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Hyponatremia In Falls & Fractures

October 2020 MRC2.CORP.D.00578

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Improving Awareness & Patient Outcomes

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Otsuka Pharmaceutical Development & Commercialization, Inc.

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Falls and Fractures: Incidence and Burden

- Fractures represent a serious health risk in the elderly, with a significant associated morbidity and mortality
- Approximately 13.5% of those who suffer a hip fracture die within 6 months and 24% within 1 year of the episode
- Among those who survive to 6 months, only 25-50% recover their ability to conduct their daily activities
- FRAX* includes a variety of risk factors (age, gender, alcoholism, Vitamin D, calcium, previous fractures etc.), but research shows that the list is far from complete

Ayus JC et al Nephrol Dial Transplant (2012) 27: 3725–3731.
* FRAX: WHO-developed country-specific fracture risk index of clinical risk factors

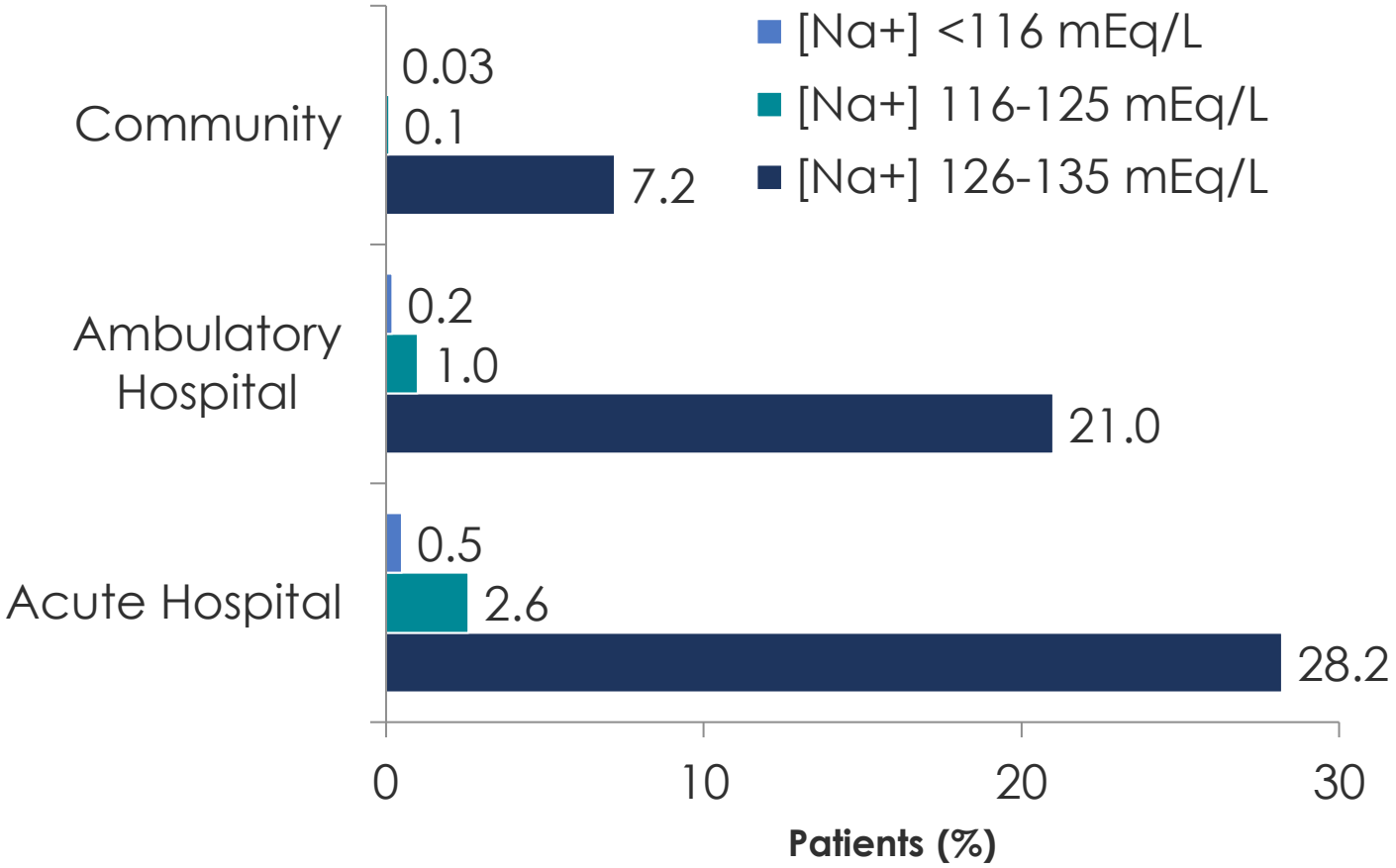
Chronic Hyponatremia: Incidence and Risk

