Lifestyle & Dietary Interventions in Diabetic Kidney Disease

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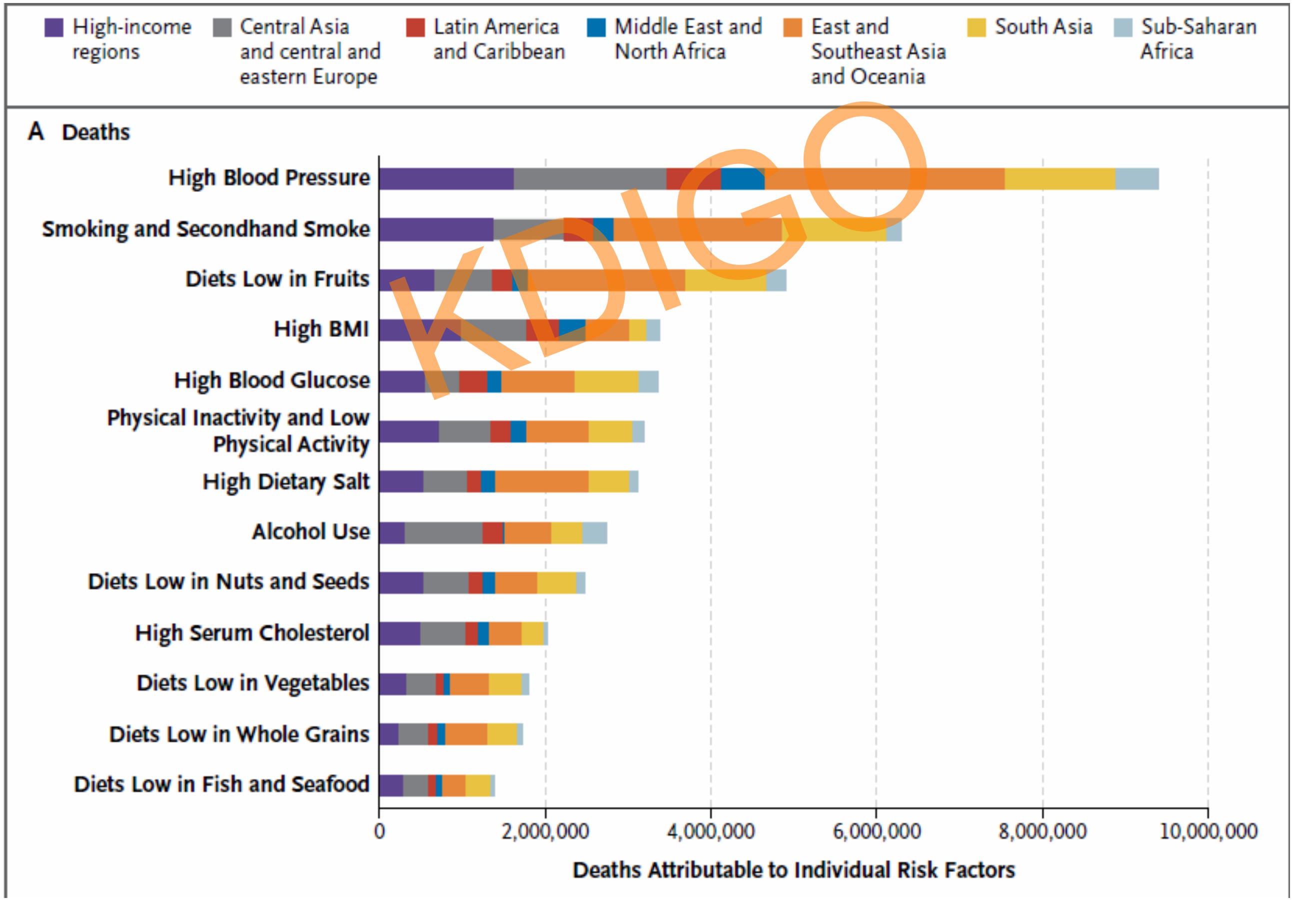
Disclosure of Interests

No relevant disclosures

Global impact

Deaths attributed to behavioural & dietary factors



Ezzati, M *NEJM* 2013; 369:954-64

Lifestyle & Dietary Potential

Dietary
- Restrict dietary salt
- Fruit and vegetables
- Mediterranean diet
- Dietary fibre
- Calorie control
- Limited cola beverages

Physical exercise

Weight reduction

Smoking cessation

Alcohol reduction

Increase fitness

Improve blood pressure

Improve glycemic control

Reduce albuminuria

Improve survival, vascular health, etc.

What should we do?

What can we do?

Lifestyle & Dietary Potential

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- Restrict dietary salt
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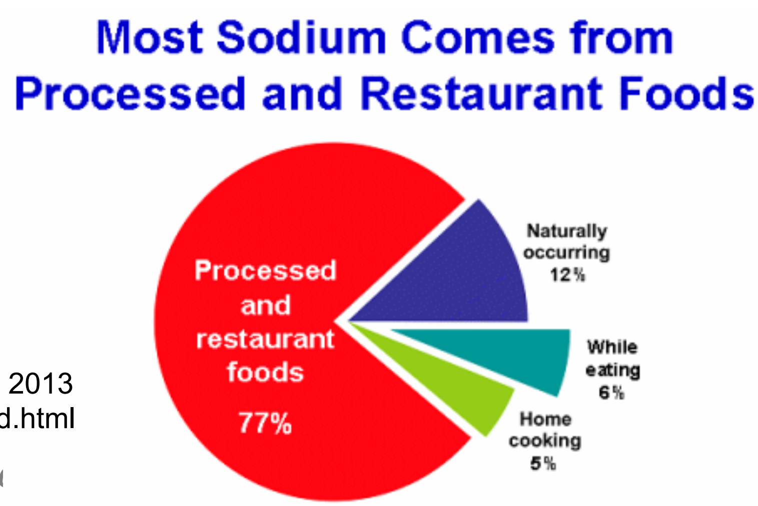
Dietary Sodium

Adult population sodium intake

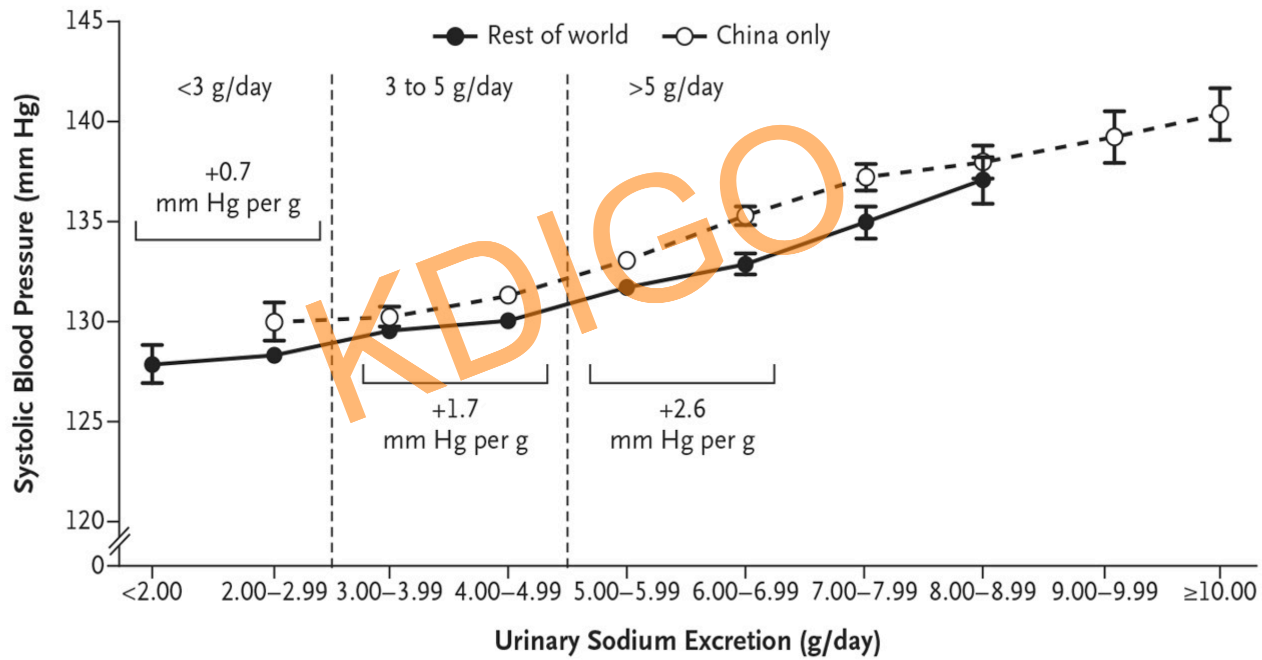
	Sodium (g/d)	Salt - sodium chloride (g/d)	Sodium (mmol)
Mean global consumption[1]	3.95	10.0	172
Regional mean consumption[1]	2.2 to 5.5	5.5 to 14.0	95 to 240
WHO dietary recommendations, (2013)	2.0	5.1	87
US Dietary Guidelines (2010)	2.3	5.8	100

