Keynote Address

Chronic Kidney Disease; Global and Sri Lankan Perspectives

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Global perspective; aetiology of kidney disease

- Diabetes
- Hypertension
- Primary glomerulonephritis
- Infections
- Collagen disorders
- Environmental toxins
- Drugs
- Herbal products
- Hereditary factors
- Others

CKD due to environmental factors is not unique to Sri Lanka

- Nicaragua
- El Salvador
- Costa Rica
- Croatia
- Bulgaria
- Serbia
- Japan
- Others ……..

Mystérieuse épidémie au Nicaragua

LE MONDE SCIENCE ET TECHNO | 23.09.2013 à 16h31 • Mis à jour le 26.09.2013 à 23h34 | Par Lise Barnéoud

Chronic Kidney Disease of uncertain origin (CKDu) in Sri Lanka

- Direct request was made by the Hon. Minister of Health to the Director General, World Health Organization for technical advise
- WHO reviewed all available data in 2008/2009
- In 2008/2009, data were inadequate to provide any technical advise

National Research Project-CKDu

Aim

To conduct research to develop strategies for prevention and control of CKDu.

- Leadership of His Excellency the President and the Honorable Minister of Health
- Led by the Ministry of Health with technical support from WHO
- Funded by the National Science Foundation and WHO

- Acknowledgements

  The National CKDu project team, WHO country team

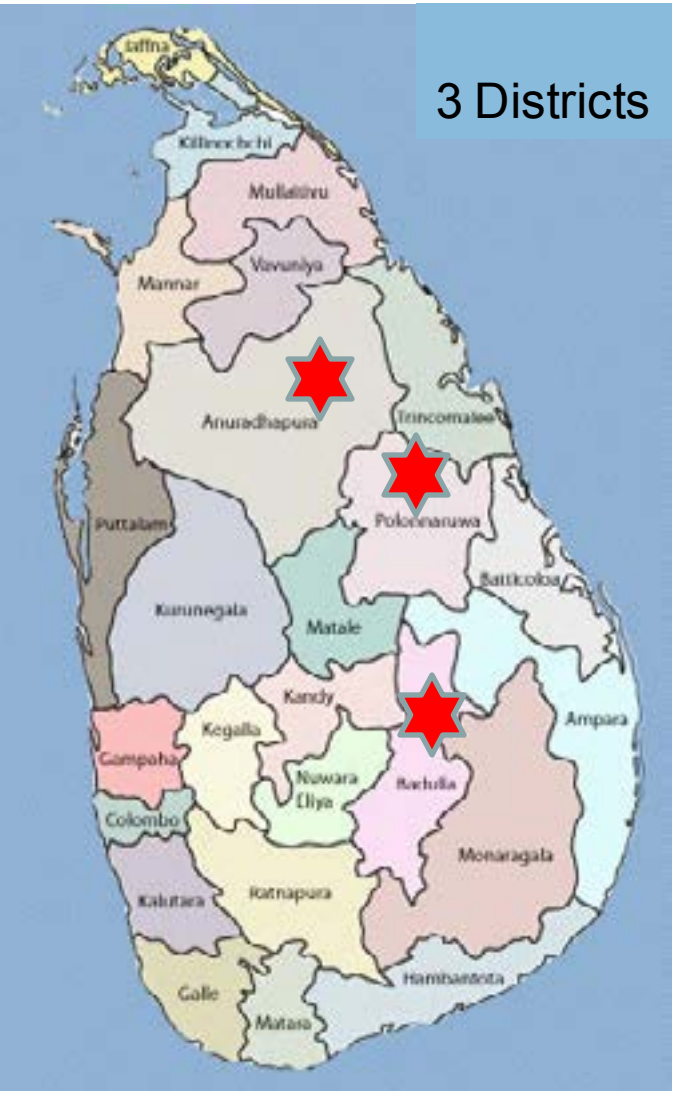
  People, patients and families

  Government officials and Grama Niladaris

Set of multifacted studies

1. Population prevalence
2. CKDu risk factors
3. Exposure to nephrotoxic heavy metals
4. Heavy metal în food and water
5. Heavy metals in soil, fertilizers and pesticides
6. Role of protective factors and genetic factors
7. Role of other metals
8. Exposure to pesticides
9. Nephrotoxic herbal remedies
10. Randomized controlled trial on treatment
11. Socioeconomic and productivity impact

Population prevalence



6 Divisional Secretariat Areas

22 Gramaniladhari Divisions

2200 Households

(100 Houses from each GN)

Respons e Rate **74%**

6,698 total eligible

6,132 responded to questionnaire

4,941 sampled (15-70 years)

Case Definition of Chronic Kidney Disease of Uncertain Aetiology

- **Urine ACR** ≥ 30 mg/g on two occasions
- No **past history** of ureteric calculi, glomerulonephritis, pyelonephritis or snake bite
- Not on treatment for diabetes
- Normal **HbA1C** (< 6.5%)
- If on treatment for hypertension, BP < 140/90m if not on treatment BP < 160/100
- CKDu Stages 1,2,3,4 (CKD EPI collaboration)

Population prevalence

- Age standardized prevalence of CKDu :
  females 16.9% (95% CI: 15.5- 18.3)
  males12.9% (95% CI:11.5-14.4)

- Severe stages of CKDu seen more frequently in males
  stage 3: males vs females = 23.2%vs 7.4%
  stage 4 : males vs females = 22.0% vs 7.3%) ($p<0.001$).

