middle income countries (LMICs), is witnessing a disturbing growth in NCDs.[1] The country faces this epidemiologic transition while continuing to grapple with the problem of communicable diseases, which still remain a significant burden.[2] With this knowledge, the Department of Health and Family Welfare in Punjab, India, worked closely with the Post Graduate Institute of Medical Education and Research, Chandigarh, India, and medical colleges in the state to conduct the first representative survey of NCDs in the state of Punjab in 2014 and 2015.

The goal of this survey was to collect critical and up to date data on risk factors for NCDs in Punjab, with the hope of improving health planning and implementation of state initiatives, such as the National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular disease and Stroke (NPCDCS).[3] This survey provides a wealth of data on both risk factors for kidney disease and kidney disease itself, comparable to data collected in the United States from the National Health and Nutrition Examination Survey (NHANES).

Previous work utilizing data from this source have shown an alarmingly high prevalence of hypertension (40.1%) and pre-hypertension (40.8%) in the region, with approximately 70% of these individuals being unaware of their condition.[4] Similarly, although less prevalent, diabetes was found in 8.3% (6.3% with pre-diabetes) participants, with only 18% of individuals being aware of their disease.[5] Since diabetes and hypertension are two of the key risk factors for kidney disease, we hypothesized that the state of Punjab may be experiencing or on the verge of experiencing a significant burden of kidney disease.

Therefore, in the current study we sought to examine the prevalence of CKD (using both low glomerular filtration rate and albuminuria criteria) and risk factors for CKD, comparing the

Punjab to a representative sample of individuals from the US National Health and Nutrition Examination Survey (NHANES). In addition, we also sought to compare the magnitude of the associations between risk factors and CKD in the two samples.

MATERIALS AND METHODS

Study Sample

The STEPS survey of non-communicable disease (NCD) risk factors was carried out from June 2014 to August 2015 in Punjab.[3] A multi-stage stratified sampling design was used to generate representative data for two age-groups (18-44, 45-69), sex, and area of residence in the state. A total of 5,127 adults, ages 18-69 years, participated in the survey. The overall response rate for STEP1/2 and STEP 3 was 95% and 93% respectively. Data were collected in three steps: Socio-demographic and behavioral information was collected in Step 1, physical measurements such as height, weight and blood pressure were done in Step 2, and biochemical measurements were undertaken to assess salt intake, blood glucose, triglycerides and cholesterol levels in Step 3. This analysis included individuals from STEP 3 of the survey, which was carried out in a subset of 2700 participants. The individuals used in STEP 3 were selected by taking a sub-sample of half of the study participants considering resource constraints. Every 2nd individual contacted for STEP 1 and 2 was subjected to STEP 3. A total of 2,002 individuals who had complete data on both albuminuria and serum creatinine were analyzed. Specific sample weights were available for the individuals included in STEP 3.

The US data for comparison were from the 2013-2014 National Health and Nutrition Examination Survey (NHANES), included 5,057 individuals. Multi-stage stratified sampling

design was used to collect data representative of the US general population. [6] The NHANES is supported by the National Center for Health Statistics and was designed to assess the health and nutritional status of adults and children in the United States. The study combines interviews, physical examinations, laboratory tests, and participant lifestyle surveys. Individuals between the ages of 18 and 69 years, with complete information on estimated glomerular filtration rate and albuminuria, were examined to match with the Punjab sample.

Patient and Public Involvement

The research question was assessed using existing data taken from large, representative surveys, which contained more health questions and health measures than those presented in this work. The aim of the larger studies were to assess the overall health of each region, focused on diseases of global health impact, rather than individual patient priorities. The NHANES program began in the early 1960s, as a series of surveys focusing on different population groups or health topics over time. Participants were not involved in the design of the study, recruitment, or conduct of the study. NHANES participants receive their results from their examination as a preliminary report when leaving the exam center. A final report of findings is sent to each participant through the mail 12-16 weeks after their exam. Participants are free to discuss their results with their doctor and to keep for their own medical records.

Similarly, the Punjab STEPS survey was a state-level public health effort undertaken to estimate the burden of many non-communicable diseases in that region. The government funded study, similar to NHANES did not enlist patient opinion during study design, but did have a plan to provide results to participants if abnormal and warranting medical follow-up.

Measures

In the Punjab, collection of blood and urine samples were done in the mornings, after participants had fasted overnight. Samples were centrifuged using a mini-centrifuge and separated serum was stored in ice boxes then transferred daily to a nearest public health institute with facility for -20^0 C storage. Samples were transported to the central laboratory weekly. Collection of all the biochemical tests was at household level. Urine albumin-to-creatinine ratio was performed as a point-of-care field test using the URS 2AC strip that tests for 2 parameters microalbumin and creatinine (Biosense Technologies, Thane, Maharashtra, India). Calibration of the instruments and validation of field testing kits in a proportion of samples, was performed by the central biochemistry laboratory at PGIMER, Chandigarh per their standard protocol. Point-of –care field testing has been validated previously. [7,8] Laboratory measurements of serum creatinine (IDMS standardized assays) were made on Modular P 800 autoanalyzer (Roche Diagnostics, Germany) using commercially available kits (Roche Diagnostics, Germany). In the US NHANES sample, urine samples were processed, stored, and shipped to University of Minnesota, Minneapolis, MN for analysis. Detailed instructions on specimen collection and processing are discussed in the NHANES Laboratory Procedures Manual (LPM - https://wwwn.cdc.gov/nchs/data/nhanes/2015-2016/manuals/2016_MEC_Laboratory_Procedures_Manual.pdf). Vials were stored under appropriate frozen (-30°C) conditions until they are shipped to University of Minnesota for testing. The NHANES quality assurance and quality control (QA/QC) protocols meet the 1988 Clinical Laboratory Improvement Act mandates. Detailed QA/QC instructions are discussed in the NHANES LPM. A solid-phase fluorescent immunoassay was employed for the measurement

of human urinary albumin is described by Chavers et al. [9] Contract laboratories randomly perform repeat testing on 2% of all specimens.

Kidney function was assessed by estimated glomerular filtration rate (eGFR), calculated with using the CKD-Epi formula in both samples, employing the coefficients for White race in India.[10] Albuminuria was defined as a urine albumin to creatinine ratio (ACR) > 30 mg/g. Kidney disease was also assessed using the KDIGO risk categories, which places individuals into four risk groups for mortality based on their eGFR and ACR levels (low risk: eGFR > 60 and ACR < 30; moderately high risk: eGFR 45-59 with ACR < 30 or eGFR > 60 with ACR 30-300; high risk: eGFR 30-44 with ACR < 30, eGFR 45-59 with ACR 30-300, or eGFR > 60 with ACR > 300; or very high risk: eGFR < 30, eGFR 30-44 with ACR > 30, or eGFR 45-59 with ACR > 300.[11]

Risk factors for kidney disease were defined similarly between the two samples. Diabetes was defined by presence of any of the following: being told by a doctor they had diabetes, taking medication for diabetes (including medication from traditional healers in India), or fasting glucose > 126 mg/dl. Hypertension was defined as any of the following: being told by a doctor they had hypertension, taking medications for hypertension, or having systolic blood pressure (SBP) > 140mmHg or diastolic blood pressure (DBP) > 90mmHg.

Different cut-points for identifying obesity were used between samples to account for the differences in stature. In the US, the WHO definition was employed where underweight was defined as BMI < 18.5, normal weight as BMI 18.5 – 24.99, overweight as BMI 25 – 29.99, and obese as BMI ≥ 30 kg/m^2. In Punjab obesity was defined using the same criteria as other published papers using this survey data with underweight being defined as BMI < 18.5, normal weight as BMI 18.5 – 22.99, overweight as BMI 23 – 26.99, and obese as BMI ≥ 27 kg/m^2.[1-3]

Statistical Analysis

Demographic, socio-economic, anthropometric, health status, and markers of kidney disease were compared between counties using sample weighted t-tests for means or Chi-square tests for categorical variables. ACR was expressed as the median value due to its highly right-skewed nature. Associations between patient characteristics and risk factors for kidney disease with laboratory markers of kidney disease were modeled using modified Poisson regression with robust errors. This modeling approach was chosen, as opposed to logistic regression, because it yields estimates of prevalence ratios (PRs), rather than odds ratios.[12,13] PR estimates were determined for the kidney disease risk factors within each country in a single model using interactions between a country indicator variable and each measure. Age and sex were considered as demographic variables. A sensitivity analysis was performed, stratifying the models by sex.

Analysis of de-identified data received from the Punjab WHO Steps Survey for this study was deemed IRB exempt by the University of Michigan IRB. NHANES data is publically available for use by researchers and does not require an IRB approval.

RESULTS

Many differences exist between individuals in Punjab and the US, as shown in Table 1. The mean age was approximately four years younger in Punjab ($p<0.0001$), with a higher proportion of men (58.2% vs. 48.9%, $p<0.0001$) compared with the US. The US had a much higher percentage of both high school or higher education and private health insurance coverage

(p<0.0001). Overall body size was very different, with Punjab residents being 6 cm shorter, weighing 18 kilograms less, having 10 cm smaller waist circumference, and BMI lower by 4.6 kg/m^2 (all p<0.0001). Comparison of obesity by categories showed a higher percentage of individuals in Punjab as underweight (11.3% vs. 1.5% in the US) and a higher proportion of obese individuals in the US (37.9% vs. 28.9%, p<0.0001), while proportions of those in the normal or overweight categories were very similar. While smoking was higher in the US, hypertension was much more common in Punjab (48.2% vs. 33.4%, p<0.0001). No differences were seen in the prevalence of diabetes, cardiovascular disease, or triglyceride levels, although the US had higher total cholesterol levels (4.9 vs. 3.9 mmol/L [189 vs. 150 mg/dL] in Punjab, p<0.0001).