- Hyponatremia, defined as serum [Na^+] < 135mEq/L, is the most common electrolyte disorder in the community (10%), in the nursing home (20%)[1] and in the hospital setting (30%)[2]
- Chronic hyponatremia is common in heart failure, SIADH and cirrhosis[2]
- Though mild-moderate chronic hyponatremia (Na^+ of 135 – 125 mEq/L) is considered "asymptomatic", it is increasingly implicated as a risk factor for osteoporosis, falls and fractures and neuro-cognitive disabilities, especially in the elderly[3]

Hyponatremia is associated with cognitive deficits and falls even at a sodium range of 130-135[4]

1Ayus et al, 2012, Nephrol Dial Transplant (2012) 27: 3725–3731; 2. Verbalis JG et al. The Journal of Medicine. 2013:126(10A);S5-S41; 3. Afshinnia F et al. Osteoporos Int. 2015 Sep;26(9):2291-8. 4. Gunathilake et al. JAGS. 2013;61(10).1838-39.

Hyponatremia Prevalence

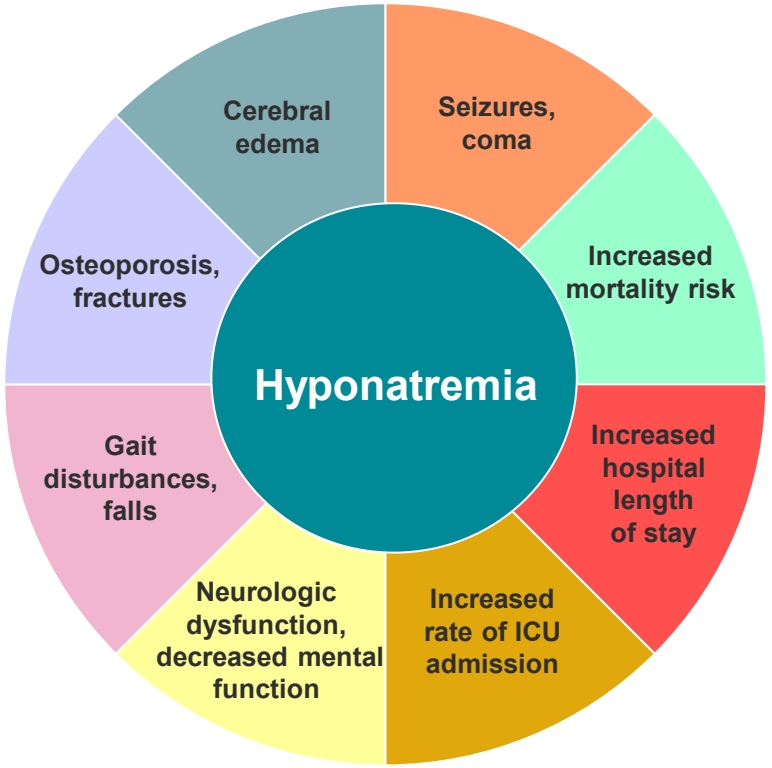


Data from the Tan Tock Seng Hospital in Singapore, based on 303,557 samples from 120,137 patients available for analysis.

Hawkins RC. *Clin Chim Acta*. 2003;337: 169-72.