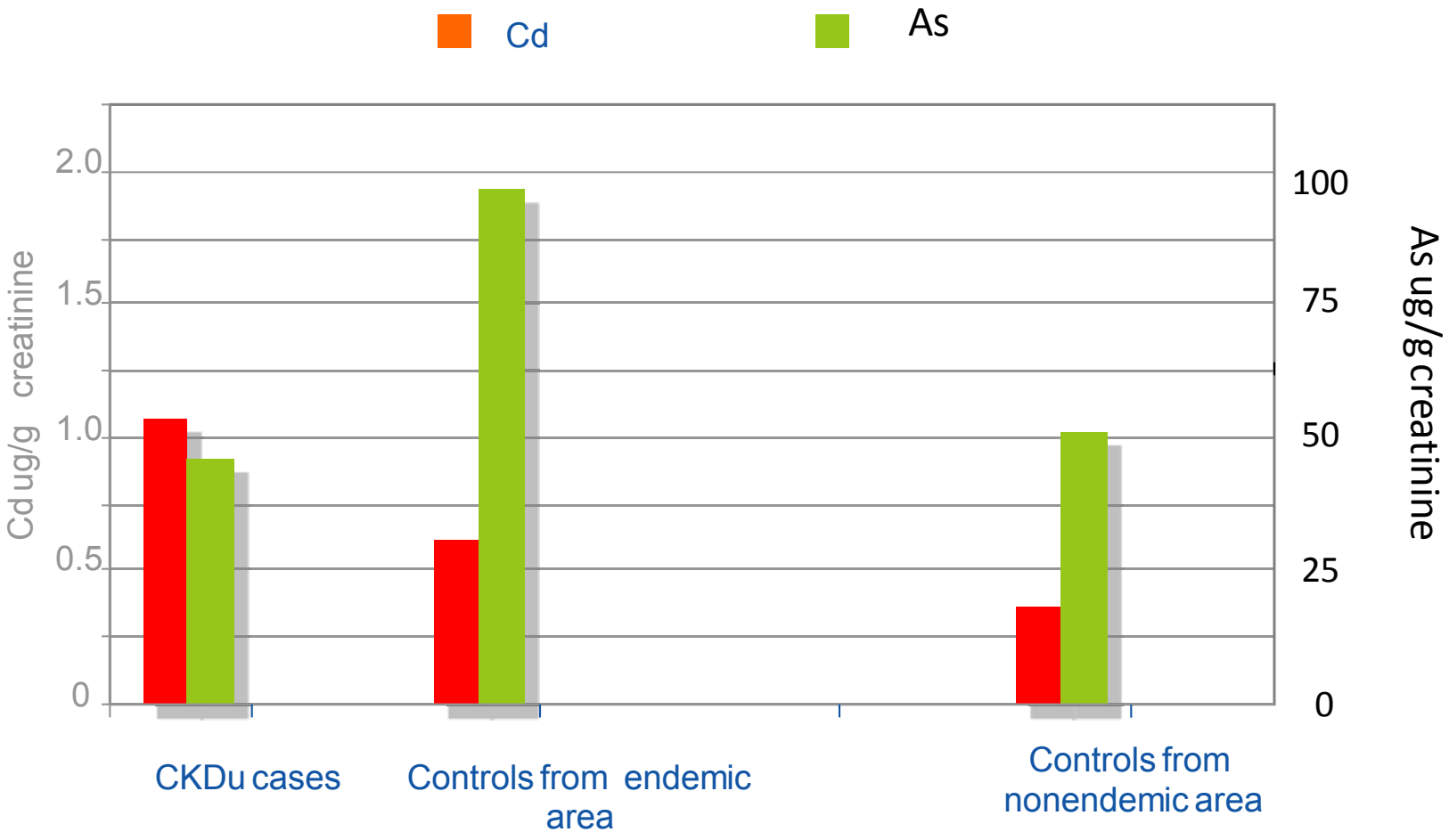
2

CKDu risk factors

- Being > 39 years increased the risk of CKDu (OR 1.926, 95% CI 1.561-2.376, $p<0.001$).
- Engaging in chena/vegetable cultivation increased the risk of CKDu by 19.5%
- Positive family history in parents or siblings in 20%

3

Heavy metals in urine



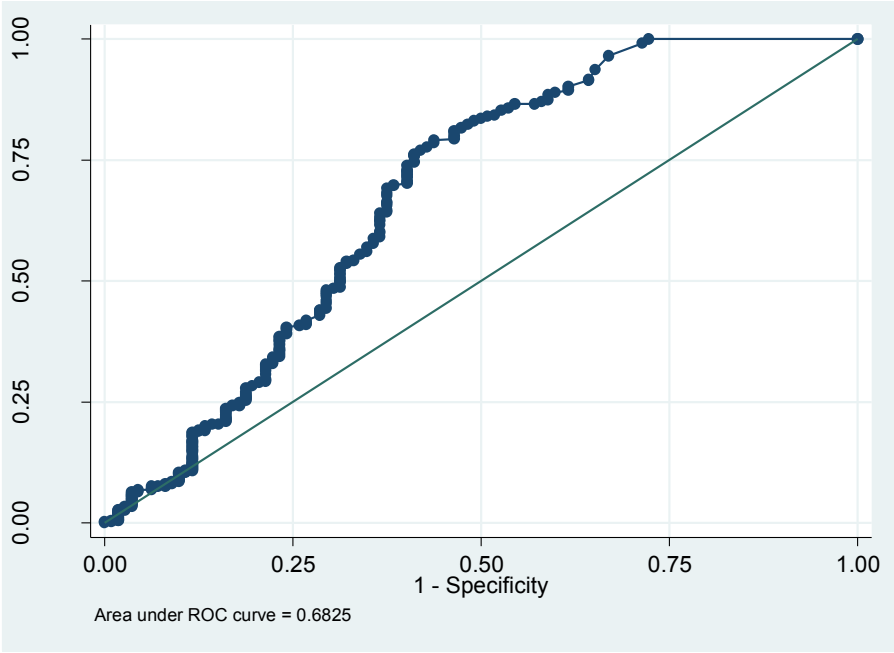
Urine lead, sodium, potassium, calcium, magnesium, copper, zinc and uranium analyzed