Table 1: Comparison of Weighted Survey Sample Participant Characteristics between the Adult Populations in the State of Punjab, India and the United States

Measure	Punjab (2014-2015)		US (2013-2014)		P value
	N	Mean (SE) or %	N	Mean (SE) or %	
Age (years)	2,002	38.3 (0.60)	5,057	42.5 (0.38)	<0.0001
Male (%)	2,002	58.2%	5,057	48.9%	0.0001
Education to high school or above (%)	2,002	43.4%	4,718	85.3%	<0.0001
Health Insurance (%)	2,002	6.2%	5,052	79.8%	<0.0001
Height (cm)	1,986	163.0 (0.37)	5,008	169.0 (0.31)	<0.0001
Weight (Kg)	1,993	65.4 (0.6)	5,006	83.5 (0.54)	<0.0001
BMI (kg/m^2) *	1,982	24.6 (0.23)	5,000	29.2 (0.20)	<0.0001
Underweight	1,982	11.3	5,000	1.5	<0.0001
Normal		29.5		29.1	
Overweight		30.3		31.5	
Obese		28.9		37.9	
Waist (cm)	1,995	89.0 (0.62)	4,836	98.8 (0.38)	<0.0001
Current smoker (%)	2,002	7.5%	5,057	21.6%	<0.0001
Diabetes (%)	1,043	7.7%	5,057	8.9%	0.42
Hypertension (%)	2,000	48.2%	5,057	33.4%	<0.0001
CVD (%)	1,989	4.6%	5,057	3.4%	0.08
Triglyceride (mmol/L)	2,001	1.4 (0.04)	2,294	1.4 (0.04)	0.35
Total cholesterol (mmol/L)	2,002	3.9 (0.06)	4,812	4.9 (0.02)	<0.0001
Serum Creatinine (μmol/L)	2,002	61.9 (0.9)	4,798	77.8 (0.9)	<0.0001
eGFR (mL/min/1.73m^2)	2,002	114.8 (1.1)	4,798	97.8 (0.6)	<0.0001
eGFR < 60 ml/min/1.73m^2	2,002	2.0%	4,798	3.8%	<0.0001
Urine Albumin (g/L; median)	1,928	0.2 (0.03)	4,971	0.07 (0.002)	<0.0001
Urine Creatinine (μmol/L; median)	1,928	7,242 (265)	4,971	9,275 (292)	<0.0001
ACR (mg/mmol; median) ±	1,928	2.5 (0.25)	4,971	0.66 (0.007)	<0.0001
ACR > 3 mg/mmol	1,928	46.7%	4,971	8.9%	<0.0001

CVD: cardiovascular disease.
eGFR: estimated glomerular filtration rate.
ACR: urine albumin: creatinine ratio.
* Different BMI cut-points used for obesity:
US: Underweight < 18.5, normal = 18.5 - 24.9, overweight = 25 – 29.9, obese 30+
India: Underweight < 18, normal = 18 - 22.9, overweight = 23 – 24.9, obese 25+
± Median employed to examine differences in urine measurements due to high degree of risk-skew.

Although Punjab had a lower prevalence of eGFR < 60 ml/min/1.73m^2 (2.0% vs. 3.8%, p<0.0001), the prevalence of albuminuria was five times higher (46.7% vs. 8.9%, p<0.0001).

When assessing kidney function using the KDIGO risk categories (Table 2), the high prevalence of high UACR lead to 46.2% of participants in Punjab being classified as “moderately high risk”, compared to only 9.1% in the US. In contrast, Punjab had only 1.4% in the “high risk” or “extremely high risk” groups compared to 2.1% in the US (Figure 1).

Table 2: Prevalence of Albuminuria and eGFR KDIGO Risk Categories among Adults in Punjab and United States

Punjab, India				Albuminuria categories			Total
				A1	A2	A3	
				Normal to mildly increased	Moderately increased	Severely increased	
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol	
GFR categories (ml/min/1.73 m^2)	G1	Normal to high	≥90	46.7 (40.7-52.6)	42.0 (35.3-48.7)	0.2 (0-0.7)	88.9 (86.0-91.8)
	G2	Mildly decreased	60-89	5.7 (3.6-7.6)	3.5 (2.4-4.7)	0	9.2 (6.8-11.5)
	G3a	Mildly to mod decreased	45-59	0.7 (0.1-1.3)	0.5 (0-1.0)	0	1.2 (0.3-2.1)
	G3b	Mod to severe decreased	30-44	0.3 (0-0.7)	0.5 (0-1.1)	0	0.8 (0.1-1.5)
	G4	Severely decreased	15-29	0.03 (0-0.08)	0.01 (0-0.02)	0	0.04 (0-0.09)
	G5	Kidney failure	<15	0	0	0	0
Total				53.4 (46.3-60.2)	46.5 (39.5-53.5)	0.2 (0-0.7)	100

United States				Albuminuria categories			Total
				A1	A2	A3	
				Normal to mildly increased	Moderately increased	Severely increased	
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol	
GFR categories (ml/min/1.73 m^2)	G1	Normal to high	≥90	60.7 (58.1-63.1)	4.8 (4.0-5.6)	0.5 (0.3-0.7)	66.0 (63.1-68.9)
	G2	Mildly decreased	60-89	28.1 (25.6-30.7)	2.2 (1.5-2.7)	0.1 (0.05-0.2)	30.4 (27.7-33.1)
	G3a	Mildly to mod decreased	45-59	2.1 (1.4-2.7)	0.4 (0.2-0.7)	0.2 (0-0.3)	2.7 (1.9-3.5)
	G3b	Mod to severe decreased	30-44	0.3 (0.1-0.4)	0.2 (0.03-0.4)	0.1 (0.02-0.2)	0.6 (0.4-0.8)
	G4	Severely decreased	15-29	0.05 (0.0-0.1)	0.05 (0.01-1.0)	0.09 (0-0.2)	0.2 (0.05-0.3)
	G5	Kidney failure	<15	0	0.06 (0-0.2)	0.07 (0.01-0.1)	0.1 (0.01-0.3)
Total				91.2 (90.0-92.5)	7.7 (6.6-8.8)	1.1 (0.8-1.3)	100

Lightest gray = Low Risk
Light gray = Moderately High Risk
Medium gray = High Risk
Dark gray = Very High Risk

To compare the magnitude of association between traditional risk factors for CKD between the two samples, we modeled prevalence ratios in each country within one model to allow for the associations to be compared statistically (Table 3). When examining low eGFR (< 60 ml/min/1.73m^2) as the outcome, male participants in Punjab showed a much lower prevalence compared with females (prevalence ratio: PR=0.22, p=0.007); while no association was seen in the US between sex and low eGFR (PR=1.09, p=0.56). These associations were significantly different from each other with p=0.006. Another difference between the associations and outcome was seen for hypertension (p=0.008), where a non-significant lower prevalence ratio was observed in Punjab (PR=0.75, p=0.43) and a strong positive association was seen in the US (PR=2.24, p<0.0001). Similar positive associations were seen in both samples for older age, higher education level, CVD, and DM on the prevalence of low eGFR.

Table 3b displays the associations between patient factors and the prevalence of albuminuria. Significant differences between the samples was again seen with sex and the outcome (p=0.02). No association between sex and albuminuria was seen in Punjab, where in the US males had a lower prevalence of albuminuria (PR=0.77, p=0.004). While in both samples hypertension and DM were associated with a higher prevalence of albuminuria, the magnitude of association was much stronger in the US (PR=1.19 in Punjab vs. PR=1.93 in the US for hypertension and PR=1.32 in Punjab vs. PR=2.54 in the US for DM). Current smoking was associated with albuminuria only in the US (PR=1.34, p=0.002), while higher total cholesterol was associated with albuminuria in the Punjab (PR=1.11 per 0.5 mmol/L higher total cholesterol).

When combining low eGFR and albuminuria into a composite (CKD) outcome (Table 3c) more differences were found between the samples in certain associations. Significantly larger associations were found in the US for the relationship between older age, hypertension, DM, and BMI; while a larger association was seen between total cholesterol and the composite CKD measure in the Punjab.

Table 3: Prevalence Ratios for Markers of CKD by Risk Factors

A. Low eGFR (eGFR < 60 ml/min/1.73m^2)

Measure	Punjab			US			P-value for interaction
	PR	95% CI	P	PR	95% CI	P	
Age (per 10 years)	1.73	1.29 – 2.31	0.0002	2.14	1.82 – 2.52	<0.0001	0.20
Male (vs. Female)	0.22	0.07 – 0.66	0.007	1.09	0.81 – 1.47	0.56	***0.006***
Education high school + (vs. no)	1.86	0.84 – 4.10	0.13	1.53	1.06 – 2.20	0.02	0.66
Current smoker (vs. no)	2.32	0.31 – 1.74	0.41	0.92	0.63 – 1.34	0.66	0.38
Hypertension (vs. no)	0.75	0.37 – 1.52	0.43	2.24	1.51 – 3.33	<0.0001	***0.008***
DM (vs. no)	2.75	1.17 – 6.48	0.02	1.76	1.27 – 2.44	0.0007	0.34
CVD (vs. no)	1.11	0.34 – 3.60	0.87	1.98	1.20 – 1.38	0.0002	0.35
Total Cholesterol (per 20 mg/dl, per 0.5 mmol/L)	1.09	0.73 – 1.64	0.67	0.92	0.76 – 1.11	0.36	0.44
BMI (per 5 Kg/m^2)	0.82	0.59 – 1.15	0.25	1.13	1.04 – 1.23	0.006	0.07
Obesity:							
Underweight	1.24	0.26 – 5.95	0.79	1.45	0.36 – 5.89	0.60	0.88
Healthy weight	1.00	-	ref	1.00	-	ref	
Overweight	2.63	1.09 – 6.34	0.03	1.31	0.83 – 2.07	0.25	0.17
Obese	0.73	0.27 – 1.95	0.53	1.40	0.91 – 2.14	0.13	0.23