1. Global Burden of Diseases Nutrition and Chronic Diseases Expert Group
Mozaffarian D, *NEJM* 2014;371:624-634



CDC accessed Nov 2013
http://www.cdc.gov/salt/food.html

Sodium intake associated with BP



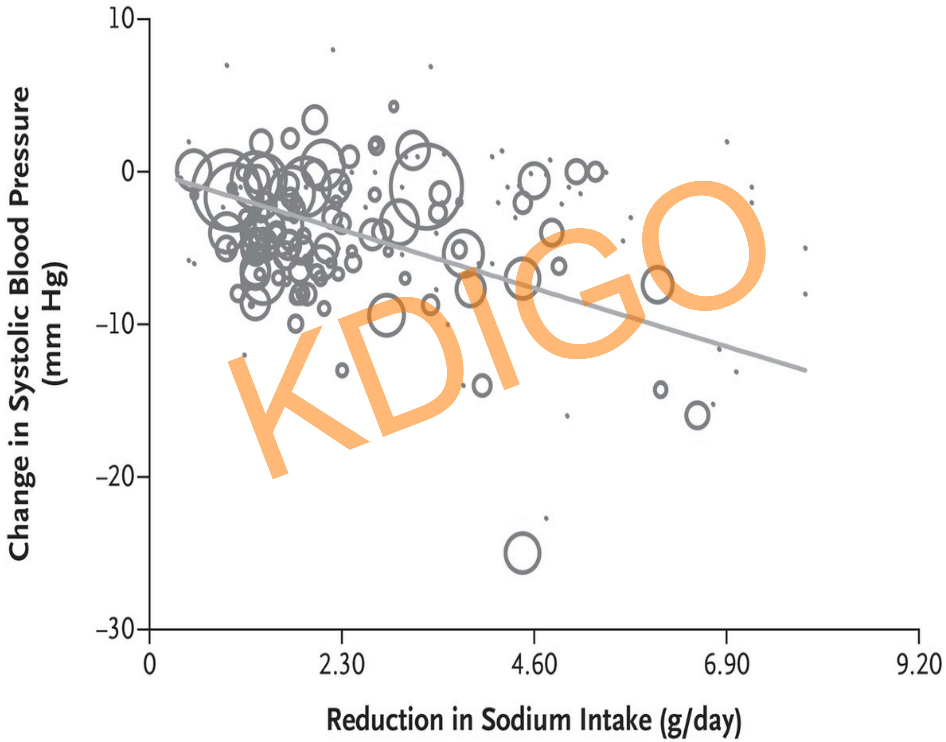
No. of Participants

	<2.00	2.00–2.99	3.00–3.99	4.00–4.99	5.00–5.99	6.00–6.99	7.00–7.99	8.00–8.99	9.00–9.99	≥10.00
China		1876	6,012	9,794	10,101	7177	4093	2035	1002	952
Other countries	1613	7384	15,101	16,015	10,810	5211	2048	992		

Country GDP inversely associated with Na, positively associated with K excretion (P<0.001)

PURE – Prospective Urban Rural Epidemiology
n=51290, aged 35-70 years
Mente A, NEJM 2014;371:601-611

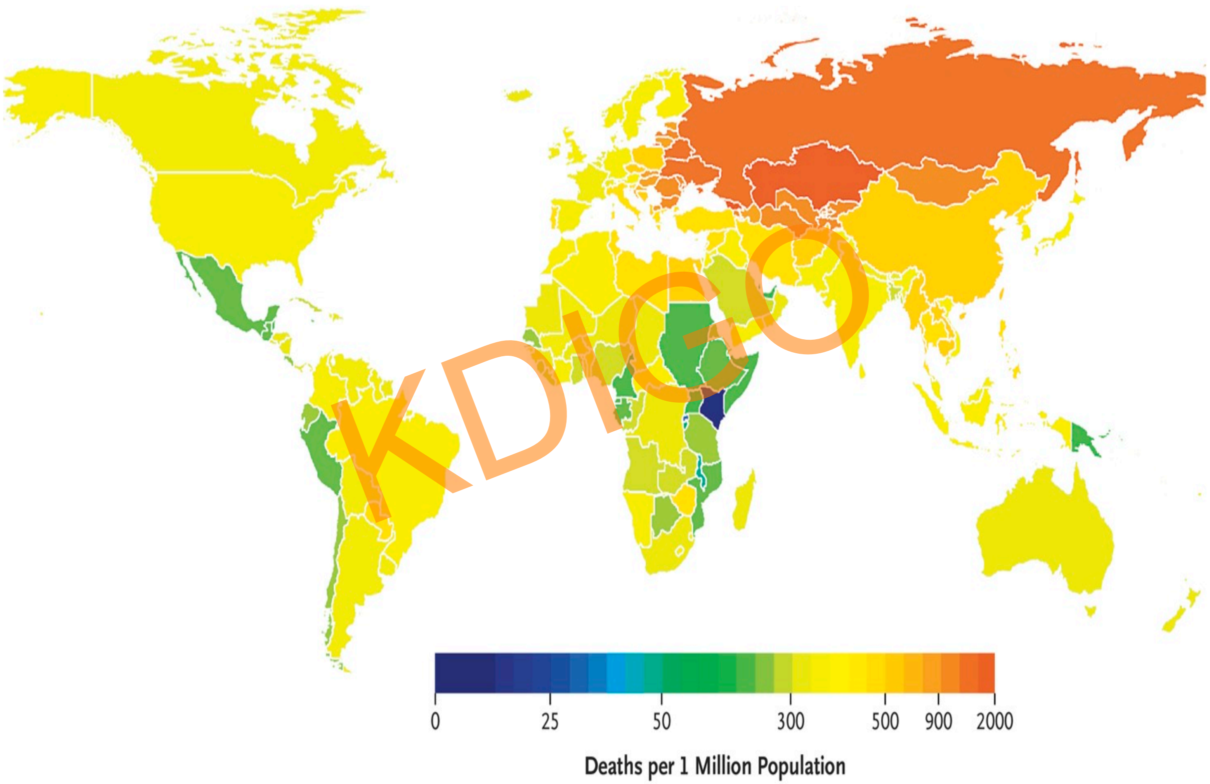
Reducing sodium reduces BP



Each reduction in sodium of 2.30g/d (100mmol/d) reduced SBP by 3.82mmHg (3.08-4.55)

Global Burden of Diseases Nutrition and Chronic Diseases Expert Group
Mozaffarian D, *NEJM* 2014;371:624-634

Estimated CV deaths attributed to salt



Absolute Cardiovascular Mortality Attributed to Sodium Consumption of More than 2.0 g per Day in 2010
Modelled from associations of sodium intake and blood pressure, and of blood pressure and cardiovascular mortality

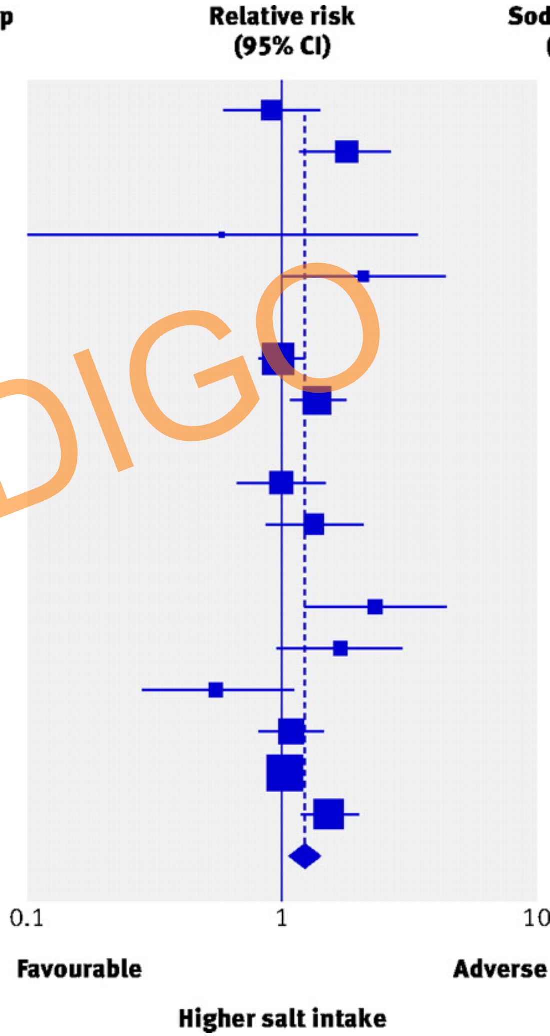
1.65million (1.10-2.22) excess CV deaths in 2010

Mozaffarian D, *NEJM* 2014;371:624-634

Risk of incident stroke associated with higher compared with lower salt intake in 14 population cohorts from 10 published prospective studies including 154 282 participants and 5346 events