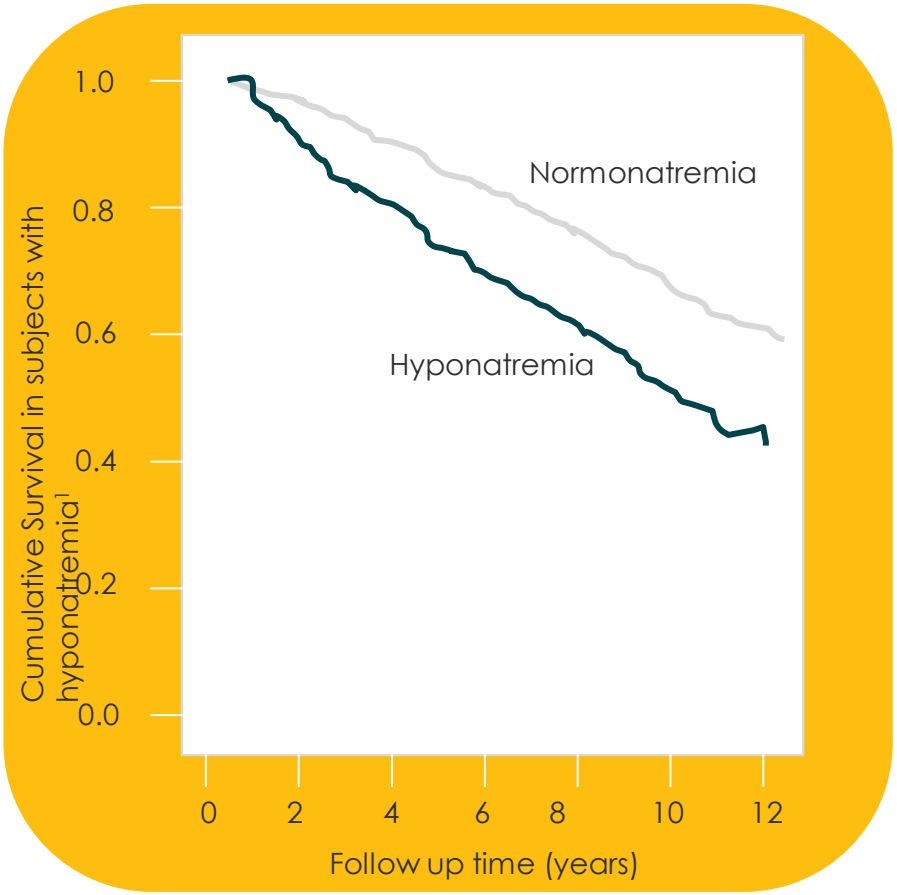
Consequences of Hyponatremia

Hyponatremia can have a wide and variable range of consequences[1-4]



1. Bagshaw SM, et al. *Can J Anesth*. 2009;56(2):151-167; 2. Ghali JK. *Cardiology*. 2008;111(3):147-157; 3. Zilberberg MD, et al. BMC Pulm Med. 2008;8:16; 4. Patterson JH. Pharmacotherapy 2011;31(5)

The Elderly are Particularly Susceptible to Hyponatremia, Leading to Increased Mortality



Reasons for susceptibility of elderly to HN:[2]

Increase in:

1. Antidiuretic Hormone
2. Atrial Natriuretic Peptide

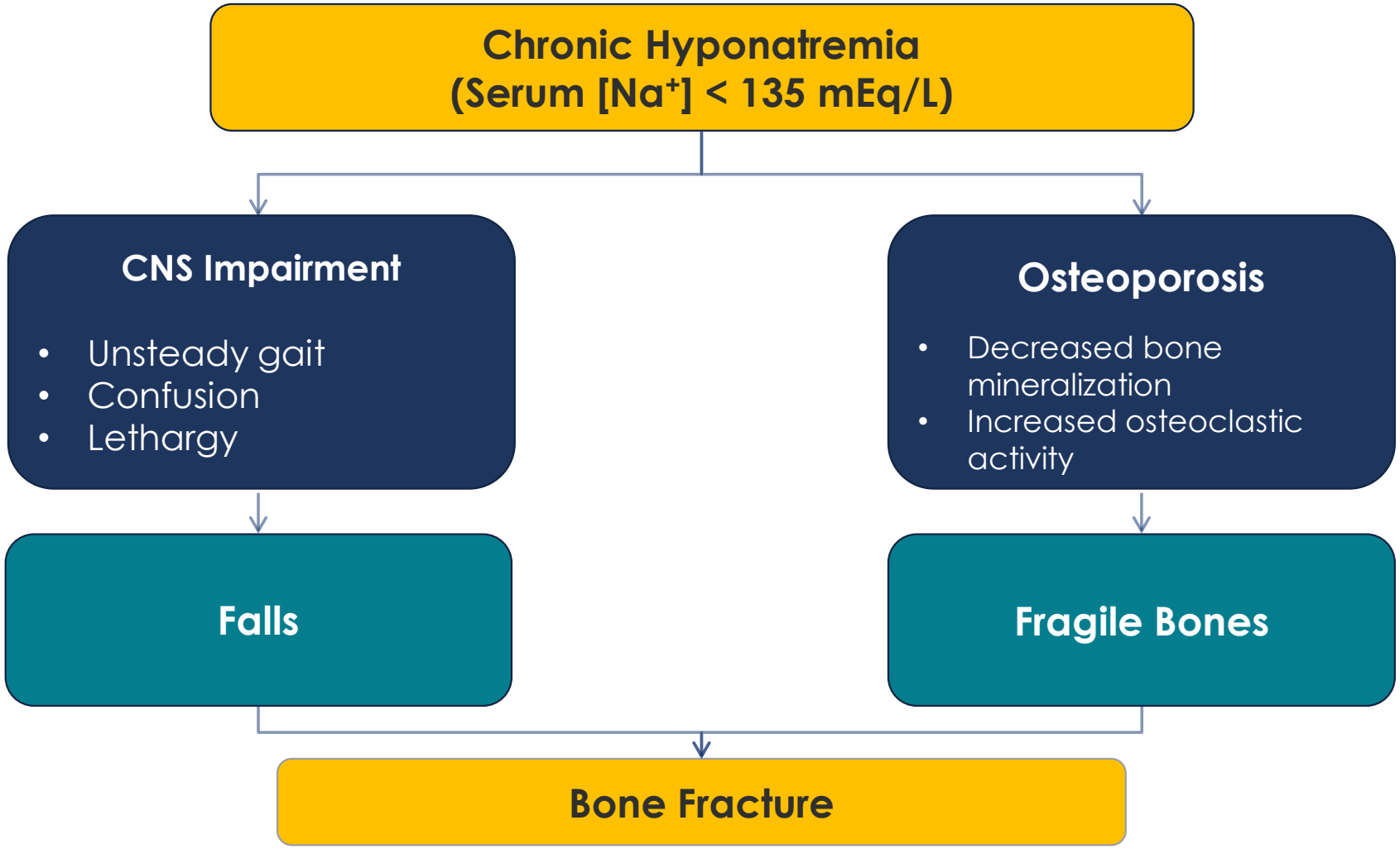
Decrease in:

1. Total body water
2. Glomerular Filtration Rate
3. Ability to concentrate urine
4. Water clearance
5. Mechanism of thirst
6. Aldosterone

Presence of HN correlated with increased risk of death for hospitalized geriatric patients: In a large cohort study (N = 4123), in-hospital mortality was higher in HN (16%) vs normonatremic (8%) patients[3]