B. Albuminuria (ACR > 30 mg/g, 3 mg/mmol)

Measure	Punjab			US			P-value for interaction
	PR	95% CI	P	PR	95% CI	P	
Age (per 10 years)	1.03	0.99 – 1.08	0.16	1.06	0.98 – 1.14	0.15	0.60
Male (vs. Female)	0.99	0.88 – 1.12	0.93	0.77	0.65 – 0.92	0.004	***0.02***
Education high school + (vs. no)	0.99	0.88 – 1.11	0.80	0.81	0.67 – 0.98	0.03	0.09
Current smoker (vs. no)	1.09	0.85 – 1.40	0.48	1.35	1.11 – 1.63	0.002	0.20
Hypertension (vs. no)	1.19	1.06 – 1.34	0.005	1.93	1.59 – 2.36	<0.0001	***<0.0001***
DM (vs. no)	1.32	1.12 – 1.56	0.0008	2.54	2.07 – 3.13	<0.0001	***<0.0001***
CVD (vs. no)	1.14	0.92 – 1.37	0.24	1.32	1.16 – 0.99	0.06	0.37
Total Cholesterol (per 20 mg/dl, per 0.5 mmol/L)	1.11	1.04 – 1.17	0.001	0.99	0.90 – 1.09	0.81	***0.05***
BMI (per 5 Kg/m^2)	0.99	0.94 – 1.03	0.54	1.04	0.98 – 1.10	0.19	0.16
Obesity:							
Underweight	0.90	0.72 – 1.11	0.32	1.20	0.56 – 2.56	0.64	0.47
Healthy weight	1.00	-	ref	1.00	-	ref	-
Overweight	0.95	0.82 – 1.10	0.48	0.93	0.72 – 1.18	0.53	0.85
Obese	0.95	0.83 – 1.09	0.48	1.01	0.80 – 1.27	0.96	0.68

C. CKD (low eGFR or Albuminuria)

Measure	Punjab			US			P-value for interaction
	PR	95% CI	P	PR	95% CI	P	
Age (per 10 years)	1.04	1.00 – 1.09	0.06	1.20	1.12 – 1.29	<0.0001	***0.0007***
Male (vs. Female)	0.97	0.86 – 1.09	0.58	0.81	0.70 – 0.94	0.007	0.0686
Education high school + (vs. no)	1.00	0.90 – 1.12	0.96	0.91	0.77 – 1.09	0.31	0.379
Current smoker (vs. no)	1.09	0.85 – 1.40	0.49	1.26	1.06 – 1.49	0.008	0.3526
Hypertension (vs. no)	1.18	1.05 – 1.33	0.006	1.87	1.57 – 2.23	<0.0001	***<0.0001***
DM (vs. no)	1.35	1.16 – 1.58	0.0002	2.11	1.77 – 2.53	<0.0001	***0.0002***
CVD (vs. no)	1.13	0.94 – 1.37	0.19	1.49	1.12 – 1.18	0.0006	0.072
Total Cholesterol (per 20 mg/dl, per 0.5 mmol/L)	1.09	1.04 – 1.16	0.002	0.97	0.88 – 1.05	0.41	***0.02***
BMI (per 5 Kg/m^2)	0.98	0.94 – 1.03	0.48	1.06	1.01 – 1.12	0.017	***0.025***
Obesity:							
Underweight	0.89	0.72 – 1.10	0.28	1.31	0.67 – 2.54	0.43	0.28
Healthy weight	1.00	-	ref	1.00	-	ref	-
Overweight	0.98	0.86 – 1.13	0.81	0.98	0.79 – 1.22	0.84	0.97
Obese	0.95	0.83 – 1.09	0.48	1.06	0.86 – 1.29	0.60	0.41

Figure 2 displays the changes in prevalence ratios comparing US to Punjab for each marker of CKD with different levels of adjustment for traditional risk factors examined in Table 3. Before accounting for any differences in participants in the two studies, the prevalence of low eGFR was much higher in the US (PR=2.16), but after accounting for demographics (age and sex) and other health measures (remaining covariates), the US has a much lower prevalence of low eGFR compared to Punjab (PR=0.13 and 0.05,

respectively), suggesting that if the US had the same patient make up as Punjab, the prevalence of low eGFR would be much lower. The findings for albuminuria and any CKD were very similar in showing that before adjustment the prevalence of either marker was much lower in the US (PR=0.24 and 0.29, respectively) and accounting for difference in demographics and health measures between the samples changed these estimates very little. These results suggest that traditional risk factors do not entirely explain the difference in prevalence seen among markers of kidney disease between the US and Punjab.

DISCUSSION

In comparing two representative samples of participants from the adult population of Punjab, India and the United States, we found a very high prevalence of albuminuria in the Punjab, with almost half of the residents with urine ACR > 3 mg/mmol (30 mg/g). This is in contrast to the prevalence of albuminuria in the US of approximately 9%. When examining glomerular filtration rate, the Punjab had much higher average eGFR and a lower prevalence of eGFR < 60 ml/min/1.73m^2 (2.0% vs. 3.8%). Because of the high prevalence of albuminuria in the Punjab, almost half the population falls into the "moderately high risk" CKD risk category per KDIGO risk stratification criteria. Even more striking is the fact that the between country differences in the prevalence estimates of albuminuria could not be explained by traditional risk factors for CKD, such as age, hypertension, and diabetes.

If true, these findings have enormous public health and resource implications for a low-middle income country such as India, specifically in the realm of CKD, cardiovascular disease and other NCDs. Currently there are no definitive estimates of prevalence of chronic kidney disease in India, as there is no ongoing national kidney registry/surveillance system. Recent

publications have suggested that 220,000 patients are diagnosed with ESRD every year.[14] It is estimated that this will result in demand for an additional 34 million dialysis sessions in India each year. Besides the growing population of patients with kidneys disease, the country is faced with a shortage of nephrologists, late referral of patients, inadequate health awareness about preventive measures, and a lack of more cost-effective alternatives like renal transplantation or peritoneal dialysis (PD).[14] It has been estimated that 70% of those who start dialysis in India eventually give up dialysis due to financial constraints or death.[15] The health care system, with most out-of-pocket expenditures borne by the households pose significant barriers to accessing health services with approximately 60 million households pushed below the poverty line in India as a result each year.[16]

We believe that our finding of the discordance observed in the prevalence of albuminuria versus lower eGFR between India and the US could be in part due to the epidemiologic transition that is occurring in countries such as India, where early evidence of kidney damage but lower prevalence of low eGFR defined kidney disease or end stage kidney disease, may be the result of higher death rates among the younger population from premature cardiovascular disease, so while early kidney disease evidenced by albuminuria is more common, prevalence of later stages of kidney disease is lower (but potentially rising). Although not to the same degree, we reported similar findings in a recent study comparing CKD between China and the US.[17] China, another country which has gone through great economic and population growth in recent years, displayed a low prevalence of advanced kidney disease (eGFR < 60 ml/min/1.73m^2), but a higher prevalence of albuminuria than the US. The strength of association between traditional risk factors, such as hypertension and diabetes, were also weaker among the Chinese sample, although the association between age and CKD prevalence was much stronger.

Supportive evidence for a high rate of albuminuria in India have been reported from the western state of Gujarat. [18] This study represents a voluntary sample of participants who were screened during a World Kidney Day Screening Camp. Even though the investigators excluded individuals at risk of albuminuria (participants with known diabetes, stone diseases, hypertension, kidney/liver/cardiac disease, hepatitis, HIV, transplant recipients, pregnant women and those < 18 years of age), they estimated a 13.8% prevalence of albuminuria in their study. This is higher than in the US general population random sample in NHANES, which includes the individuals most likely to have albuminuria.

The high prevalence of albuminuria in Punjab could be related to the metabolic syndrome known to be associated with albuminuria. [19] In this context, insulin resistance and visceral adiposity are common in developing nations and mechanistically linked with the metabolic syndrome through adipocytokines and inflammation. [20] The high prevalence of premature cardiovascular disease and hypertension can be accompanied by albuminuria from vascular dysfunction or damage, leading to disruption of the glomerular filtration barrier. Furthermore, the evidence linking kidney disease to environmental factors continues to grow. [21] Air pollution (highly prevalent in that part of the world), is associated with both endothelial dysfunction and low grade inflammation with resultant albuminuria. In the US, PM2.5 levels have been linked to the prevalence of CKD, risk of incident CKD, and its progression.[22,23] This association is also being explored outside the US with findings published from Taiwan and Korea showing similar results.[24-26] India currently has some of the highest levels of air pollution in the world. It is estimated that 1.5 million people died from the effects of air pollution in 2012. [27,28] While less studied, it is also plausible that kidney disease may be influenced by pollutants in both the water and soil as well, similar to the factors potentially underlying the

epidemic of CKD of unknown etiology, although this has not been reported from northern India, and albuminuria is not the hallmark of this latter condition. [29]

Unless actions are undertaken now to further investigate and reduce the high rate of albuminuria (albeit based on single cross-sectional estimates) reported in this study, the infrastructure and economy in India will likely not be able to optimally care for an increasing burden of those who may progress to ESRD in the not too distant future. Further, since albuminuria is also a marker of endothelial dysfunction and has been linked to cardiovascular outcomes, even at low levels, the higher risk of premature cardiovascular disease needs to be kept in mind in relation to albuminuria. [30-32]

To the best of our knowledge, this is the first study to estimate kidney disease prevalence at state level in India based on a random sample of the adult population living in a large, populous, northern Indian state. Further, it is also the first to compare prevalence of CKD between India and the US (after adjusting for patient characteristics around the same time period in the two nations). However, it is not without limitations. Because the sample from India was only from one state, the Punjab, we cannot generalize our findings to all of India. Although this is a large state, the risk factor distribution and prevalence could be different in other areas of the country.[33] In addition, the people, land and environment in India are diverse and of a highly variegated nature with significant urban-rural differences. It should also be acknowledged that the Punjab STEPS survey is cross-sectional in design and while appropriately sampled to be representative of the state, may be limited by its sample size. Lastly, both NHANES and the Punjab STEPS survey checked albuminuria and serum creatinine at a single point in time, whereas the KDIGO definition of CKD requires demonstration of persistence of these

abnormalities. We believe however, that repeat sampling of blood and urine in public health surveys, while highly desirable, is often difficult to achieve in the real world.