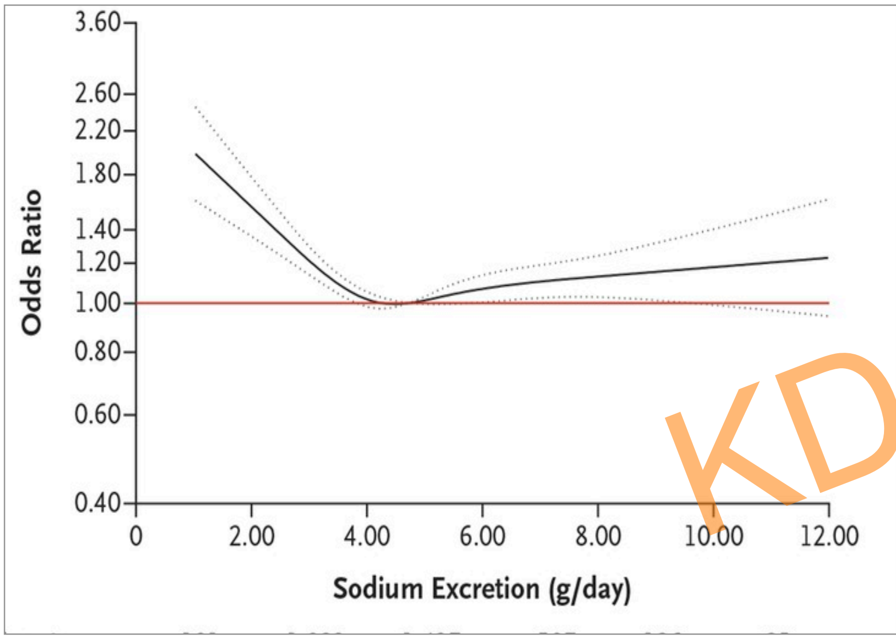
Study	Sample size	Events	Follow-up (years)	Sodium difference (mmol/day)	Relative risk (95% CI)
Kagan 1985[10]	7895	238	10	100	0.92 (0.60 to 1.42)
Hu 1992[11]	8562	104	4		1.79 (1.18 to 2.70)
Alderman 1995[6]			3.5		
Men	1900	17		150	0.59 (0.10 to 3.43)
Women	1037	6		120	2.10 (1.01 to 4.33)
He 1999[9]			19		
Normal weight	6797	430		100	0.99 (0.81 to 1.20)
Overweight	2688	250		100	1.39 (1.10 to 1.76)
Tuomilheto 2001[13]			13		
Men	1173	43		100	1.00 (0.68 to 1.48)
Women	1263	41		100	1.34 (0.87 to 2.06)
Nagata 2004[14]			7		
Men	13 355	137		110	2.34 (1.23 to 4.47)
Women	15 724	132		92	1.70 (0.96 to 3.00)
Cohen 2006[15]	7154	79	13.7	92	0.56 (0.28 to 1.11)
Geleijnse 2007[16]	1448	181	5	69	1.08 (0.81 to 1.45)
Larsson 2008[18]	26 556	2702	13.6	84	1.04 (0.93 to 1.17)
Umesawa 2008[19]	58 730	986	12.7	85	1.55 (1.20 to 2.00)
Combined effect: P=0.007	154 282	5346			1.23 (1.06 to 1.43)

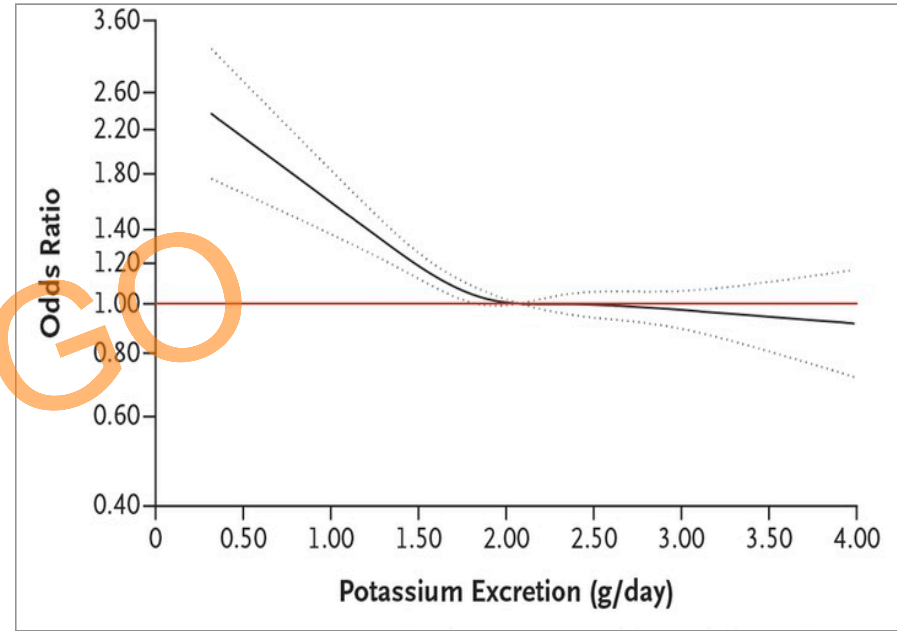
Heterogeneity: P=0.04, Egger's test: P=0.26



Strazzullo P et al. BMJ 2009;339:bmj.b4567

Sodium and potassium and cv events





<3.00g/d	3.00-3.99	4.00-5.99	6.00-6.99	≥7.00
1.27 (1.12, 1.44)	1.01 (0.93, 1.09)	1.00 (ref)	1.05 (0.94, 1.17)	1.15 (1.02, 1.30)

<1.5 g/d	1.50-1.99	2.00-2.49	2.50-3.00	≥3.00
1.00 ref	0.86 (0.77, 0.97)	0.81 (0.73, 0.91)	0.86 (0.75, 0.98)	0.78 (0.67, 0.91)

Association of estimated Na and K excretion on morning **spot** urine sample with composite of death & major cardiovascular events, mean followup 3.7 years

PURE (Prospective Urban Rural Epidemiology)
O'Donnell M. *NEJM* 2014;371:612-623

100mmolNa ≈ 2.3g sodium ≈ 5.8g salt

Long term randomised followup

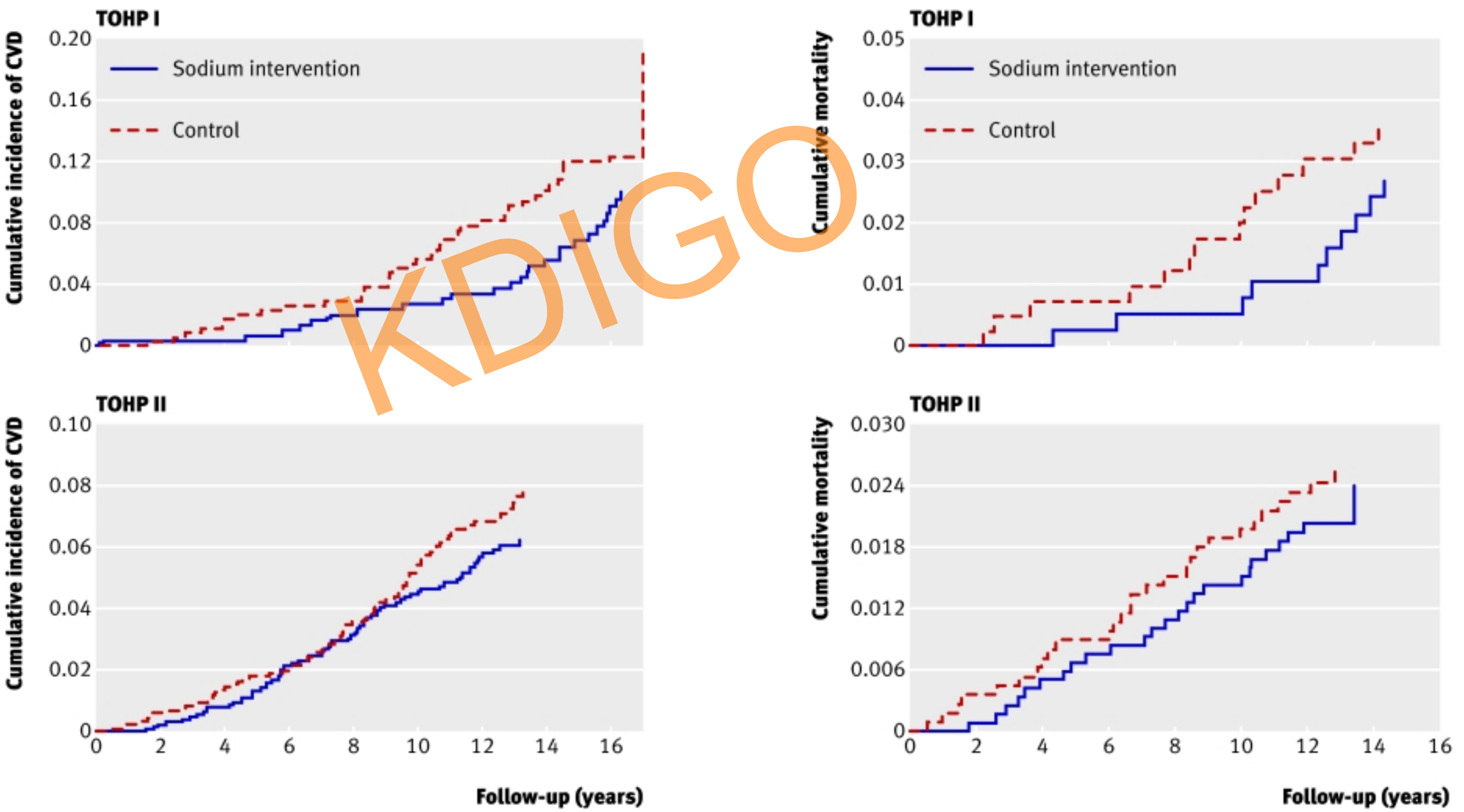
Cardiovascular events | Mortality

Randomised
n=744

Followup
n=542 (73%)

Randomised
n=2382

Followup
n=1873 (79%)