*Urine Cd in CKDu cases significantly higher compared to controls in the endemic and nonendemic areas

World Health Organization

Cadmium

•(AUC=0.682, 95% CI: 0.61-0.75,
At a cutoff value of ≥ 0.397 µg/g
sensitivity/specificity 70%, 68.3%



•Dose effect response was seen for urine cadmium and CKDu.

•Cadmium in nails was significantly higher in CKDu cases (mean 0.017 vs 0.009), ($p<0.05$).
No significant difference in cadmium in hair

Exposure to nephrotoxic heavy metals As and Pb

- Urine As and Pb in CKDu cases compared to controls showed no significant difference. Levels of As in urine was high enough to aggravate oxidative damage of Cd on kidneys.

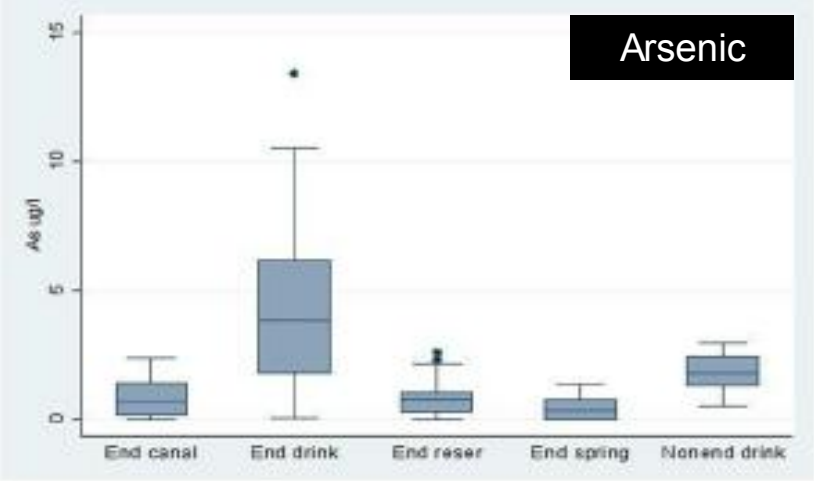
- Significant correlation between urine Cd and As and Pb

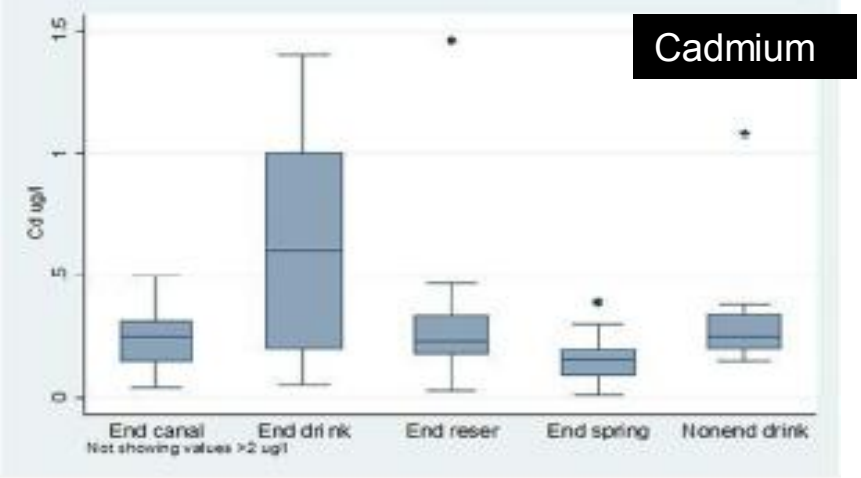
- There was no significant dose-effect relationship between As, Pb and CKDu.