Future research to confirm our findings using repeat sampling and similar studies in other states, and further examination of the association between environmental factors and kidney disease in India is urgently warranted. Such studies would benefit from having population samples from multiple states, preferably be longitudinal in nature, and have the potential to examine multiple environmental factors, while accounting for the traditional risk factors for kidney disease.

In summary, we report very high prevalence of albuminuria in a large state (the Punjab) in northern India. Albuminuria is considered an early sign of kidney damage as well as may reflect endothelial dysfunction, a harbinger of atherosclerosis-related cardiovascular disease. Progression of this early stage kidney and cardiovascular disease elevates the potential for an epidemic of ESRD and higher rates of cardiovascular disease in a country undergoing rapid epidemiologic and economic transition. Urgent action and further research is needed to determine the underlying cause(s) of these findings, in the hopes of stemming the tide of rising rates of kidney failure and cardiovascular disease. India must clearly prepare for an inevitable increase in the need for renal replacement therapy in the coming years.

COMPETING INTERESTS:

Jennifer L. Bragg-Gresham: None

JS Thakur: None

Gursimer Jeet: None

Sanjay Jain: None

Arnab Pal: None

Rajendra Prasad: None

Subramaniam Pennathur: None

Rajiv Saran: None

CONTRIBUTION STATEMENT:

Jennifer L. Bragg-Gresham: Data analysis and interpretation, manuscript writing, tables/figures creation

JS Thakur: Study design (India), data collection, manuscript planning, manuscript review and editing

Gursimer Jeet: Study design, data collection and programming, manuscript review and editing

Sanjay Jain: Study design, manuscript review and editing

Arnab Pal: Study design, manuscript review and editing

Rajendra Prasad: Study design, manuscript review and editing

Subramaniam Pennathur: Manuscript review and editing

Rajiv Saran: Study concept, data interpretation, manuscript writing, manuscript review and editing

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DATA SHARING STATEMENT

All US data from the National Health and Nutrition Examination Survey (NHANES) is publically available at https://www.cdc.gov/nchs/nhanes/index.htm. The Punjab data is available by request and approval through collaborative agreements with the sponsors. Professor JS Thakur is the Principal Investigator and can be contacted at jsthakur64@gmail.com.

FIGURE TITLES AND LEGENDS

Figure 1: Distribution of KDIGO Risk Categories among Adults in Punjab, India and the United States

Figure 2: Changes in Prevalence Ratios between Punjab and the US for Markers of CKD with Different Levels of Adjustment for Risk Factors

A. Low eGFR

B. Albuminuria

C. Any CKD

Footnote: Demographics = age, sex, and education & All = Demographics plus measures in Table 3

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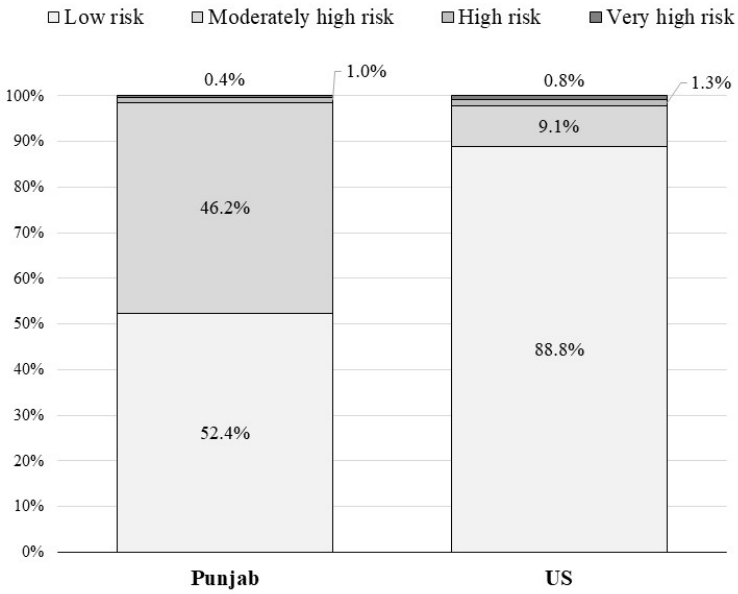

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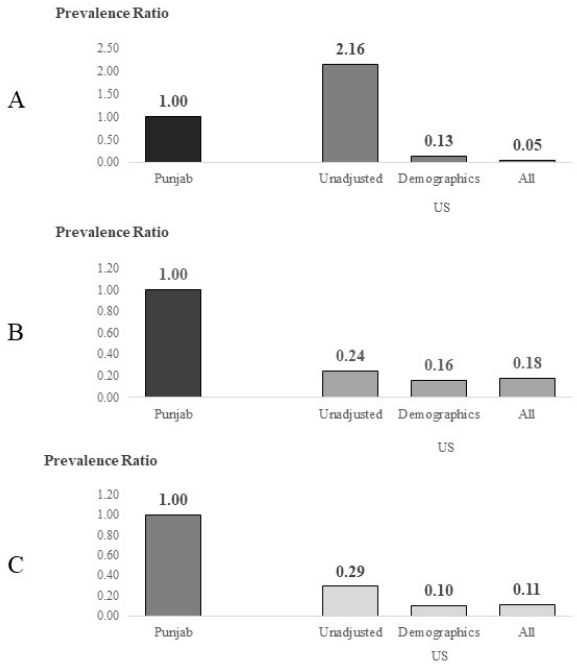

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	8
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-10
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-15

		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20-21

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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A Population-based Comparison of Chronic Kidney Disease Prevalence and Risk Factors among Adults living in the Punjab, Northern India and the United States (2013-2015)

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Running Headline: CKD Prevalence in Punjab, India

ABSTRACT

Objectives: India is witnessing a disturbing growth in non-communicable diseases (NCDs), including chronic kidney disease (CKD). Recently, a WHO STEPS survey was conducted in the state of Punjab, India to collect data from the adult population on NCD risk factors. We sought to compare the prevalence of CKD and its risk factors between this large state in northern India and the United States.

Setting: Samples were drawn from both locations, Punjab, India and the US, using multi-stage stratified sampling designs to collect data representative of the general population.

Participants: Data from 2,002 participants in the Punjab survey (2014-2015) and 5,057 in the US (National Health and Nutrition Examination Survey (NHANES; 2013-2014), between the ages of 18-69 years were examined.

Primary and secondary outcome measures: Modified Poisson regression was employed to compare prevalence rates between the two samples for markers of CKD and its risk factors. All analyses used sampling weights.

Results: The average age in the Punjab sample was significantly lower than the US (38.3 vs. 42.5 years, $p<0.0001$). While smoking and obesity were higher in the US, hypertension was much more common in Punjab (48.2% vs. 33.4%, $p<0.0001$). Significant differences were seen in the prevalence of CKD, with lower prevalence of eGFR < 60 ml/min/1.73m^2 (2.0% vs. 3.8%, $p<0.0001$), but markedly higher prevalence of albuminuria (46.7% vs. 8.9%, $p<0.0001$) in Punjab. These differences could not be explained by traditional risk factors such as diabetes and hypertension.

Conclusions: We report a strikingly high prevalence of albuminuria in Punjab, India, compared with the United States. This requires further study and may have enormous public

health implications for future burden of progressive CKD, end stage kidney disease, morbidity, mortality, and specifically for elevated risk or presence of cardiovascular disease in the northern state of Punjab, India.

Funding came from the National Health Mission, Punjab, India, JST and the Centers for Disease Control and Prevention, Atlanta, GA, USA.

STRENGTHS AND LIMITATIONS OF THIS STUDY

Strengths:

- Representative Samples from both the State of Punjab, India and the United States
- Uniform laboratory testing for identification of kidney disease
- Comprehensive data collection on anthropomorphic measurements, laboratory measurements, comorbid conditions, and health behaviors

Limitations:

- Cross-sectional study design cannot establish causality
- Because the sample from India was only from one state, the Punjab, we cannot generalize our findings to all of India

INTRODUCTION

The state of Punjab - indeed all of India, similar to other low and middle income countries (LMICs), is witnessing a disturbing growth in NCDs.[1] The country faces this epidemiologic transition while continuing to grapple with the problem of communicable diseases, which still remain a significant burden.[2] With this knowledge, the Department of Health and Family Welfare in Punjab, India, worked closely with the Post Graduate Institute of Medical Education and Research, Chandigarh, India, and medical colleges in the state to conduct the first representative survey of NCDs in the state of Punjab in 2014 and 2015.

The goal of this survey was to collect critical and up to date data on risk factors for NCDs in Punjab, with the hope of improving health planning and implementation of state initiatives, such as the National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular disease and Stroke (NPCDCS).[3] This survey provides a wealth of data on both risk factors for kidney disease and kidney disease itself, comparable to data collected in the United States from the National Health and Nutrition Examination Survey (NHANES).

Previous work utilizing data from this source have shown an alarmingly high prevalence of hypertension (40.1%) and pre-hypertension (40.8%) in the region, with approximately 70% of these individuals being unaware of their condition.[4] Similarly, although less prevalent, diabetes was found in 8.3% (6.3% with pre-diabetes) participants, with only 18% of individuals being aware of their disease.[5] Since diabetes and hypertension are two of the key risk factors for kidney disease, we hypothesized that the state of Punjab may be experiencing or on the verge of experiencing a significant burden of kidney disease.