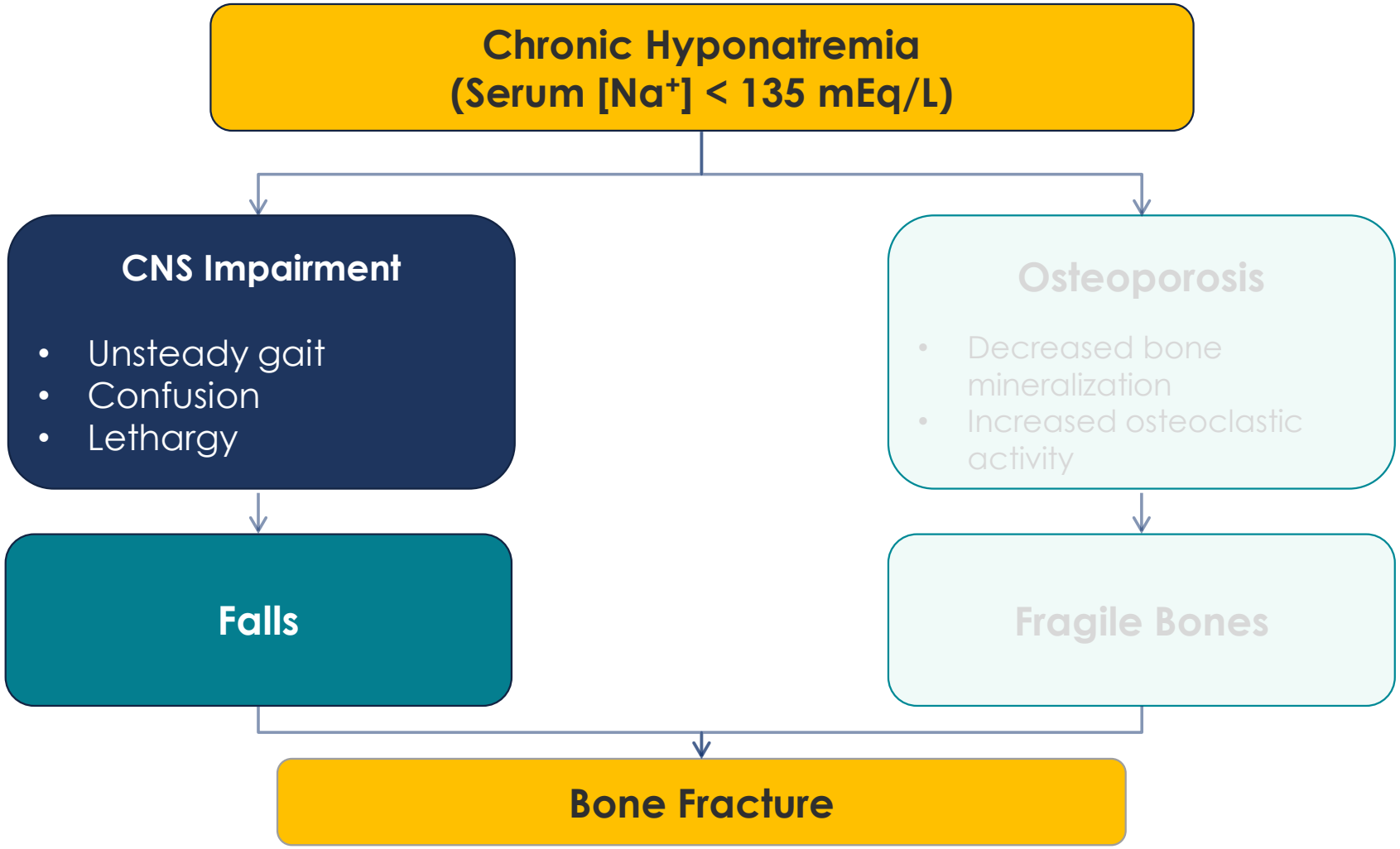
1. Figure adapted from Hoorn et al, J Bone&Min Res 26(8): 1822-1828. 2. Luckey AE, Parsa CJ Arch Surg 2003; 138(10) : 1055-1060. 3. Terzain C et al. J Gen Intern Med. 1994;9(2):89-91.

Association of Chronic Hyponatremia and Bone Fractures



Adapted from Ayus et al. Nephrol Dial Transplant. 2012 Oct;27(10):3725-31.

Chronic Hyponatremia and CNS Impairment



Adapted from Ayus et al. Nephrol Dial Transplant. 2012 Oct;27(10):3725-31.