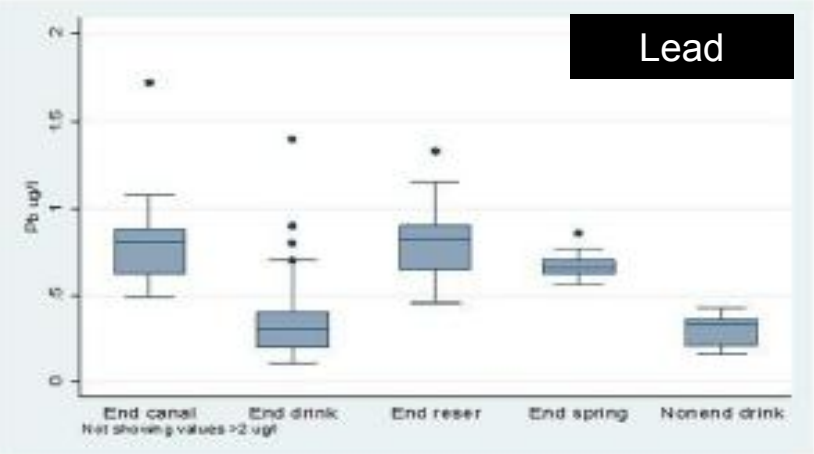
Heavy metals in water

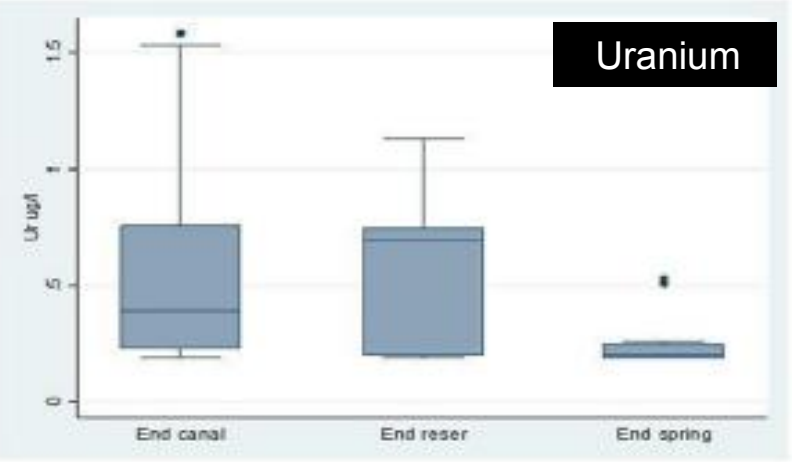
- Samples from endemic (n=222) and nonendemic (n=12) areas
  - wells,
  - tube wells,
  - irrigation canals,
  - pipe-borne water,
  - reservoirs
  - natural springs

RESULTS OF WATER ANALYSIS









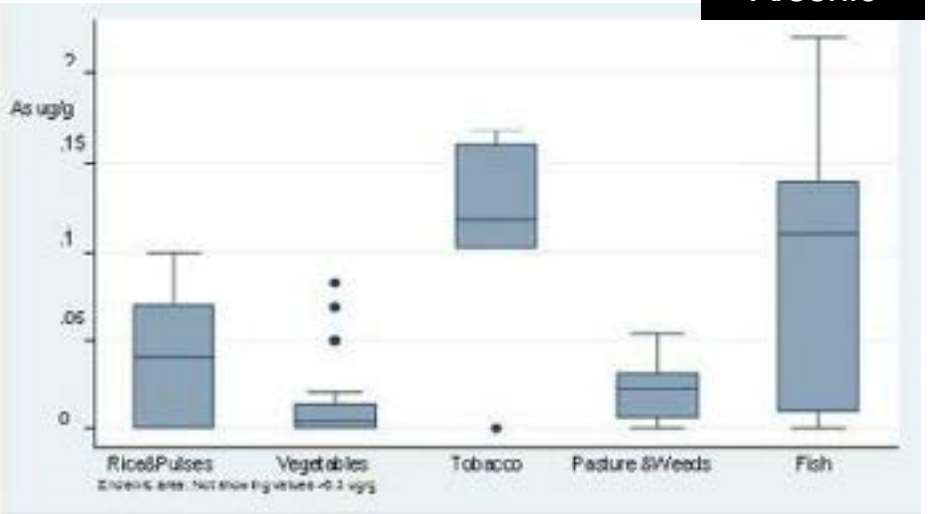
As levels were 22.2 ug/l and 9.8 ug/l in two samples taken from a canal and a reservoir
Cd was 3.46 ug/l in one sample from a reservoir
Pb was 12.3 ug/l in one sample from a reservoir in the endemic area .

Heavy metals in food, pasture and weeds

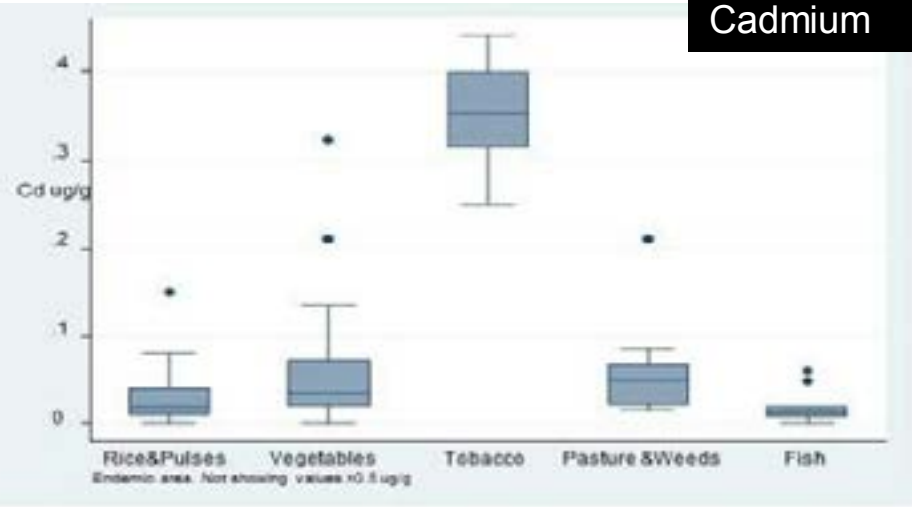
- Samples were obtained from endemic (n= 119) and non-endemic areas (n=32).
- Food items, weeds, pasture
  - rice
  - pulses
  - fresh water fish
  - vegetables
  - coconut
  - yams and roots
  - tobacco
  - betel leaf
  - pasture
  - weeds