Therefore, in the current study we sought to examine the prevalence of CKD (using both low glomerular filtration rate and albuminuria criteria) and risk factors for CKD, comparing the

Punjab to a representative sample of individuals from the US National Health and Nutrition Examination Survey (NHANES). In addition, we also sought to compare the magnitude of the associations between risk factors and CKD in the two samples.

MATERIALS AND METHODS

Study Sample

The STEPS survey of non-communicable disease (NCD) risk factors was carried out from June 2014 to August 2015 in Punjab.[3] A multi-stage stratified sampling design was used to generate representative data for two age-groups (18-44, 45-69), sex, and area of residence in the state. A total of 5,127 adults, ages 18-69 years, participated in the survey. The overall response rate for STEP1/2 and STEP 3 was 95% and 93% respectively. Data were collected in three steps: Socio-demographic and behavioral information was collected in Step 1, physical measurements such as height, weight and blood pressure were done in Step 2, and biochemical measurements were undertaken to assess salt intake, blood glucose, triglycerides and cholesterol levels in Step 3. This analysis included individuals from STEP 3 of the survey, which was carried out in a subset of 2700 participants. The individuals used in STEP 3 were selected by taking a sub-sample of half of the study participants considering resource constraints. Every 2nd individual contacted for STEP 1 and 2 was subjected to STEP 3. A total of 2,002 individuals who had complete data on both albuminuria and serum creatinine were analyzed. Specific sample weights were available for the individuals included in STEP 3.

The US data for comparison were from the 2013-2014 National Health and Nutrition Examination Survey (NHANES), included 5,057 individuals. Multi-stage stratified sampling

design was used to collect data representative of the US general population. [6] The NHANES is supported by the National Center for Health Statistics and was designed to assess the health and nutritional status of adults and children in the United States. The study combines interviews, physical examinations, laboratory tests, and participant lifestyle surveys. Individuals between the ages of 18 and 69 years, with complete information on estimated glomerular filtration rate and albuminuria, were examined to match with the Punjab sample.

Patient and Public Involvement

The research question was assessed using existing data taken from large, representative surveys, which contained more health questions and health measures than those presented in this work. The aim of the larger studies were to assess the overall health of each region, focused on diseases of global health impact, rather than individual patient priorities. The NHANES program began in the early 1960s, as a series of surveys focusing on different population groups or health topics over time. Participants were not involved in the design of the study, recruitment, or conduct of the study. NHANES participants receive their results from their examination as a preliminary report when leaving the exam center. A final report of findings is sent to each participant through the mail 12-16 weeks after their exam. Participants are free to discuss their results with their doctor and to keep for their own medical records.

Similarly, the Punjab STEPS survey was a state-level public health effort undertaken to estimate the burden of many non-communicable diseases in that region. The government funded study, similar to NHANES did not enlist patient opinion during study design, but did have a plan to provide results to participants if abnormal and warranting medical follow-up.

Measures

In the Punjab, collection of blood and urine samples were done in the mornings, after participants had fasted overnight. Samples were centrifuged using a mini-centrifuge and separated serum was stored in ice boxes then transferred daily to a nearest public health institute with facility for -20^0 C storage. Samples were transported to the central laboratory weekly. Collection of all the biochemical tests was at household level. Urine albumin-to-creatinine ratio was performed as a point-of-care field test using the URS 2AC strip that tests for 2 parameters microalbumin and creatinine (Biosense Technologies, Thane, Maharashtra, India). Calibration of the instruments and validation of field testing kits in a proportion of samples, was performed by the central biochemistry laboratory at PGIMER, Chandigarh per their standard protocol. Point-of –care field testing has been validated previously. [7,8] Laboratory measurements of serum creatinine (IDMS standardized assays) were made on Modular P 800 autoanalyzer (Roche Diagnostics, Germany) using commercially available kits (Roche Diagnostics, Germany). In the US NHANES sample, urine samples were processed, stored, and shipped to University of Minnesota, Minneapolis, MN for analysis. Detailed instructions on specimen collection and processing are discussed in the NHANES Laboratory Procedures Manual (LPM - https://wwwn.cdc.gov/nchs/data/nhanes/2015-2016/manuals/2016_MEC_Laboratory_Procedures_Manual.pdf). Vials were stored under appropriate frozen (-30°C) conditions until they are shipped to University of Minnesota for testing. The NHANES quality assurance and quality control (QA/QC) protocols meet the 1988 Clinical Laboratory Improvement Act mandates. Detailed QA/QC instructions are discussed in the NHANES LPM. A solid-phase fluorescent immunoassay was employed for the measurement

of human urinary albumin is described by Chavers et al. [9] Contract laboratories randomly perform repeat testing on 2% of all specimens.

Kidney function was assessed by estimated glomerular filtration rate (eGFR), calculated with using the CKD-Epi formula in both samples, employing the coefficients for White race in India.[10] Albuminuria was defined as a urine albumin to creatinine ratio (ACR) > 30 mg/g. Kidney disease was also assessed using the KDIGO risk categories, which places individuals into four risk groups for mortality based on their eGFR and ACR levels (low risk: eGFR > 60 and ACR < 30; moderately high risk: eGFR 45-59 with ACR < 30 or eGFR > 60 with ACR 30-300; high risk: eGFR 30-44 with ACR < 30, eGFR 45-59 with ACR 30-300, or eGFR > 60 with ACR > 300; or very high risk: eGFR < 30, eGFR 30-44 with ACR > 30, or eGFR 45-59 with ACR > 300.[11]

Risk factors for kidney disease were defined similarly between the two samples. Diabetes was defined by presence of any of the following: being told by a doctor they had diabetes, taking medication for diabetes (including medication from traditional healers in India), or fasting glucose > 126 mg/dl. Hypertension was defined as any of the following: being told by a doctor they had hypertension, taking medications for hypertension, or having systolic blood pressure (SBP) > 140mmHg or diastolic blood pressure (DBP) > 90mmHg.

BMI was examined as both continuous and categorical to investigate different cut-points for identifying obesity between samples, in an attempt to account for the differences in stature. In the US, the WHO definition was employed where underweight was defined as BMI < 18.5, normal weight as BMI 18.5 – 24.99, overweight as BMI 25 – 29.99, and obese as BMI ≥ 30 kg/m^2. In Punjab obesity was defined using the same criteria as other published papers using this

survey data with underweight being defined as BMI < 18.5, normal weight as BMI 18.5 – 22.99, overweight as BMI 23 – 26.99, and obese as BMI ≥ 27 kg/m^2.[1-3]

Statistical Analysis

Demographic, socio-economic, anthropometric, health status, and markers of kidney disease were compared between counties using sample weighted t-tests for means or Chi-square tests for categorical variables. ACR was expressed as the median value due to its highly right-skewed nature. Associations between patient characteristics and risk factors for kidney disease with laboratory markers of kidney disease were modeled using modified Poisson regression with robust errors. This modeling approach was chosen, as opposed to logistic regression, because it yields estimates of prevalence ratios (PRs), rather than odds ratios.[12,13] PR estimates were determined for the kidney disease risk factors within each country in a single model using interactions between a country indicator variable and each measure. PR estimates for variables other than BMI, where two parameterizations were examined, were taken from the model with BMI modeled as a continuous variable.

To compare the effect of different adjustments on the association between cohort and the markers of kidney disease, models are presented unadjusted, adjusted for demographics, and fully adjusted. Age and sex were considered as demographic variables. A sensitivity analysis was performed for each kidney disease marker, stratifying the models by sex.

Analysis of de-identified data received from the Punjab WHO Steps Survey for this study was deemed IRB exempt by the University of Michigan IRB. NHANES data is publically available for use by researchers and does not require an IRB approval.

RESULTS

Many differences exist between individuals in Punjab and the US, as shown in Table 1. The mean age was approximately four years younger in Punjab ($p<0.0001$), with a higher proportion of men (58.2% vs. 48.9%, $p<0.0001$) compared with the US. The US had a much higher percentage of both high school or higher education and private health insurance coverage ($p<0.0001$). Overall body size was very different, with Punjab residents being 6 cm shorter, weighing 18 kilograms less, having 10 cm smaller waist circumference, and BMI lower by 4.6 kg/m^2 (all $p<0.0001$). Comparison of obesity by categories showed a higher percentage of individuals in Punjab as underweight (11.3% vs. 1.5% in the US) and a higher proportion of obese individuals in the US (37.9% vs. 28.9%, $p<0.0001$), while proportions of those in the normal or overweight categories were very similar. While smoking was higher in the US, hypertension was much more common in Punjab (48.2% vs. 33.4%, $p<0.0001$). No differences were seen in the prevalence of diabetes, cardiovascular disease, or triglyceride levels, although the US had higher total cholesterol levels (4.9 vs. 3.9 mmol/L [189 vs. 150 mg/dL] in Punjab, $p<0.0001$).