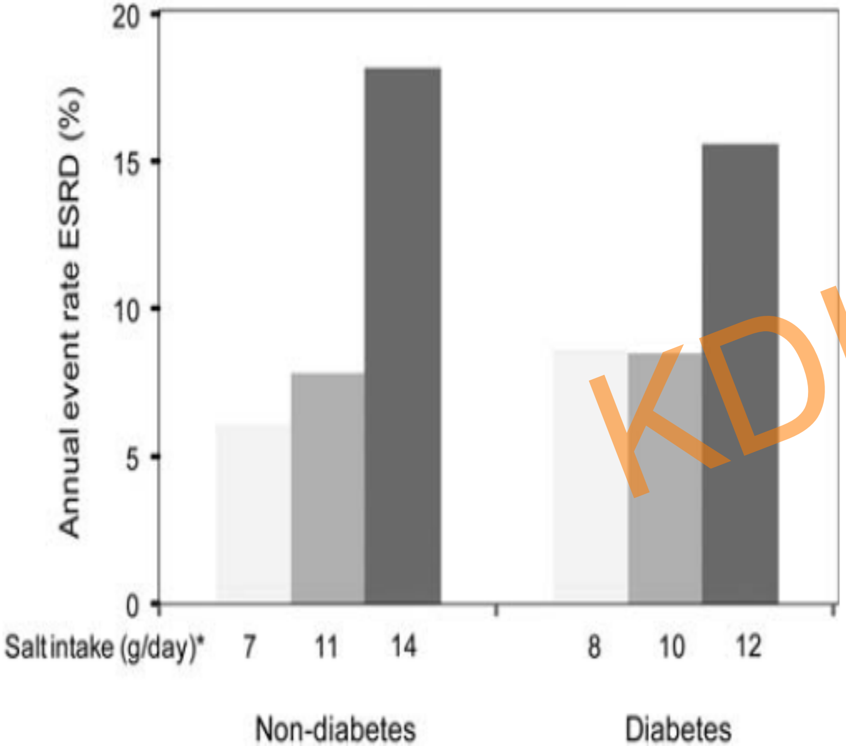
TOHP RCT

RR 0.75 (0.57 to 0.99) p=0.04

RR 0.80 (0.51 to 1.26) p=0.34

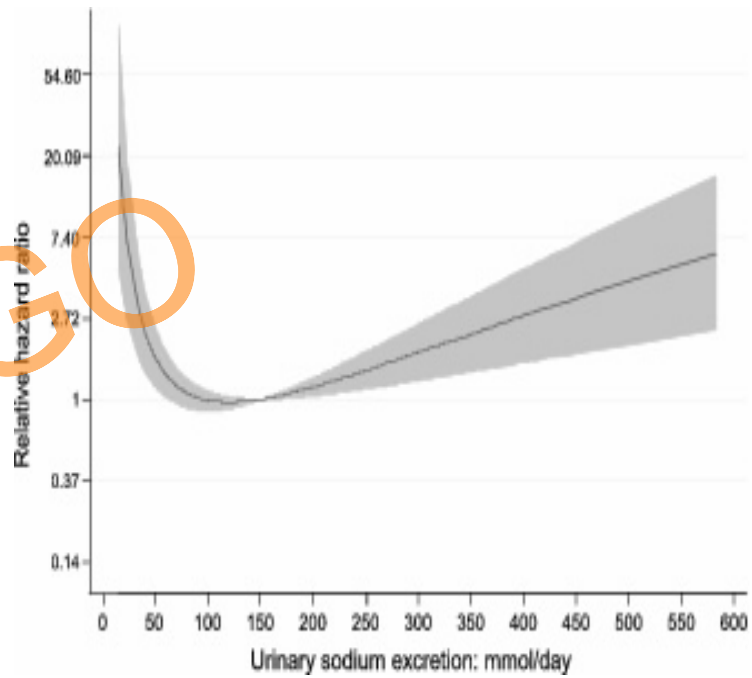
Cook *BMJ* 2007; 334(7599): 885

Salt intake in kidney disease



ESKD rate according to salt intake in the people with CKD (REIN and RENAAL-IDNT trials)

Vegter *JASN* 2012



Mortality rate according to salt intake in people with DM1 and CKD (FinnDiane study)

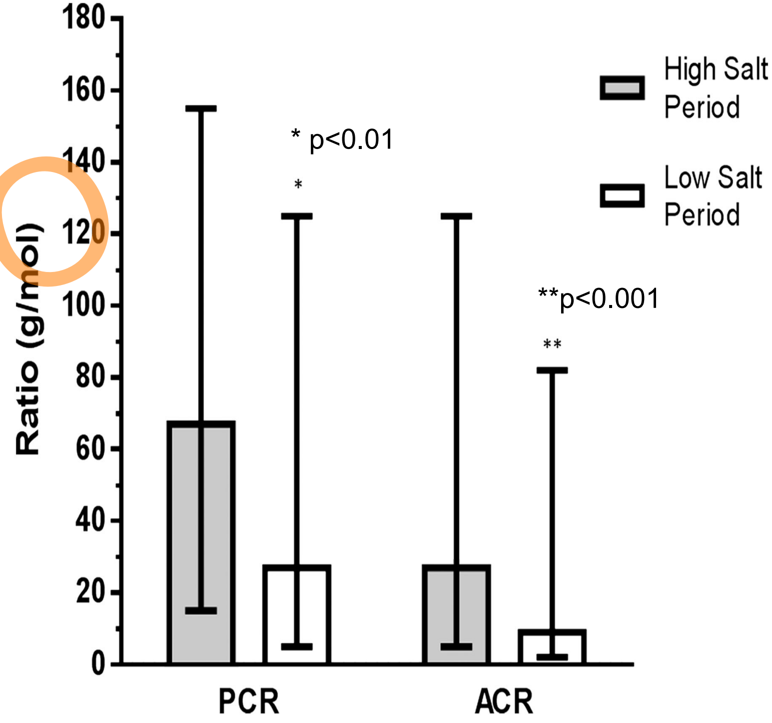
Thomas *Diabetes Care* 2011

100mmolNa ≈ 2.3g sodium ≈ 5.8g salt

RCTs of altered Na intake in CKD

Short term cross-over RCTs of altered sodium intake in people with CKD show reductions in albuminuria

- n=20-169
- Periods: 2-6 weeks
- Intervention: placebo-matched sodium supplement on background low sodium diet in 3 of 4 trials
- Differences in sodium intake of 55-93mmol/d (3.2-5.5g salt/d)
- Reductions achieved in addition to those of RAAS blockade in 3 of 4 trials



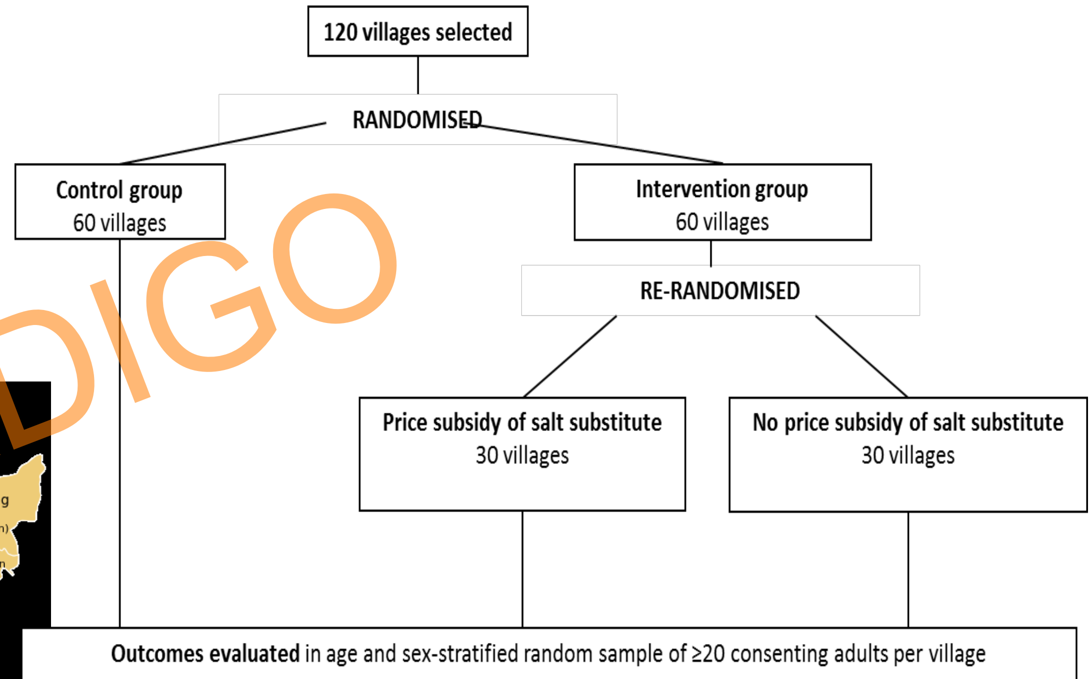
Median urinary PCR and ACR during high and low salt periods

McMahon E *JASN* 2013;24:2096-2103

He *Hypertension* 2009
Slagman *BMJ* 2011
Ekinci *Diabetes Care* 2009
McMahon *JASN* 2013