Brain Adaptation to Chronic Hyponatremia

Chronic adaptation to hyponatremia is necessitated by three facts:

- Sodium cannot cross the blood-brain-barrier, only water can[1]
- Due to the confines of the skull, only a small degree of brain swelling is compatible with life and cells must find ways remove excess fluid[1]
- Rapid electrolyte-based adaptation accounts for only 65% of the observed brain volume regulation[2]

1. Sterns RH. Disorders of plasma sodium. N Engl J Med. 2015 Mar 26;372(13):1269. 2. Giuliani C, Peri A. Effects of Hyponatremia on the Brain. J Clin Med. 2014 Oct 28;3(4):1163-77.

Brain Adaptation to Chronic Hyponatremia

Glial astrocytes selectively swell during hyponatremia, sparing neurons

Skull limits brain swelling and necessitates adaptation

Rapid acute adaptation through extrusion of inorganic intracellular solutes (sodium, potassium, and chloride) and osmotic obligatory water

Slower essential adaptation in chronic hyponatremia by loss of small organic osmolytes (glutamate, taurine, glycine, myo-inositol)

Loss of glutamate →decreased synaptic release of excitatory neurotransmitters →gait instability

Giuliani C, Peri A. J Clin Med. 2014 Oct 28;3(4):1163-77. Figure adapted from Adrogue HJ et al. *N Engl J Med.* 2000;342:1581-9.

Chronic Hyponatremia Leads to Decreased Cerebral Osmolytes

	Grey Matter (mmol/kg wet wt)			**White Matter** (mmol/kg wet wt)		
	Control (10)	HN (11)	p-value	Control (7)	HN (3)	p-value
NAA	8.84±1.05	7.87±1.21	<0.05	8.68±0.78	7.12±0.56	<0.01
Cr	8.39±0.72	6.78±0.48	<0.0001	6.64±0.29	5.72±0.43	<0.01
Cho	1.68±1.30	1.08±0.12	<0.0001	1.90±0.20	1.07±0.15	<0.001
ml	8.97±1.68	4.58±1.17	<0.0001	8.04±0.33	6.42±0.75	<0.001

…And Correction Leads to Recovery of Osmolytes

NAA: N-acetyl-aspartate
Cr: Creatine/phosphocreatine
Cho: Choline containing compounds
mI: myo-inositol

Videen JS, Michaelis T, Pinto P, Ross BD. J Clin Invest. 1995 Feb;95(2):788-93.