Table 1: Comparison of Weighted Survey Sample Participant Characteristics between the Adult Populations in the State of Punjab, India and the United States

Measure	Punjab (2014-2015)		US (2013-2014)		P value
	N	Mean (SE) or %	N	Mean (SE) or %	
Age (years)	2,002	38.3 (0.60)	5,057	42.5 (0.38)	<0.0001
Male (%)	2,002	58.2%	5,057	48.9%	0.0001
Education to high school or above (%)	2,002	43.4%	4,718	85.3%	<0.0001
Health Insurance (%)	2,002	6.2%	5,052	79.8%	<0.0001
Height (cm)	1,986	163.0 (0.37)	5,008	169.0 (0.31)	<0.0001
Weight (Kg)	1,993	65.4 (0.6)	5,006	83.5 (0.54)	<0.0001
BMI (kg/m^2) *	1,982	24.6 (0.23)	5,000	29.2 (0.20)	<0.0001
Underweight	1,982	11.3	5,000	1.5	<0.0001
Normal		29.5		29.1	
Overweight		30.3		31.5	
Obese		28.9		37.9	
Waist (cm)	1,995	89.0 (0.62)	4,836	98.8 (0.38)	<0.0001
Current smoker (%)	2,002	7.5%	5,057	21.6%	<0.0001
Diabetes (%)	1,043	7.7%	5,057	8.9%	0.42
Hypertension (%)	2,000	48.2%	5,057	33.4%	<0.0001
CVD (%)	1,989	4.6%	5,057	3.4%	0.08
Triglyceride (mmol/L)	2,001	1.4 (0.04)	2,294	1.4 (0.04)	0.35
Total cholesterol (mmol/L)	2,002	3.9 (0.06)	4,812	4.9 (0.02)	<0.0001
Serum Creatinine (μmol/L)	2,002	61.9 (0.9)	4,798	77.8 (0.9)	<0.0001
eGFR (mL/min/1.73m^2)	2,002	114.8 (1.1)	4,798	97.8 (0.6)	<0.0001
eGFR < 60 ml/min/1.73m^2	2,002	2.0%	4,798	3.8%	<0.0001
Urine Albumin (g/L; median)	1,928	0.2 (0.03)	4,971	0.07 (0.002)	<0.0001
Urine Creatinine (μmol/L; median)	1,928	7,242 (265)	4,971	9,275 (292)	<0.0001
ACR (mg/mmol; median) ±	1,928	2.5 (0.25)	4,971	0.66 (0.007)	<0.0001
ACR > 3 mg/mmol	1,928	46.7%	4,971	8.9%	<0.0001

CVD: cardiovascular disease.
eGFR: estimated glomerular filtration rate.
ACR: urine albumin: creatinine ratio.
* Different BMI cut-points used for obesity:
US: Underweight < 18.5, normal = 18.5 - 24.9, overweight = 25 – 29.9, obese 30+
India: Underweight < 18, normal = 18 - 22.9, overweight = 23 – 24.9, obese 25+
± Median employed to examine differences in urine measurements due to high degree of risk-skew.

Although Punjab had a lower prevalence of eGFR < 60 ml/min/1.73m^2 (2.0% vs. 3.8%, p<0.0001), the prevalence of albuminuria was five times higher (46.7% vs. 8.9%, p<0.0001).

When assessing kidney function using the KDIGO risk categories (Table 2), the high prevalence of high UACR lead to 46.2% of participants in Punjab being classified as “moderately high risk”, compared to only 9.1% in the US. In contrast, Punjab had only 1.4% in the “high risk” or “extremely high risk” groups compared to 2.1% in the US (Figure 1).

Table 2: Prevalence of Albuminuria and eGFR KDIGO Risk Categories among Adults in Punjab and United States

Punjab, India				Albuminuria categories			Total
				A1	A2	A3	
				Normal to mildly increased	Moderately increased	Severely increased	
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol	
GFR categories (ml/min/1.73 m^2)	G1	Normal to high	≥90	**46.7 (40.7-52.6)**	**42.0 (35.3-48.7)**	**0.2 (0-0.7)**	**88.9 (86.0-91.8)**
	G2	Mildly decreased	60-89	**5.7 (3.6-7.6)**	**3.5 (2.4-4.7)**	**0**	**9.2 (6.8-11.5)**
	G3a	Mildly to mod decreased	45-59	**0.7 (0.1-1.3)**	**0.5 (0-1.0)**	**0**	**1.2 (0.3-2.1)**
	G3b	Mod to severe decreased	30-44	**0.3 (0-0.7)**	**0.5 (0-1.1)**	**0**	**0.8 (0.1-1.5)**
	G4	Severely decreased	15-29	**0.03 (0-0.08)**	**0.01 (0-0.02)**	**0**	**0.04 (0-0.09)**
	G5	Kidney failure	<15	**0**	**0**	**0**	**0**
Total				**53.4 (46.3-60.2)**	**46.5 (39.5-53.5)**	**0.2 (0-0.7)**	**100**

United States				Albuminuria categories			Total
				A1	A2	A3	
				Normal to mildly increased	Moderately increased	Severely increased	
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol	
GFR categories (ml/min/1.73 m^2)	G1	Normal to high	≥90	**60.7 (58.1-63.1)**	**4.8 (4.0-5.6)**	**0.5 (0.3-0.7)**	**66.0 (63.1-68.9)**
	G2	Mildly decreased	60-89	**28.1 (25.6-30.7)**	**2.2 (1.5-2.7)**	**0.1 (0.05-0.2)**	**30.4 (27.7-33.1)**
	G3a	Mildly to mod decreased	45-59	**2.1 (1.4-2.7)**	**0.4 (0.2-0.7)**	**0.2 (0-0.3)**	**2.7 (1.9-3.5)**
	G3b	Mod to severe decreased	30-44	**0.3 (0.1-0.4)**	**0.2 (0.03-0.4)**	**0.1 (0.02-0.2)**	**0.6 (0.4-0.8)**
	G4	Severely decreased	15-29	**0.05 (0.0-0.1)**	**0.05 (0.01-1.0)**	**0.09 (0-0.2)**	**0.2 (0.05-0.3)**
	G5	Kidney failure	<15	**0**	**0.06 (0-0.2)**	**0.07 (0.01-0.1)**	**0.1 (0.01-0.3)**
Total				**91.2 (90.0-92.5)**	**7.7 (6.6-8.8)**	**1.1 (0.8-1.3)**	**100**

Green = Low Risk
Yellow = Moderately High Risk
Orange = High Risk
Red = Very High Risk

To compare the magnitude of association between traditional risk factors for CKD between the two samples, we modeled prevalence ratios in each country within one model to allow for the associations to be compared statistically (Table 3). When examining low eGFR (< 60 ml/min/1.73m^2) as the outcome, male participants in Punjab showed a much lower prevalence compared with females (prevalence ratio: PR=0.22, p=0.007); while no association was seen in the US between sex and low eGFR (PR=1.09, p=0.56). These associations were significantly different from each other with p=0.006. Another difference between the associations and outcome was seen for hypertension (p=0.008), where a non-significant lower prevalence ratio was observed in Punjab (PR=0.75, p=0.43) and a strong positive association was seen in the US (PR=2.24, p<0.0001). Similar positive associations were seen in both samples for older age, higher education level, CVD, and DM on the prevalence of low eGFR (Table 3a).

Table 3b displays the associations between patient factors and the prevalence of albuminuria. Significant differences between the samples was again seen with sex and the outcome (p=0.02). No association between sex and albuminuria was seen in Punjab, where in the US males had a lower prevalence of albuminuria (PR=0.77, p=0.004). While in both samples hypertension and DM were associated with a higher prevalence of albuminuria, the magnitude of association was much stronger in the US (PR=1.19 in Punjab vs. PR=1.93 in the US for hypertension and PR=1.32 in Punjab vs. PR=2.54 in the US for DM). Current smoking was associated with albuminuria only in the US (PR=1.34, p=0.002), while higher total cholesterol was associated with albuminuria in the Punjab (PR=1.11 per 0.5 mmol/L higher total cholesterol).

When combining low eGFR and albuminuria into a composite (CKD) outcome (Table 3c) more differences were found between the samples in certain associations. Significantly larger associations were found in the US for the relationship between older age, hypertension, DM, and BMI; while a larger association was seen between total cholesterol and the composite CKD measure in the Punjab.

Table 3: Prevalence Ratios for Markers of CKD by Risk Factors

A. Low eGFR (eGFR < 60 ml/min/1.73m^2)

Measure	Punjab			US			P-value for interaction
	PR	95% CI	P	PR	95% CI	P	
US (vs. Punjab)	1.00	-	-	0.05	0.004 – 0.71	***0.03***	-
Age (per 10 years)	1.73	1.29 – 2.31	0.0002	2.14	1.82 – 2.52	<0.0001	0.20
Male (vs. Female)	0.22	0.07 – 0.66	0.007	1.09	0.81 – 1.47	0.56	***0.006***
Education high school + (vs. no)	1.86	0.84 – 4.10	0.13	1.53	1.06 – 2.20	0.02	0.66
Current smoker (vs. no)	2.32	0.31 – 1.74	0.41	0.92	0.63 – 1.34	0.66	0.38
Hypertension (vs. no)	0.75	0.37 – 1.52	0.43	2.24	1.51 – 3.33	<0.0001	***0.008***
DM (vs. no)	2.75	1.17 – 6.48	0.02	1.76	1.27 – 2.44	0.0007	0.34
CVD (vs. no)	1.11	0.34 – 3.60	0.87	1.98	1.20 – 1.38	0.0002	0.35
Total Cholesterol (per 20 mg/dl, per 0.5 mmol/L)	1.09	0.73 – 1.64	0.67	0.92	0.76 – 1.11	0.36	0.44
BMI (per 5 Kg/m^2)	0.82	0.59 – 1.15	0.25	1.13	1.04 – 1.23	0.006	0.07
Obesity:							
Underweight	1.24	0.26 – 5.95	0.79	1.45	0.36 – 5.89	0.60	0.88
Healthy weight	1.00	-	ref	1.00	-	ref	
Overweight	2.63	1.09 – 6.34	0.03	1.31	0.83 – 2.07	0.25	0.17
Obese	0.73	0.27 – 1.95	0.53	1.40	0.91 – 2.14	0.13	0.23