CRHI: Cluster RCT of salt reduction

- 120 villages
- 18 months duration
- Multipronged intervention
- Outcomes assessment sample
  - ≥20 people/village randomly selected from an age/gender stratified sample



clinicaltrials.gov NCT01259700

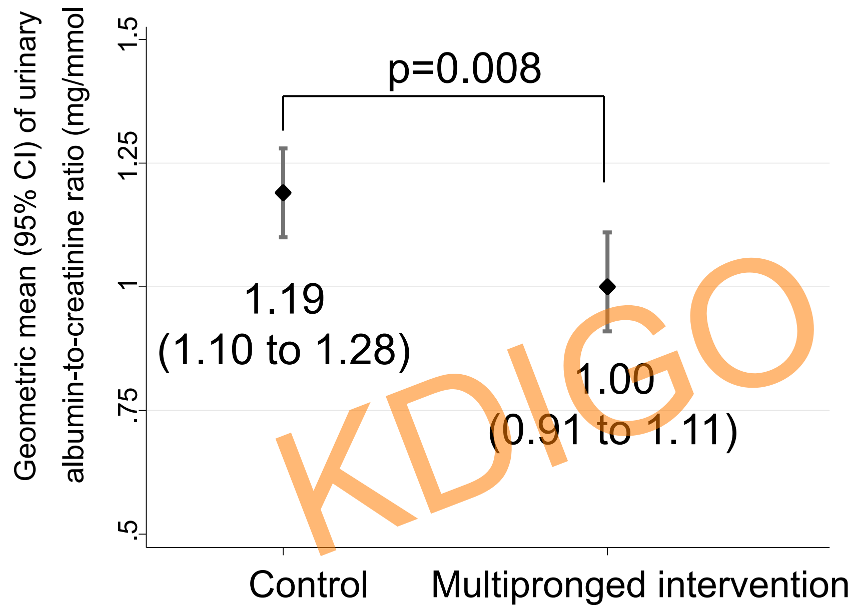
Jardine, 2015, unpublished

Intervention impact on Na, K

Compared with participants from control villages: (n=928)	Participants from intervention villages (n=975)
Urinary Na (mmol/day)	-14 (-27 to -1)
Equivalent reduction in salt (g/day)	0.82 (0.06 to 1.58)
Urinary K (mmol/day)	7 (4 to 10)
Urinary Na/K ratio	-0.9 (-1.2 to -0.5)
SBP (mmHg)	-1.0 (-3.4 to 1.4)
DBP (mmHg)	-0.7 (-2.3 to 0.9)
Use of BP lowering agents, %	-3.8 (-0.09 to -7.6)

Jardine, 2015, unpublished

Sodium reduction lowered uACR



15% drop in log transformed uACR (95%CI 4.3-25.2)

OR (95%CI)	Participants from control villages (n=928)	Participants from intervention villages (n=975)	p
Any albuminuria	1.00 (reference)	0.67 (0.46 to 0.99)	0.04
Microalbuminuria	1.00 (reference)	0.70 (0.47 to 1.06)	0.09
Macroalbuminuria	1.00 (reference)	0.48 (0.18 to 1.32)	0.16

Jardine, 2015, unpublished

Mediterranean Diet

Mediterranean diet RCT

PREDIMED

RCT, Spain, N=7447,
Primary endpoint:
MI, stroke, cv death
Stopped at median 4.8 years FU

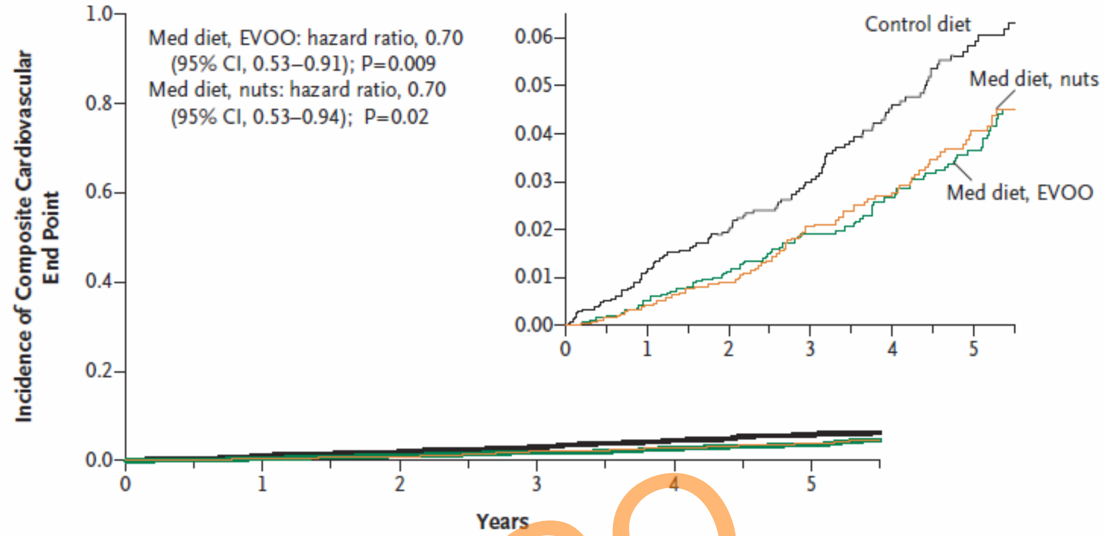
Estruch, R. *NEJM* 2013; 368:1279--90

Table 2. Baseline Characteristics of the Participants According to Study Group.*

Characteristic	Mediterranean Diet with EVOO (N=2543)	Mediterranean Diet with Nuts (N=2454)	Control Diet (N=2450)
Female sex — no. (%)†	1493 (58.7)	1326 (54.0)	1463 (59.7)
Age — yr†	67.0±6.2	66.7±6.1	67.3±6.3
Race or ethnic group — no. (%)			
White, from Europe	2470 (97.1)	2390 (97.4)	2375 (96.9)
Hispanic, from Central or South America	35 (1.4)	29 (1.2)	38 (1.6)
Other	38 (1.5)	35 (1.4)	37 (1.5)
Smoking status — no. (%)			
Never smoked	1572 (61.8)	1465 (59.7)	1527 (62.3)
Former smoker	618 (24.3)	634 (25.8)	584 (23.8)
Current smoker	353 (13.9)	355 (14.5)	339 (13.8)
Body-mass index†‡			
Mean	29.9±3.7	29.7±3.8	30.2±4.0
<25 — no. (%)	195 (7.7)	204 (8.3)	164 (6.7)
25–30 — no. (%)	1153 (45.3)	1163 (47.4)	1085 (44.3)
>30 — no. (%)	1195 (47.0)	1087 (44.3)	1201 (49.0)
Type 2 diabetes — no. (%)†‖	1282 (50.4)	1143 (46.6)	1189 (48.5)
Dyslipidemia — no. (%)**	1821 (71.6)	1799 (73.3)	1763 (72.0)
Family history of premature CHD — no. (%)††	576 (22.7)	532 (21.7)	560 (22.9)
Medication use — no. (%)			
ACE inhibitors	1236 (48.6)	1223 (49.8)	1216 (49.6)
Statins	1039 (40.9)	964 (39.3)	983 (40.1)

PREDIMED

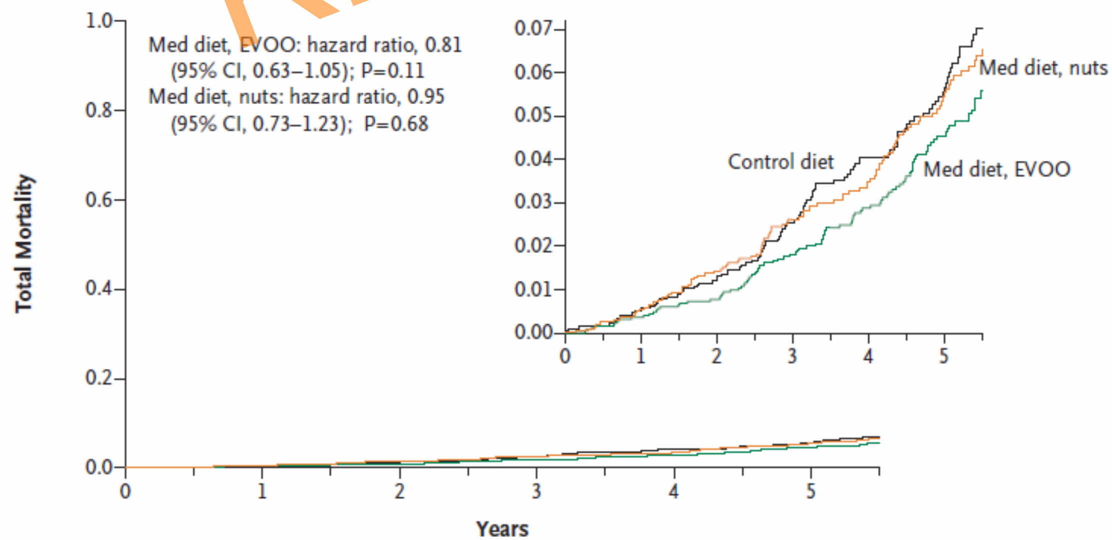
A Primary End Point (acute myocardial infarction, stroke, or death from cardiovascular causes)



No. at Risk

Control diet	2450	2268	2020	1583	1268	946
Med diet, EVOO	2543	2486	2320	1987	1687	1310
Med diet, nuts	2454	2343	2093	1657	1389	1031