RESULTS OF FOOD ANALYSIS

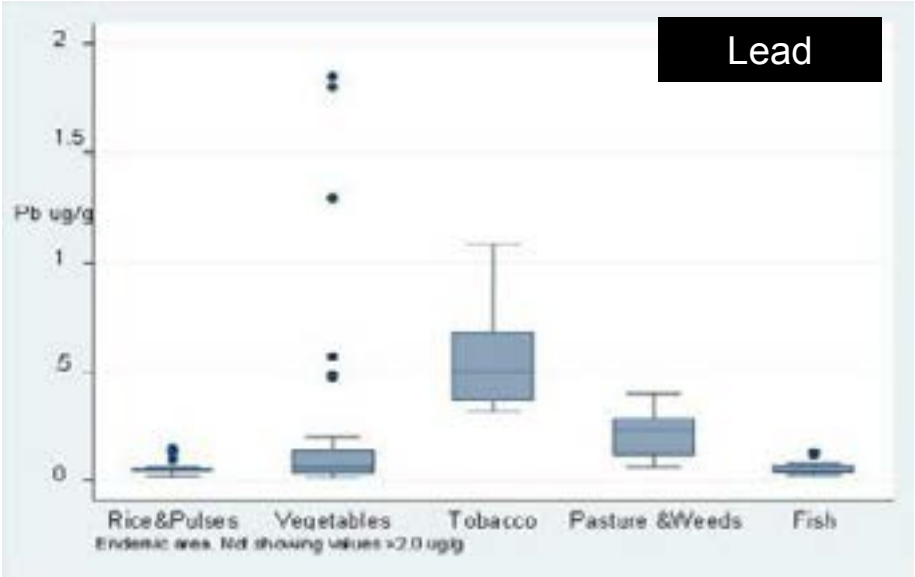
Arsenic



Cadmium



Lead



maximum <u>cadmium</u> permitted by the Codex Alimentarius for vegetables is **0.2 mg/kg** and by the Commission of the European Communities is **0.05 mg/kg**

maximum concentration of cadmium stipulated for certain types of fish by the Commission of the European Communities is **0.05 mg/kg**.

maximum concentration of <u>lead</u> stipulated for vegetables by the Commission of the European communities is **0.10 mg/kg** .

Cadmium in food and tobacco

- The maximum concentration of Cd in vegetables in the endemic area and in the nonendemic areas were 0.322 and 0.063 mg/kg respectively.

(maximum Cd permitted by the Codex Alimentarius for vegetables is **0.2 mg/kg)**

- Cd in certain vegetables such as lotus root and in tobacco were high. Endemic higher than nonendemic

  Lotus : mean 0.413 vs 0.023

- Cd in freshwater fish in the endemic area were above stipulated levels.

- Cd in rice in both endemic and nonendemic areas were less than the allowable limit (0.2 mg/Kg) Endemic area 0.033, 0.018, 0.006, 0.15

- Levels of Pb in certain vegetables in the endemic area were above stipulated levels.

FOOD

Key Finding

Provisional tolerable weekly intake (PTWI)

- **Cadmium** → - **2.52**(ug/kg)*
- **Arsenic** - **0.015**(mg/kg) (under revision)
- **Lead** - **0.025**(mg/kg)

Since the cadmium content of certain food items in the endemic area is above stipulated levels, the total weekly intake of cadmium in people living in the endemic area could exceed these safe limits, with detrimental effects on the kidneys, particularly in vulnerable people and those with predisposing factors.

Soil analysis (endemic 88, nonendemic 41)

Source		Arsenic (ug/g)		Cadmium (ug/g)		Lead (ug/g)	
		Endemic Area (EA)	Non Endemic Area (NEA)	Endemic Area (EA)	Non Endemic Area (NEA)	Endemic Area (EA)	Non Endemic Area (NEA)
Paddy EA(n=45) NEA (n=21)	Mean	0.16	0.17	0.49	0.45	16.54	14.49
	Median	0.11	0.08	0.43	0.40	15.75	16.95
	Minimum	0.00	0.01	0.16	0.01	5.03	0.02
	Maximum	0.85	0.99	0.56	1.61	34.54	39.95
Chena EA(n=20) NEA (n=10)	Mean	0.06	0.40	0.40	0.59	15.41	14.84
	Median	0.04	0.29	0.36	0.55	13.82	13.93
	Minimum	0.00	0.09	0.17	0.34	8.25	5.42
	Maximum	0.22	1.57	1.27	0.93	28.33	26.1
Vegetable Plot EA(n=23) NEA (n=10)	Mean	0.11	0.27	3.48	0.47	17.46	18.01
	Median	0.07	0.24	0.37	0.41	16.76	18.03
	Minimum	0.00	0.08	0.16	0.29	6.69	5.57
	Maximum	0.46	0.53	70.00	0.84	41.02	32.87
Crop land EA (n=6) NEA (n=2)	Mean	0.05	0.13	0.60	0.28	20.55	7.96
	Median	0.06	0.13	0.5	0.28	20.29	7.96
	Minimum	0.00	0.09	0.17	0.24	9.98	3.15
	Maximum	0.01	0.18	1.47	0.33	32.1	12.77
Reservoir EA (n=6) NEA (n=3)	Mean	0.60		0.66		19.16	
	Median	0.50		0.52		17.16	
	Minimum	0.17		0.15		7.11	
	Maximum	0.43		1.36		33.49	