B. Albuminuria (ACR > 30 mg/g, 3 mg/mmol)

Measure	Punjab			US			P-value for interaction
	PR	95% CI	P	PR	95% CI	P	
US (vs. Punjab)	1.00	-	-	0.18	0.08 – 0.38	<0.0001	-
Age (per 10 years)	1.03	0.99 – 1.08	0.16	1.06	0.98 – 1.14	0.15	0.60
Male (vs. Female)	0.99	0.88 – 1.12	0.93	0.77	0.65 – 0.92	0.004	***0.02***
Education high school + (vs. no)	0.99	0.88 – 1.11	0.80	0.81	0.67 – 0.98	0.03	0.09
Current smoker (vs. no)	1.09	0.85 – 1.40	0.48	1.35	1.11 – 1.63	0.002	0.20
Hypertension (vs. no)	1.19	1.06 – 1.34	0.005	1.93	1.59 – 2.36	<0.0001	***<0.0001***
DM (vs. no)	1.32	1.12 – 1.56	0.0008	2.54	2.07 – 3.13	<0.0001	***<0.0001***
CVD (vs. no)	1.14	0.92 – 1.37	0.24	1.32	1.16 – 0.99	0.06	0.37
Total Cholesterol (per 20 mg/dl, per 0.5 mmol/L)	1.11	1.04 – 1.17	0.001	0.99	0.90 – 1.09	0.81	***0.05***
BMI (per 5 Kg/m^2)	0.99	0.94 – 1.03	0.54	1.04	0.98 – 1.10	0.19	0.16
Obesity:							
Underweight	0.90	0.72 – 1.11	0.32	1.20	0.56 – 2.56	0.64	0.47
Healthy weight	1.00	-	ref	1.00	-	ref	-
Overweight	0.95	0.82 – 1.10	0.48	0.93	0.72 – 1.18	0.53	0.85
Obese	0.95	0.83 – 1.09	0.48	1.01	0.80 – 1.27	0.96	0.68

C. CKD (low eGFR or Albuminuria)

Measure	Punjab			US			P-value for interaction
	PR	95% CI	P	PR	95% CI	P	
US (vs. Punjab)	1.00	-	-	0.11	0.05 – 0.22	<0.0001	-
Age (per 10 years)	1.04	1.00 – 1.09	0.06	1.20	1.12 – 1.29	<0.0001	***0.0007***
Male (vs. Female)	0.97	0.86 – 1.09	0.58	0.81	0.70 – 0.94	0.007	0.0686
Education high school + (vs. no)	1.00	0.90 – 1.12	0.96	0.91	0.77 – 1.09	0.31	0.379
Current smoker (vs. no)	1.09	0.85 – 1.40	0.49	1.26	1.06 – 1.49	0.008	0.3526
Hypertension (vs. no)	1.18	1.05 – 1.33	0.006	1.87	1.57 – 2.23	<0.0001	***<0.0001***
DM (vs. no)	1.35	1.16 – 1.58	0.0002	2.11	1.77 – 2.53	<0.0001	***0.0002***
CVD (vs. no)	1.13	0.94 – 1.37	0.19	1.49	1.12 – 1.18	0.0006	0.072
Total Cholesterol (per 20 mg/dl, per 0.5 mmol/L)	1.09	1.04 – 1.16	0.002	0.97	0.88 – 1.05	0.41	***0.02***
BMI (per 5 Kg/m^2)	0.98	0.94 – 1.03	0.48	1.06	1.01 – 1.12	0.017	***0.025***
Obesity:							
Underweight	0.89	0.72 – 1.10	0.28	1.31	0.67 – 2.54	0.43	0.28
Healthy weight	1.00	-	ref	1.00	-	ref	-
Overweight	0.98	0.86 – 1.13	0.81	0.98	0.79 – 1.22	0.84	0.97
Obese	0.95	0.83 – 1.09	0.48	1.06	0.86 – 1.29	0.60	0.41

Unadjusted and less fully adjusted models are presented in Supplemental Tables 1-3 for each of the kidney disease markers. As shown in Figure 2, which displays the changes in prevalence ratios comparing US to Punjab for each marker of CKD for different levels of adjustments, only low eGFR showed a marked change. . Before accounting for any differences in participants in the two studies, the prevalence of low eGFR was much higher in the US

(PR=2.16), but after accounting for demographics (age and sex) and other health measures (remaining covariates), the US has a much lower prevalence of low eGFR compared to Punjab (PR=0.13 and 0.05, respectively), suggesting that if the US had the same patient make up as Punjab, the prevalence of low eGFR would be much lower. The findings for albuminuria and any CKD were very similar in showing that before adjustment the prevalence of either marker was much lower in the US (PR=0.24 and 0.29, respectively) and accounting for difference in demographics and health measures between the samples changed these estimates very little. These results suggest that traditional risk factors do not entirely explain the difference in prevalence seen among markers of kidney disease between the US and Punjab.

In a sensitivity analysis, examining the association between risk factors and each kidney marker separately by sex, no significant changes in association direction or magnitude were detected (data not shown).

DISCUSSION

In comparing two representative samples of participants from the adult population of Punjab, India and the United States, we found a very high prevalence of albuminuria in the Punjab, with almost half of the residents with urine ACR > 3 mg/mmol (30 mg/g). This is in contrast to the prevalence of albuminuria in the US of approximately 9%. When examining glomerular filtration rate, the Punjab had much higher average eGFR and a lower prevalence of eGFR < 60 ml/min/1.73m^2 (2.0% vs. 3.8%). Because of the high prevalence of albuminuria in the Punjab, almost half the population falls into the “moderately high risk” CKD risk category per KDIGO risk stratification criteria. Even more striking is the fact that the between country

differences in the prevalence estimates of albuminuria could not be explained by traditional risk factors for CKD, such as age, hypertension, and diabetes.

If true, these findings have enormous public health and resource implications for a low-middle income country such as India, specifically in the realm of CKD, cardiovascular disease and other NCDs. Currently there are no definitive estimates of prevalence of chronic kidney disease in India, as there is no ongoing national kidney registry/surveillance system. Recent publications have suggested that 220,000 patients are diagnosed with ESRD every year.[14] It is estimated that this will result in demand for an additional 34 million dialysis sessions in India each year. Besides the growing population of patients with kidneys disease, the country is faced with a shortage of nephrologists, late referral of patients, inadequate health awareness about preventive measures, and a lack of more cost-effective alternatives like renal transplantation or peritoneal dialysis (PD).[14] It has been estimated that 70% of those who start dialysis in India eventually give up dialysis due to financial constraints or death.[15] The health care system, with most out-of-pocket expenditures borne by the households pose significant barriers to accessing health services with approximately 60 million households pushed below the poverty line in India as a result each year.[16]

We believe that our finding of the discordance observed in the prevalence of albuminuria versus lower eGFR between India and the US could be in part due to the epidemiologic transition that is occurring in countries such as India, where early evidence of kidney damage but lower prevalence of low eGFR defined kidney disease or end stage kidney disease, may be the result of higher death rates among the younger population from premature cardiovascular disease, so while early kidney disease evidenced by albuminuria is more common, prevalence of later stages of kidney disease is lower (but potentially rising). Although not to the same degree, we reported

similar findings in a recent study comparing CKD between China and the US.[17] China, another country which has gone through great economic and population growth in recent years, displayed a low prevalence of advanced kidney disease (eGFR < 60 ml/min/1.73m^2), but a higher prevalence of albuminuria than the US. The strength of association between traditional risk factors, such as hypertension and diabetes, were also weaker among the Chinese sample, although the association between age and CKD prevalence was much stronger.

Supportive evidence for a high rate of albuminuria in India have been reported from the western state of Gujarat. [18] This study represents a voluntary sample of participants who were screened during a World Kidney Day Screening Camp. Even though the investigators excluded individuals at risk of albuminuria (participants with known diabetes, stone diseases, hypertension, kidney/liver/cardiac disease, hepatitis, HIV, transplant recipients, pregnant women and those < 18 years of age), they estimated a 13.8% prevalence of albuminuria in their study. This is higher than in the US general population random sample in NHANES, which includes the individuals most likely to have albuminuria.

The high prevalence of albuminuria in Punjab could be related to the metabolic syndrome known to be associated with albuminuria. [19] In this context, insulin resistance and visceral adiposity are common in developing nations and mechanistically linked with the metabolic syndrome through adipocytokines and inflammation. [20] The high prevalence of premature cardiovascular disease and hypertension can be accompanied by albuminuria from vascular dysfunction or damage, leading to disruption of the glomerular filtration barrier. Furthermore, the evidence linking kidney disease to environmental factors continues to grow. [21] Air pollution (highly prevalent in that part of the world), is associated with both endothelial dysfunction and low grade inflammation with resultant albuminuria. In the US, PM2.5 levels

have been linked to the prevalence of CKD, risk of incident CKD, and its progression.[22,23] This association is also being explored outside the US with findings published from Taiwan and Korea showing similar results.[24-26] India currently has some of the highest levels of air pollution in the world. It is estimated that 1.5 million people died from the effects of air pollution in 2012. [27,28] While less studied, it is also plausible that kidney disease may be influenced by pollutants in both the water and soil as well, similar to the factors potentially underlying the epidemic of CKD of unknown etiology, although this has not been reported from northern India, and albuminuria is not the hallmark of this latter condition. [29]

Unless actions are undertaken now to further investigate and reduce the high rate of albuminuria (albeit based on single cross-sectional estimates) reported in this study, the infrastructure and economy in India will be faced with a daunting task of needing to care for an increasing burden of those progressing to ESRD, in the not too distant future. Further, since albuminuria is also a marker of endothelial dysfunction and has been linked to cardiovascular outcomes, even at low levels, the higher risk of premature cardiovascular disease needs to be kept in mind in relation to albuminuria. [30-32]

To the best of our knowledge, this is the first study to estimate kidney disease prevalence at state level in India based on a random sample of the adult population living in a large, populous, northern Indian state. Further, it is also the first to compare prevalence of CKD between India and the US (after adjusting for patient characteristics around the same time period in the two nations). However, it is not without limitations. Because the sample from India was only from one state, the Punjab, we cannot generalize our findings to all of India. Although this is a large state, the risk factor distribution and prevalence could be different in other areas of the country.[33] In addition, the people, land and environment in India are diverse and of a highly

variegated nature with significant urban-rural differences. It should also be acknowledged that the Punjab STEPS survey is cross-sectional in design and while appropriately sampled to be representative of the state, may be limited by its sample size. The Punjab STEPS survey also employed commercially available point-of-care test strips, to assess albuminuria, whereas in the US, this was assessed on the urine collected in a central laboratory. Lastly, both NHANES and the Punjab STEPS survey checked albuminuria and serum creatinine at a single point in time, whereas the KDIGO definition of CKD requires demonstration of persistence of these abnormalities. We believe however, that repeat sampling of blood and urine in public health surveys, while highly desirable, is often difficult to achieve in the real world. Variations in albuminuria both within the same patient and across populations are possible; however, only single readings of albuminuria were available for each participant in this study.