B Total Mortality



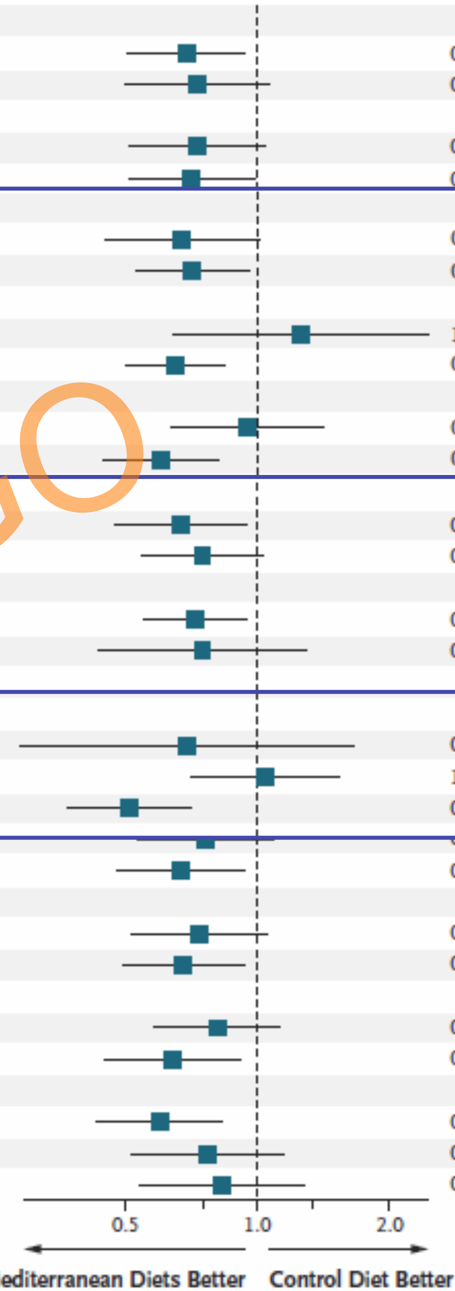
No. at Risk

Control diet	2450	2268	2026	1585	1272	948
Med diet, EVOO	2543	2485	2322	1988	1690	1308
Med diet, nuts	2454	2345	2097	1662	1395	1037

Estruch, R. *NEJM* 2013; 368:1279--90

PREDIMED

Subgroup	Combined Mediterranean Diets	Control Diet	Hazard Ratio (95% CI)	P Value for Interaction
	no. of participants with primary end-point event/total no. of participants			
Sex				0.62
Male	107/2178	64/987	0.69 (0.51–0.94)	
Female	72/2819	45/1463	0.73 (0.50–1.07)	
Age				0.84
<70 yr	86/3272	47/1504	0.73 (0.52–1.05)	
≥70 yr	93/1725	62/946	0.71 (0.51–0.98)	
Diabetes				0.63
No	58/2572	40/1261	0.67 (0.45–1.01)	
Yes	121/2425	69/1189	0.71 (0.53–0.96)	
Hypertension				0.06
No	40/885	11/400	1.25 (0.64–2.45)	
Yes	139/4112	98/2050	0.65 (0.50–0.84)	
Dyslipidemia				0.06
No	77/1377	36/687	0.95 (0.64–1.42)	
Yes	102/3620	73/1763	0.60 (0.44–0.80)	
Smoking				0.75
Never	80/3037	54/1527	0.67 (0.47–0.94)	
Ever	99/1960	55/923	0.75 (0.54–1.03)	
Family history of premature CHD				0.97
No	144/3889	87/1890	0.72 (0.55–0.94)	
Yes	35/1108	22/560	0.75 (0.43–1.29)	
BMI				0.05
<25	18/399	7/164	0.69 (0.29–1.67)	
25–30	88/2316	37/1085	1.04 (0.71–1.54)	
>30	73/2282	65/1201	0.51 (0.37–0.71)	
<Median	[illegible]	[illegible]	[illegible]	
≥Median	92/2436	61/1273	0.67 (0.48–0.93)	
Waist-to-height ratio				0.82
<Median	81/2549	47/1182	0.74 (0.52–1.06)	
≥Median	98/2448	62/1268	0.68 (0.50–0.94)	
Baseline score for adherence to Mediterranean diet				0.44
<9 (low)	93/2178	61/1256	0.81 (0.58–1.12)	
≥9 (high)	86/2819	48/1194	0.64 (0.45–0.92)	
End-point components				
Stroke	81/4997	58/2450	0.61 (0.44–0.86)	
Myocardial infarction	68/4997	38/2450	0.77 (0.52–1.15)	
Death from cardiovascular causes	57/4997	30/2450	0.83 (0.54–1.29)	



Estruch, R. *NEJM* 2013; 368:1279--90

Effective Interventions for Dietary Behavioural Change

Changing dietary behaviour

- SR of RCTs with interventions to enhance adherence to dietary advice
- 38 studies, 9445 participants

Interventions that improved at least one adherence outcome

Phone follow up, video, contract, feedback, nutritional tools, multiple interventions

– Contradictory: often didn't improve all adherence outcomes
– Most effective in short term but usually not in longer term

Interventions with no proven effect

Group sessions, individual sessions, reminders, restriction, behavioural change techniques

Desroches, S. *Cochrane Database*; 2013 (2)

Weight loss

Weight loss for cv protection

Look AHEAD RCT

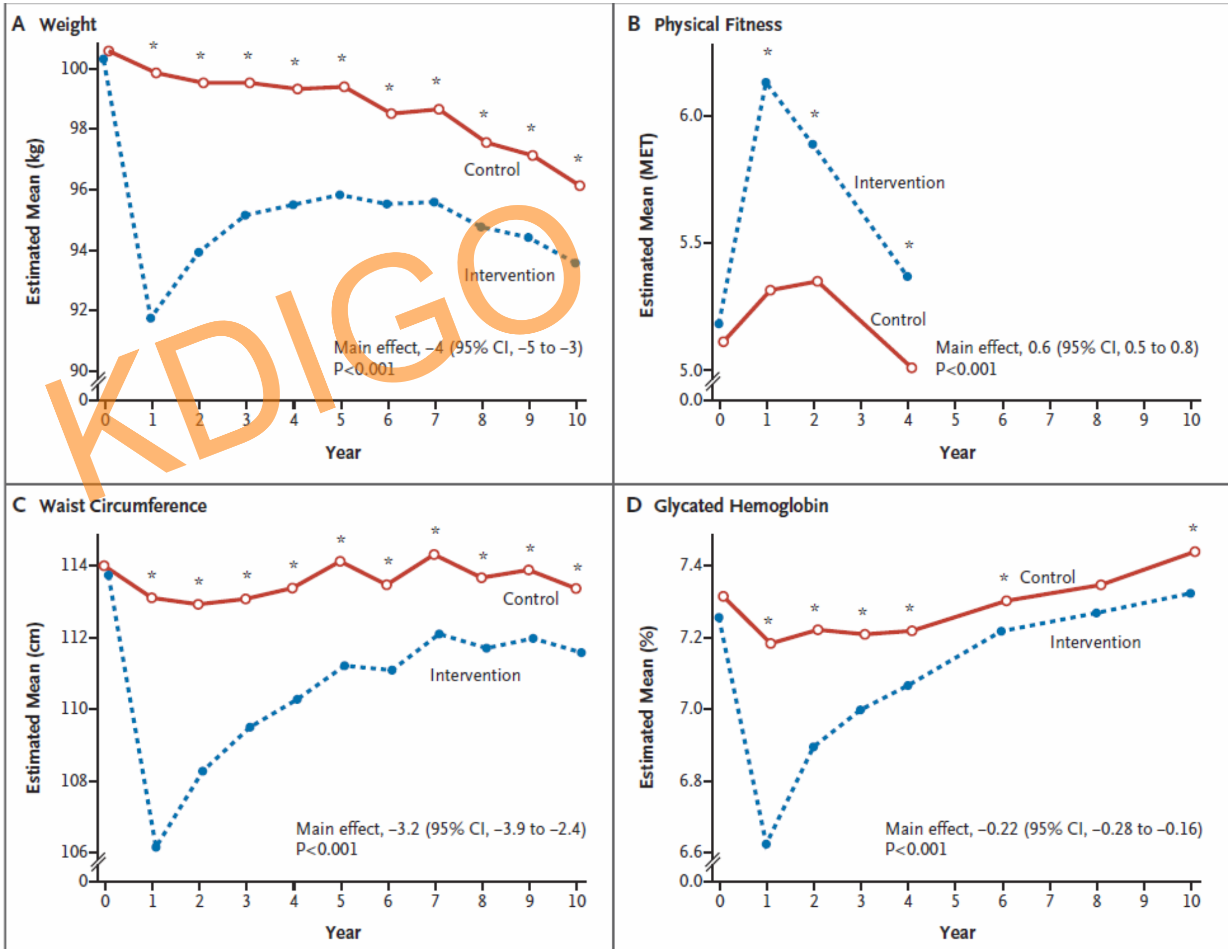
n=5145, US

DM2 and BMI≥25.0

Intervention:

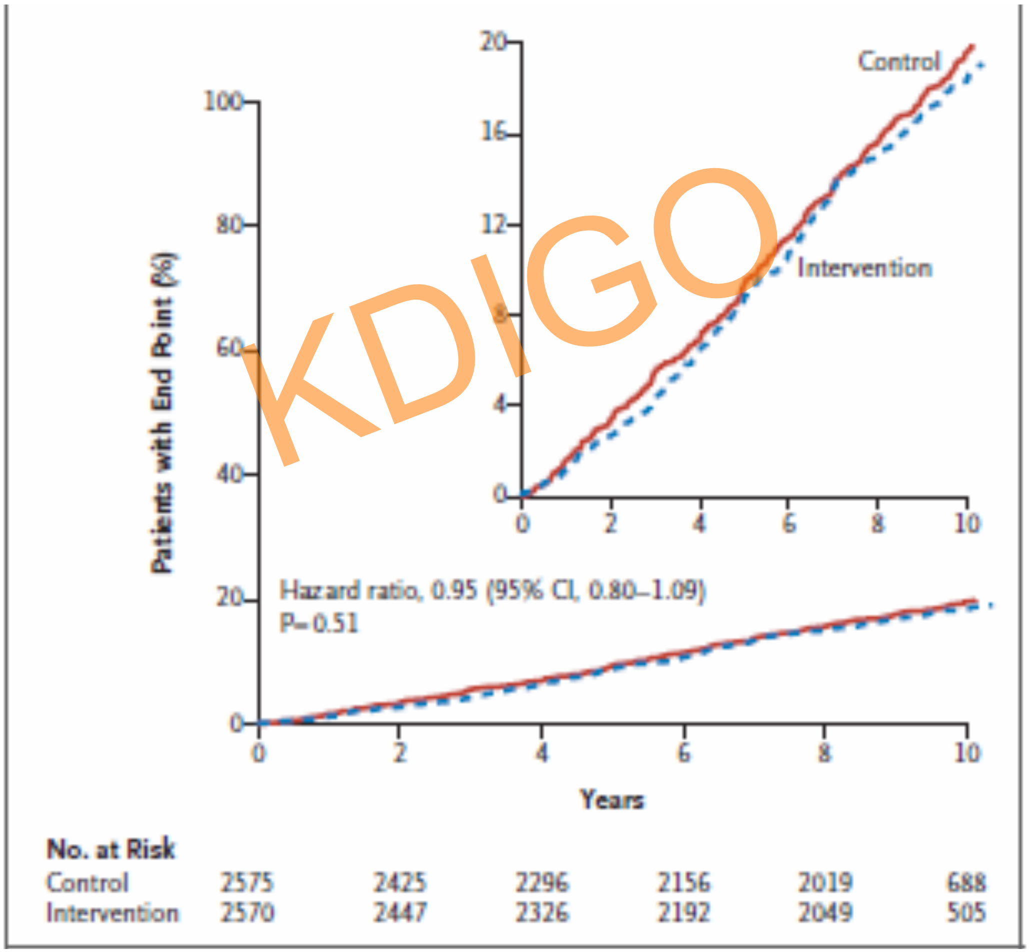
- reduced caloric intake
- increased physical activity

Stopped: median 9.6 yrs FU



N Engl J Med 2013;369:145-54.

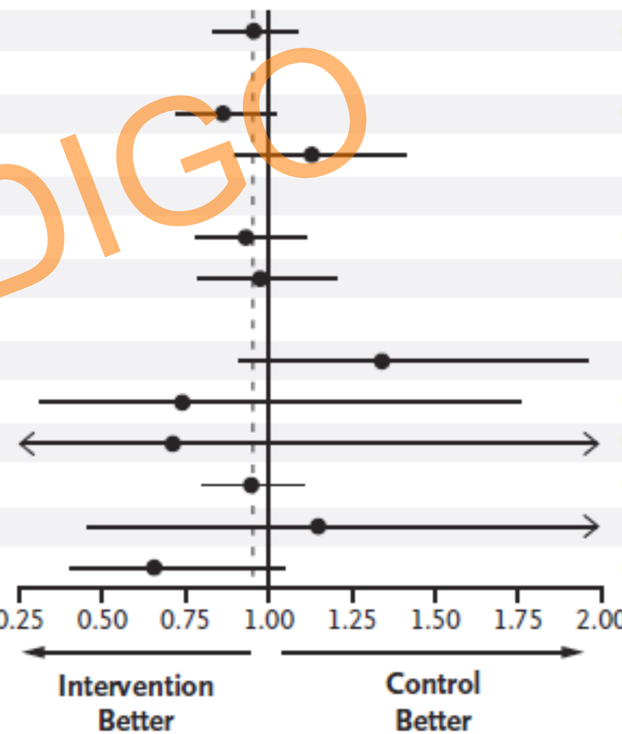
Intervention & cv outcomes



N Engl J Med 2013;369:145-54.

Look AHEAD subgroup analyses

Subgroup	Control	Intervention	Hazard Ratio (95% CI)	P Value for Interaction
	no. of events (rate/100 person-yr)			
Overall	418 (1.92)	403 (1.83)	0.95 (0.83–1.09)	
Cardiovascular disease at baseline				0.06
No	274 (1.42)	240 (1.23)	0.86 (0.72–1.02)	
Yes	144 (5.92)	163 (6.56)	1.13 (0.90–1.42)	
Sex				0.73
Male	245 (2.94)	232 (2.72)	0.93 (0.78–1.11)	
Female	173 (1.29)	171 (1.26)	0.97 (0.79–1.20)	
Race or ethnic group				0.17
Black	46 (1.32)	63 (1.82)	1.34 (0.91–1.96)	
Native American	13 (1.18)	10 (0.86)	0.74 (0.31–1.76)	
Asian or Pacific Islander	3 (1.67)	1 (0.38)	0.71 (0.06–8.28)	
White	303 (2.19)	286 (2.06)	0.94 (0.80–1.11)	
Other	10 (2.35)	12 (2.96)	1.15 (0.45–2.89)	
Hispanic	43 (1.54)	31 (1.06)	0.66 (0.41–1.05)	



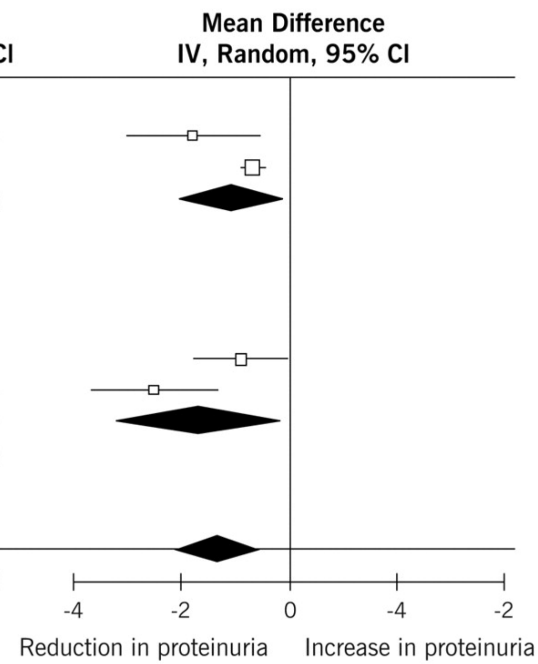
N Engl J Med 2013;369:145-54.

Weight loss in CKD

- SR: 13 studies (2 RCTs but not ITT analysis, 11 observational studies): mostly low to moderate quality, small body of evidence

Effect of nonsurgical interventions on urinary protein excretion in CKD

	After weight loss			Before weight loss				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
1.13.1 Observational studies								
Saiki 2005	1.5	1.28	22	3.27	2.63	22	19.6%	-1.77 (-2.99, -0.55)
Solerte 1989	0.62	0.3	24	1.28	0.51	24	34.9%	5.50 (-0.90, -0.42)
Subtotal (95% CI)			**46**			**46**	**54.5%**	**-1.05 (-2.08, -0.01)**
Heterogeneity: Tau²= 0.41; Chi²=3.05, df=1 (P=0.03); I²=67%								
Test for overall effect: Z=1.98 (P=0.05)								
1.13.2 Randomized studies								
Morales 2003	1.9	1.4	20	2.8	1.4	20	25.3%	-0.90 (-1.73, -0.03)
Praga 1995	0.4	0.6	9	2.9	1.7	9	20.2%	-2.50 (-3.68, -1.32)
Subtotal (95% CI)			**29**			**29**	**45.5%**	**-1.65 (-3.21, -0.08)**
Heterogeneity: Tau²= 0.00; Chi²=0.04, df=1 (P=0.85); I²=0%								
Test for overall effect: Z=0.33 (P=0.74)								
Total (95% CI)			**75**			**75**	**100.0%**	**-1.31 (-2.11, -0.51)**
Heterogeneity: Tau²= 0.46; Chi²=11.77, df=3 (P=0.008); I²=75%								
Test for overall effect: Z=1.10 (P=0.27)								
Test for subgroup differences: Chi²=4.12, df=1 (P=0.04); I²=75.7%								