RESULTS OF SOIL ANALYSIS

The level of **Cadmium** in surface soil in the endemic area (n = 94, excluding samples from reservoirs), was 1.16 µg/g compared to 0.49 µg/g in the non-endemic area (n = 45,excluding samples from reservoirs)

Heavy metals in weedicides and pesticides

	Arsenic (ug/g)		Cadmium (ug/g)		Lead (ug/g)	
	Endemic Area (EA) **n=26**	Non Endemic Area (NEA) **n=8**	Endemic Area (EA) **n=26**	Non Endemic Area (NEA) **n=8**	Endemic Area (EA) **n=26**	Non Endemic Area (NEA) **n=8**
Mean	6.73	3.81	0.77	0.76	40.62	15.65
Median	1.68	1.38	0.31	0.3	1.79	1.89
Minimum	0.01	0.01	0.05	0.05	0.83	1.01
Maximum	94.93	13.15	9.34	2.0	930.81	56.39

Heavy metals in phosphate fertilizer

	Cadmium (ug/g)		Lead (ug/g)		Arsenic (ug/g)	
	Endemic Area (EA) **n=13**	Non Endemic Area (NEA) **n=6**	Endemic Area (EA) **n=13**	Non Endemic Area (NEA) **n=6**	Endemic Area (EA) **n=13**	Non Endemic Area (NEA) **n=6**
Mean	2.98	0.49	94.23	20.29	0.06	0.43
Median	0.04	0.03	1.42	0.65	0.04	0.19
Minimum	0.01	0.01	0.17	0.09	0.00	0.00
Maximum	30.79	1.28	823.41	98.52	0.19	1.22

The maximum acceptable levels for Cadmium, Lead and Arsenic, in phosphate fertilizer product, at 1% of the nutrient level, are 4 µg/g, 20 µg/g and 2 µg/g, respectively

A total of 19 samples analyzed (TSP – 6, MOP – 3, Urea – 7, Mixed - 3)

Other metals and protective factors in CKDu

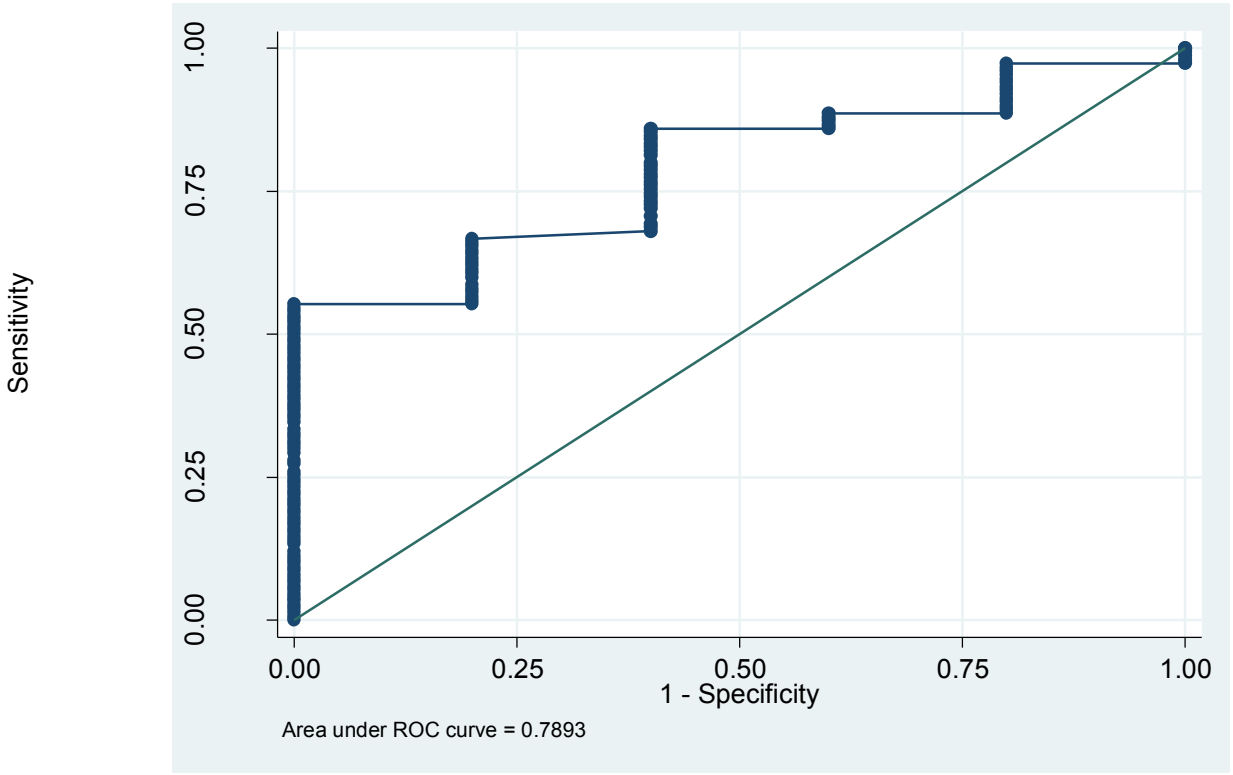
- Serum aluminium, calcium, magnesium, copper, zinc, titanium, chromium, sodium, potassium were within normal limits

- Serum selenium ranged from 50.0 – 121.8 µg/l

(reference range 54-163 µg/l).