Future research to confirm our findings using repeat sampling and similar studies in other states, and further examination of the association between environmental factors and kidney disease in India is urgently warranted. Such studies would benefit from having population samples from multiple states, preferably be longitudinal in nature, and have the potential to examine multiple environmental factors, while accounting for the traditional risk factors for kidney disease.

In summary, we report very high prevalence of albuminuria in a large state (the Punjab) in northern India. Albuminuria is considered an early sign of kidney damage as well as may reflect endothelial dysfunction, a harbinger of atherosclerosis-related cardiovascular disease. Progression of this early stage kidney and cardiovascular disease elevates the potential for an epidemic of ESRD and higher rates of cardiovascular disease in a country undergoing rapid epidemiologic and economic transition. Urgent action and further research is needed to

determine the underlying cause(s) of these findings, in the hopes of stemming the tide of rising rates of kidney failure and cardiovascular disease. India must clearly prepare for an inevitable increase in the need for renal replacement therapy in the coming years.

COMPETING INTERESTS:

Jennifer L. Bragg-Gresham: None

JS Thakur: None

Gursimer Jeet: None

Sanjay Jain: None

Arnab Pal: None

Rajendra Prasad: None

Subramaniam Pennathur: None

Rajiv Saran: None

CONTRIBUTION STATEMENT:

Jennifer L. Bragg-Gresham: Data analysis and interpretation, manuscript writing, tables/figures creation

JS Thakur: Study design (India), data collection, manuscript planning, manuscript review and editing

Gursimer Jeet: Study design, data collection and programming, manuscript review and editing

Sanjay Jain: Study design, manuscript review and editing

Arnab Pal: Study design, manuscript review and editing

Rajendra Prasad: Study design, manuscript review and editing

Subramaniam Pennathur: Manuscript review and editing

Rajiv Saran: Study concept, data interpretation, manuscript writing, manuscript review and editing

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DATA SHARING STATEMENT

All US data from the National Health and Nutrition Examination Survey (NHANES) is publically available at https://www.cdc.gov/nchs/nhanes/index.htm. The Punjab data is available by request and approval through collaborative agreements with the sponsors. Professor JS Thakur is the Principal Investigator and can be contacted at jsthakur64@gmail.com.

FIGURE TITLES AND LEGENDS

Figure 1: Distribution of KDIGO Risk Categories among Adults in Punjab, India and the United States

Figure 2: Changes in Prevalence Ratios between Punjab and the US for Markers of CKD with Different Levels of Adjustment for Risk Factors

A. Low eGFR

B. Albuminuria

C. Any CKD

Footnote: Demographics = age, sex, and education & All = Demographics plus measures in Table 3 (Current smoker, Hypertension, DM, CVD, Total Cholesterol, Obesity as BMI categories)

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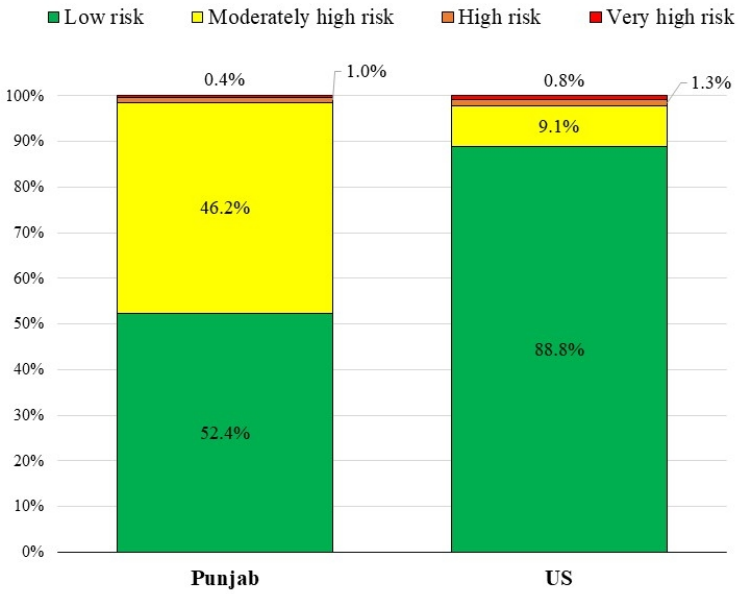

Figure 1: Distribution of KDIGO Risk Categories among Adults in Punjab, India and the United States

254x190mm (96 x 96 DPI)

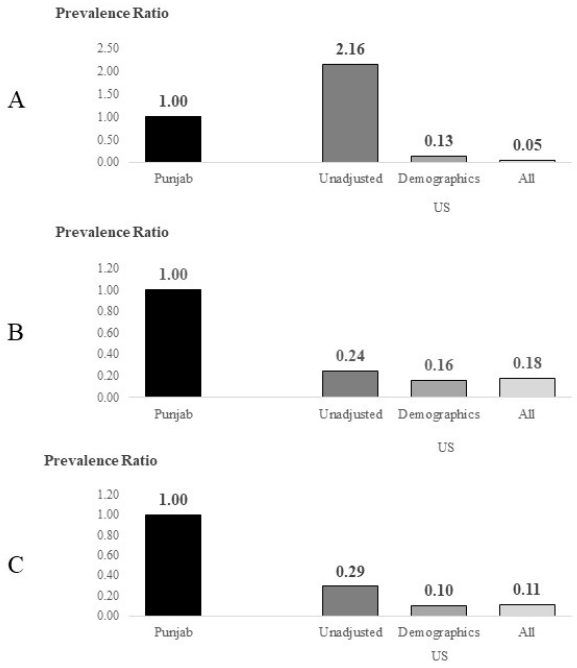

Figure 2: Changes in Prevalence Ratios between Punjab and the US for Markers of CKD with Different Levels of Adjustment for Risk Factors

A. Low eGFR

B. Albuminuria

C. Any CKD

Footnote: Demographics = age, sex, and education & All = Demographics plus measures in Table 3 (Current smoker, Hypertension, DM, CVD, Total Cholesterol, Obesity as BMI categories)

254x190mm (96 x 96 DPI)

Supplemental Table 1: Changes in Prevalence Ratios for Low eGFR between Punjab and the US for Markers of CKD with Different Levels of Adjustment for Risk Factors

Unadjusted:

Measure	Punjab			US			P-value for interaction
	PR	95% CI	P	PR	95% CI	P	
US (vs. Punjab)	1.00	-	-	2.16	1.51 – 3.13	<0.0001	-

Adjusted for Demographics:

Measure	Punjab			US			P-value for interaction
	PR	95% CI	P	PR	95% CI	P	
US (vs. Punjab)	1.00	-	-	0.13	0.02 – 0.73	0.02	-
Age (per 10 years)	1.83	1.38 – 2.42	<0.0001	2.61	2.28 – 3.03	<0.0001	***0.03***
Male (vs. Female)	0.23	0.08 – 0.66	0.001	1.16	0.87 – 1.54	0.32	***0.004***
Education high school + (vs. no)	1.69	0.80 – 3.57	0.17	1.45	1.01 – 2.11	0.047	0.74

Supplemental Table 2: Changes in Prevalence Ratios for Albuminuria between Punjab and the US for Markers of CKD with Different Levels of Adjustment for Risk Factors

Unadjusted:

Measure	Punjab			US			P-value for interaction
	PR	95% CI	P	PR	95% CI	P	
US (vs. Punjab)	1.00	-	-	0.24	0.22 – 0.27	<0.0001	-

Adjusted for Demographics:

Measure	Punjab			US			P-value for interaction
	PR	95% CI	P	PR	95% CI	P	
US (vs. Punjab)	1.00	-	-	0.16	0.11 – 0.24	<0.0001	-
Age (per 10 years)	1.09	1.02 – 1.13	<0.0001	1.27	1.19 – 1.36	<0.0001	***<0.0001***
Male (vs. Female)	1.05	0.91 – 1.13	0.41	0.78	0.66 – 0.93	0.007	***0.006***
Education high school + (vs. no)	0.96	0.86 – 1.07	0.45	0.73	0.60 – 0.88	0.001	***0.02***

Supplemental Table 3: Changes in Prevalence Ratios for Any CKD between Punjab and the US for Markers of CKD with Different Levels of Adjustment for Risk Factors

Unadjusted:

Measure	Punjab			US			P-value for interaction
	PR	95% CI	P	PR	95% CI	P	
US (vs. Punjab)	1.00	-	-	0.29	0.26 – 0.32	<0.0001	-

Adjusted for Demographics:

Measure	Punjab			US			P-value for interaction
	PR	95% CI	P	PR	95% CI	P	
US (vs. Punjab)	1.00	-	-	0.10	0.07 – 0.15	<0.0001	-
Age (per 10 years)	1.09	1.05 – 1.14	<0.0001	1.42	1.34 – 1.51	<0.0001	***<0.0001***
Male (vs. Female)	1.02	0.91 – 1.13	0.76	0.82	0.71 – 0.96	0.01	***0.03***
Education high school + (vs. no)	0.98	0.87 – 1.09	0.65	0.84	0.70 – 0.99	0.04	0.14

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	8
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-10
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-15

		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20-21

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.