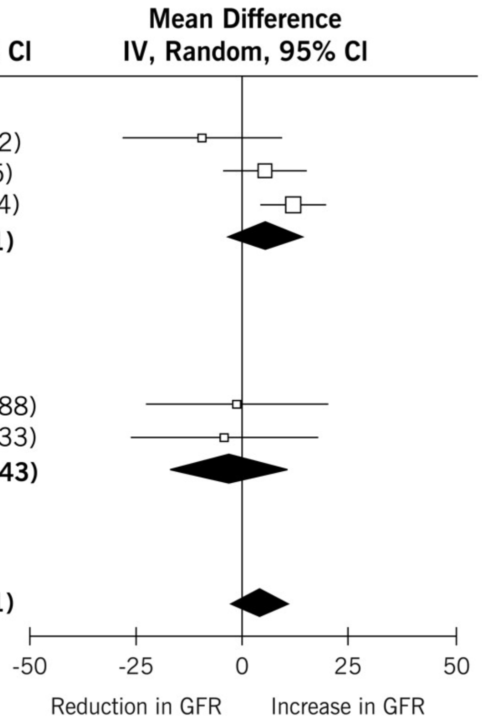


Navaneethan, S. *CJASN* 2009; 4(10):1565-1574

Weight loss for GFR

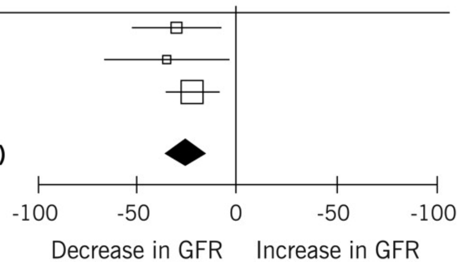
Effect of nonsurgical interventions on GFR in CKD

Study or Subgroup	After weight loss Mean	SD	Total	Before weight loss Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.12.1 Observational studies								
Cook 2009	35.5	19.6	12	44.8	26	12	13.0%	-9.30 (-27.72, 9.12)
Saiki 2005	46.1	14.6	22	40.6	17.9	22	29.7%	5.50 (-4.15, 15.15)
Solerte 1989	91	13	24	79	14	24	36.3%	12.00 (4.36, 19.64)
Subtotal (95% CI)			**58**			**58**	**79.1%**	**5.54 (-4.12, 15.21)**
Heterogeneity: Tau^2= 40.52; Chi^2=4.69, df=2 (P=0.10); I^2=57%								
Test for overall effect: Z=1.12 (P=0.26)								
1.12.2 Randomized studies								
Morales 2003	67	34.1	20	68.1	33.6	20	10.6%	-1.10 (-22.08, 19.88)
Praga 1995	99	25	9	103	21	9	10.3%	-4.00 (-25.33, 17.33)
Subtotal (95% CI)			**29**			**29**	**20.9%**	**-2.53 (-17.48, 12.43)**
Heterogeneity: Tau^2= 0.00; Chi^2=0.04, df=1 (P=0.85); I^2=0%								
Test for overall effect: Z=0.33 (P=0.74)								
Total (95% CI)			**87**			**87**	**100.0%**	**4.25 (-3.33, 11.81)**
Heterogeneity: Tau^2= 25.73; Chi^2=6.29, df=4 (P=0.18); I^2=36%								
Test for overall effect: Z=1.10 (P=0.27)								
Test for subgroup differences: Chi^2=1.57, df=1 (P=0.21); I^2=36.2%								



Effect of surgical interventions on GFR in CKD

Study or Subgroup	After surgery Mean	SD	Total	Before surgery Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Brochner-Mortensen 1980	123	27	8	153	16	8	24.1%	-30.00 (-51.75, -8.25)
Chagnac 2003	110	39.59	8	145	19.79	8	12.1%	-35.00 (-65.67, -4.33)
Navarro-Diaz 2006	117.9	33.99	61	140	40.96	61	63.8%	-22.10 (-35.46, -8.74)
Total (95% CI)			**77**			**77**	**1.00%**	**-25.56 (-36.23, -14.89)**
Heterogeneity: Tau^2= 000; Chi^2=0.78, df=2 (P=0.68); I^2=0%								
Test for overall effect: Z=4.70 (P=0.00001)								



Navaneethan S. CJASN 2009;4:1565-1574

Exercise

Exercise in CKD

- Comprehensive SR: 9 comparisons, 47 outcomes
- 45 studies, 1863 participants, mostly dialysis patients, short followup
- 49% classified as high risk of bias
- Exercise improved:
  - 2 fitness measures, some laboratory measures
  - SBP by 6.1 (2.2, 10,1) mmHg,
  - DBP by 2.3 (0.6, 4.1) mmHg,
  - heart rate by 6 (2, 10) bpm
- No benefit proven for cardiovascular structure

Heiwe, S. *Cochrane Database* 2011 (10)

Conclusions

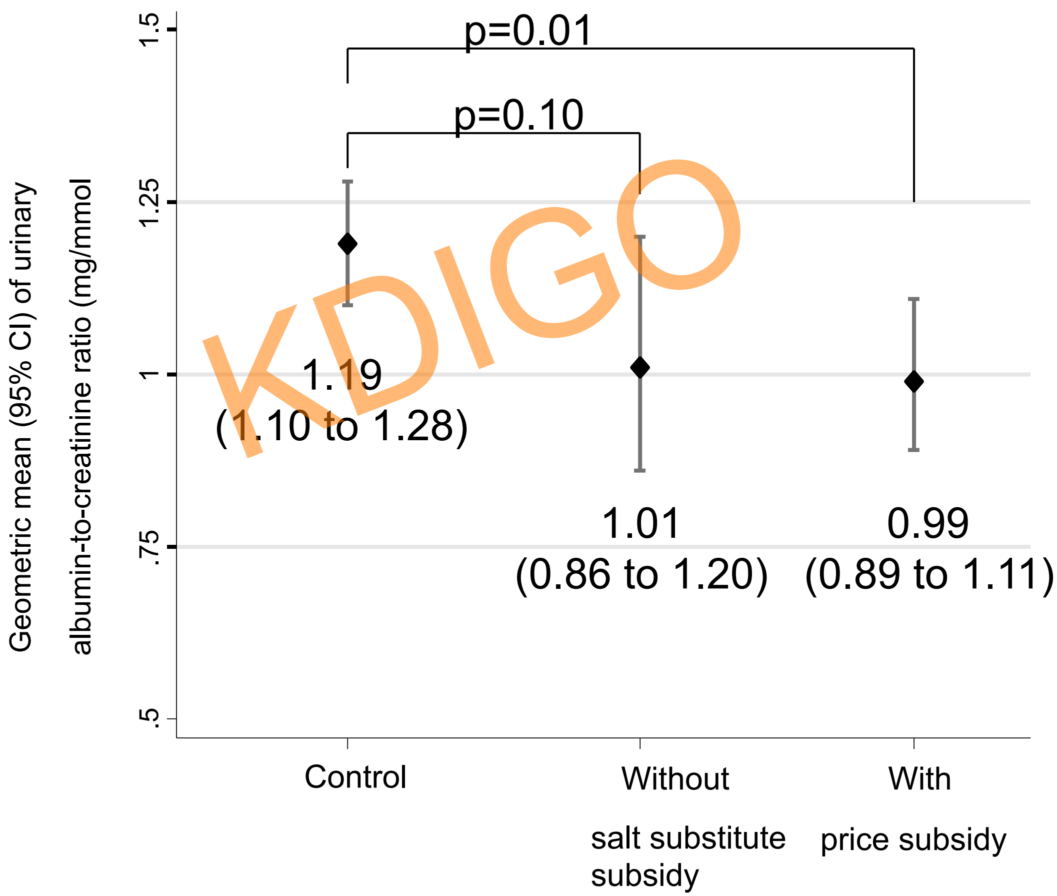
- Sodium reduction reduces albuminuria in a rural Chinese setting over the longer term
- Mediterranean diet improves cardiovascular outcomes in a Spanish setting
- Weight loss improves intermediate markers for diabetes and CKD but may be difficult to sustain
- Effective interventions for voluntary behavioural change are unclear
- Exercise improves fitness in the short term

CRHI: Impact of salt substitute?

Compared with participants from control villages: (n=928)	Participants from intervention villages Without subsidy (n=447)	Participants from intervention villages With price parity (n=528)
Urinary Na (mmol/day)	-9 (-24 to 5)	-18 (-34 to -2)
Equivalent reduction in salt (g/day)	0.53 (-0.29 to 1.4)	1.1 (0.17 to 2.0)
Urinary K (mmol/day)	5 (1 to 13)	9 (5 to 13)
Urinary Na/K ratio	-0.6 (-1.0 to -0.2)	-1.1 (-1.5 to -0.6)
SBP (mmHg)	-0.2 (-3.6 to 3.3)	-1.8 (-4.4 to 0.8)
DBP (mmHg)	-0.2 (-2.4 to 2.0)	-1.1 (-2.9 to 0.7)
Use of BP lowering agents, %	-2.9 (-1.8 to -7.6)	-4.6 (0.27 to -9.0)

Jardine, 2015, draft

CRHI: Impact of salt substitute on uACR



Jardine, 2015, draft

14% drop in log transformed uACR (95%CI +2.8 to -28.7)
16% drop in log transformed uACR (95%CI -4.2 to -26.8)

CRHI: Impact of salt substitute

OR (95%CI)	Participants from control villages (n=928)	Participants from intervention villages Without subsidy (n=447)	Participants from intervention villages With subsidy (n=528)	p for trend
Any albuminuria	1.00 (reference)	0.77 (0.44 to 1.33)	0.59 (0.37 to 0.96)	0.02
Microalbuminuria	1.00 (reference)	0.84 (0.48 to 1.47)	0.59 (0.35 to 0.98)	0.04
Macroalbuminuria	1.00 (reference)	0.22 (0.03 to 1.58)	0.71 (0.24 to 2.06)	0.41

Jardine, 2015, draft