- Serum selenium required to reach maximum glutathione peroxidise is 90 µg/L . About two thirds (63%) had Se below this cut off.

ROC curve generated with serum selenium levels



AUC=0.789, cutoff value ≥94.3μg/L sensitivity 80% and specificity 60% .

Pesticide analysis

Pesticide residues were detected in the urine from individuals with CKDu

Pesticide Residue	Frequency of detection
2,4-D	33%
3,5,6-trichloropyridinol	70%
P-nitrophenol	58%
1-naphthol	100%
2-naphthol	100%
Glyphosate	65%
Aminomethyl phosphonic acid (AMPA)	28%

Pesticide analysis

Parent Compound	Bio Marker	Reference Range (µg/l)	CKDu cases (µg/l) (Minimum, Maximum)	CKDu cases above reference limit (%)
2,4-D	2,4-D	<0.3	0.5,0.62	3.5
Pentachlorophenol	Pentachlorophenol	<2	0.3,2.2	1.7
Chlorpyrifos	3,5,6-trchloropyridinol	<11.3	0.5,34.7	10.5
Parathion	P-nitrophenol	<25	0.5,8.88	0
Carbaryl Naphthalene	1-naphthol	<19.7	0.5,45.1	10.5
Naphthalene	2-naphthol	<17.1	0.5,47.88	10.5
Glyphosate	Glyphosate	<2	0.075, 3.36	3.5
Glyphosate	AMPA	<0.5	0.075, 2.65	14

Use of Aristolochia species

- In Sri Lankan Aurvedic medicine, about 66 Aurvedic prescriptions which contain Aristolochia are available for treatment of > 20 diseases.

- Aristolochia species are used in remedies for snakebites, other poison bites, diarrhoea, fever, body pains , pain in eyes, teeth, throat and ears, post-partum depression, labour pain, indigestion, stomachache, and headache .

- *Aristolochia indica* is the major species used in these remedies.

RCT on treatment of CKDu

- A double blind placebo controlled randomized clinical trial was conducted to investigate the effect of ACEI on the progression of CKDu

- A significant improvement in the ACR in the enalapril group compared to the placebo group ($p= 0.005$)

- In both groups, the eGFR declined significantly ($p< 0.001$), during the 12 month followup with no significant difference between the two groups.

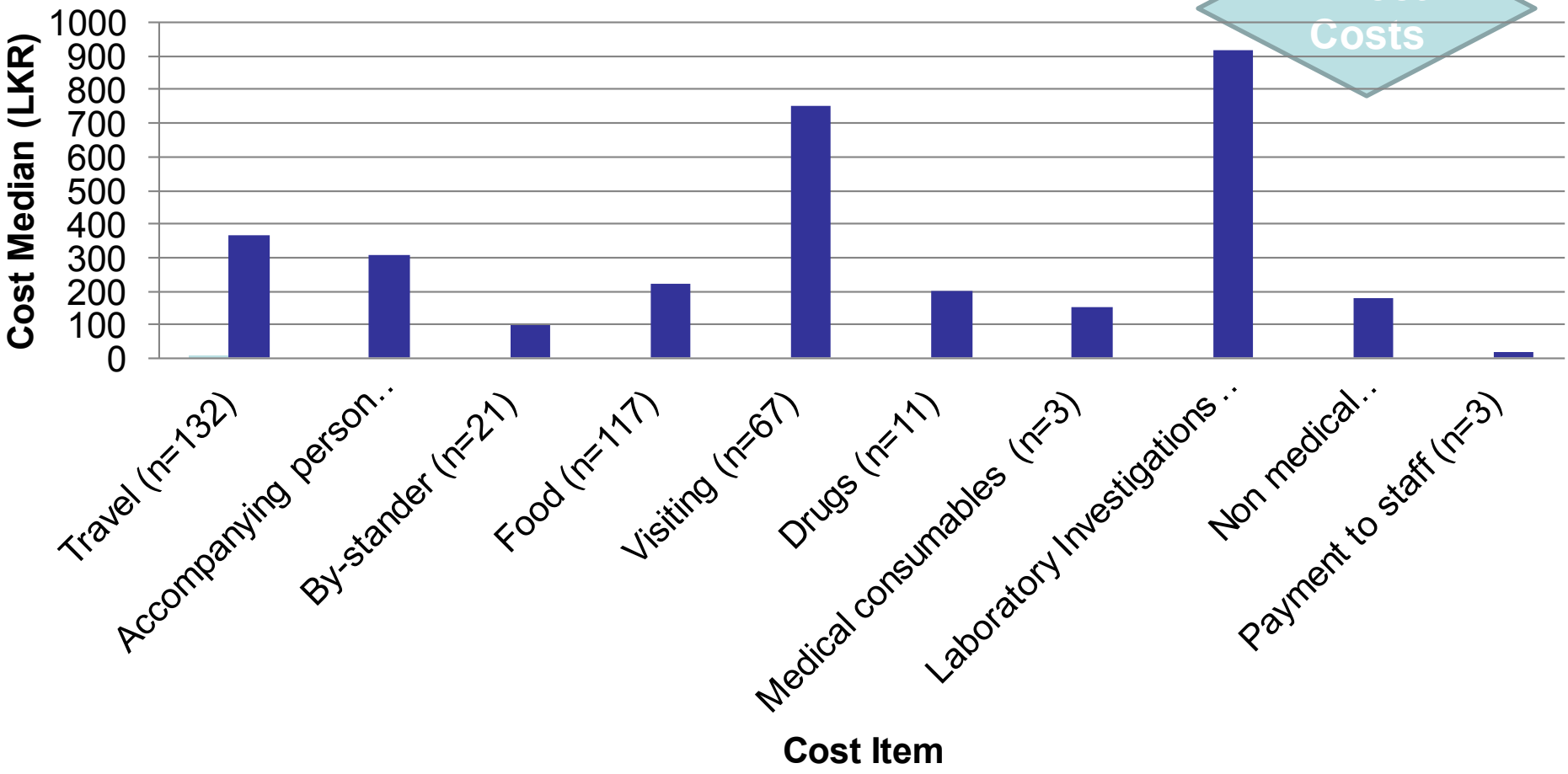
CKDu- COST TO PATIENTS

Clinic patients

74% used the bus to attend clinic

Direct cost of the last clinic visit of the participant

Direct Costs



Strengths

i) Use of a consistent case definition for CKDu

ii) Analysis of a range of biological samples from CKDu subjects

iii) Comparison of control groups within and outside the endemic area and

iv) Use of sensitive analytical techniques.

Limitations

- Prospective study was not possible at the time as little was known and because results were needs within 2 years
- Cross sectional design does not provide information on the temporal sequence between exposure and outcome
- Small sample sizes (food, soil, fertilizer)

Summary findings

1. Age standardized prevalence of CKDu is 16.9% in females and 12.9% in males. Prevalence increases with age.
2. The aetiology of CKDu is multifactorial
3. Factors that appear to play a role in the aetiology of CKDu include:
   - **Chronic exposure to low levels of Cd through the food chain**
   - Exposure to nephrotoxic pesticides
   - Concurrent exposure to other heavy metals
   - Deficiency of selenium
   - Genetic susceptibility
   - Use of remedies with Sapsanda
   - Other factors?
4. Water is not the source of exposure to Cd. (Fluoride and calcium in water may aggravate the effect of nephrotoxins and progression of CKDu).
5. Treatment with enalapril reduces albuminuria in CKDu patients.
6. CKDu is a major public health issue placing a heavy burden on Government health expenditure and is a cause of catastrophic expenditure for individuals and families leading to poverty and stigma in the community.

WHO Recommendations 2013

1. Supply clean **drinking water** (pipe borne) to mitigate contributing factors that may aggravate the effect of nephrotoxins including high calcium, fluoride and heat/dehydration related harmful effects on kidney.

2. Explore the use of local **rock phosphate** and regulate Cd, As, Pb in phosphate fertilizer and indiscriminate use of synthetic fertilizer.

3. Strengthen **tobacco** regulations to further protect people including children from exposure to Cd through passive smoking

4. Advice people to avoid use of **lotus roots** from the endemic area (avoid exceeding PTWI)

5. Further research e.g. explore methods to reduce the intake of Cd by plants by maintaining the **soil at neutral pH and** other affordable measures**.**

WHO Recommendations 2013

6. Ensure appropriate disposal of nickel Cd batteries, plastics, bottle lids etc and the **quality of compost**

7. Diazinon, propanil, paraquat, chlorpyriphos, carbaryl – **monitor the ban** in the NCP. Regulate the use of pesticides.

8. Regulate the use of nephrotoxic herbal medicines such as **sapsanda**

9. Create awareness (public/doctors) of the danger of inappropriate use of **nonsteroid analgesics.**

10. Provide facilities for **early diagnosis and** ACEI for **treatment.**

11. Health education to safeguard the health of the general population including farmers

12. Provide social welfare support to affected families

Multisectoral effort to implement recommendations

Ministry of Health	• Strengthening of the Health Services as per the recommendations (In progress)
Ministry of Agriculture	• Regulations on Indiscriminate use of Fertilizers /Pesticides (Cabinet Subcommittee -15 priority areas)
Ministry of Water Supply & Drainage	• Improvement of Water Quality (Already in place)
Ministry of Indigenous Medicine	• Regulatory mechanism to be initiated for reduction of use of Aristolochia (Sapsanda/Sasanda)
Ministry of Environment	• Contribution towards reduction of causative factors
Ministry of Science & Technology	• Supported the National Research effort together with WHO • Continue research in identified areas
Ministry of Social Services	• Strengthening the social service component and facilitating the provision of patient allowance at an earlier stage

Further Research

Give priority to research in actionable follow-up areas

- Policy related research for multisectoral action
- Methods to reduce the intake of cadmium by plants (soil science)
- Use of local rock phosphate and environmental friendly organic fertilizer
- Develop rice strains which require less fertilizer/resistant to pests
- Nephrotoxicity of pesticides and weedicides
- Total diet studies on heavy metals and other nephrotoxins
- Role of protective factors such as selenium
- Ways to reduce pollution of the environment including air pollution
- Longterm prospective and interventional studies for more insight on aetiologic interpretations
- Health system and social science research

What next?

- Translating available research findings into action should not be delayed . Implementation of multisectoral measures to reduce exposure of the population (with special focus on the young) to nephrotoxins is a top priority .

- Monitoring of implementation should be through time bound targets. The high level Cabinet Sub Committee and the Parliamentary Select Committee are well placed to oversee this function.

- Follow-up research should NOT be a barrier for implementing WHO recommendations.

- The population in the North Central Region including future generations need to be protected from environmental nephrotoxins; failure to do so would be a public health tragedy.