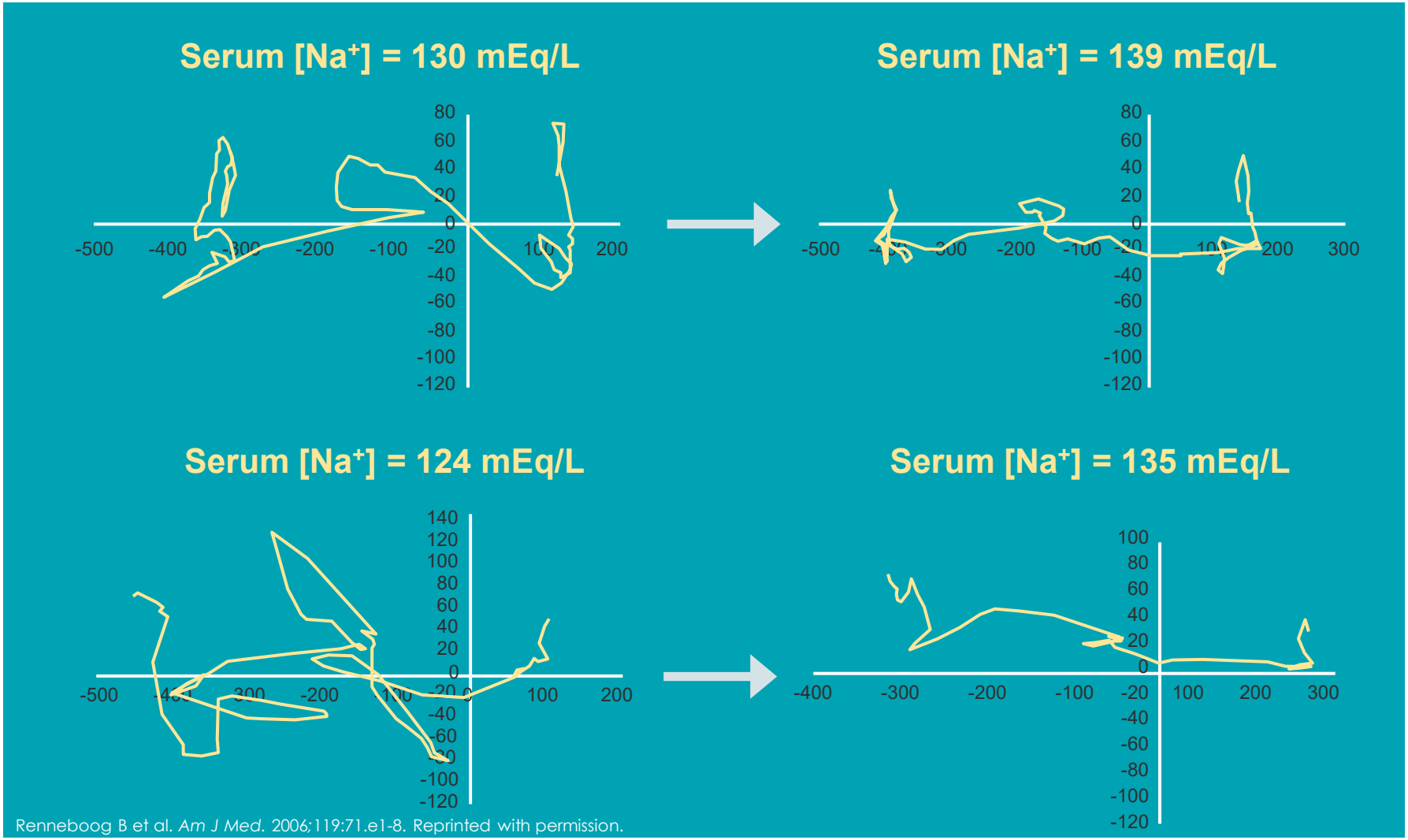
Association of Hyponatremia to CNS Symptoms, Gait Instability and Falls

Even mild, chronic hyponatremia is associated with:

- Instability of gait which stabilizes after correction of HN[1]
- Attention deficit comparable to alcohol ingestion[1]
- Cognitive impairment[2]
- Increased risk of falls[1]

1. Renneboog B et al. *Am J Med.* 2006;119:71.e1-8. 2. Gunathilake et al. JAGS. 2013;61(10).1838-39.

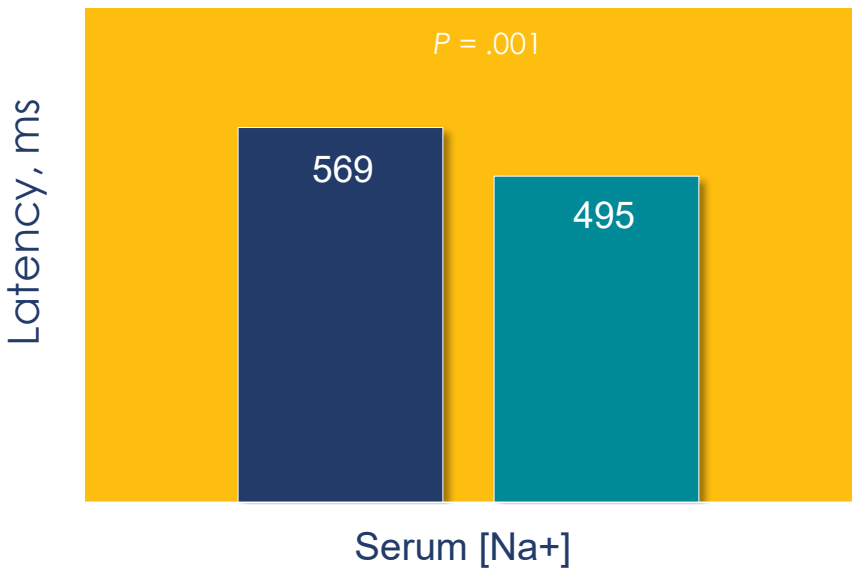
Gait in Patients After Correcting Hyponatremia



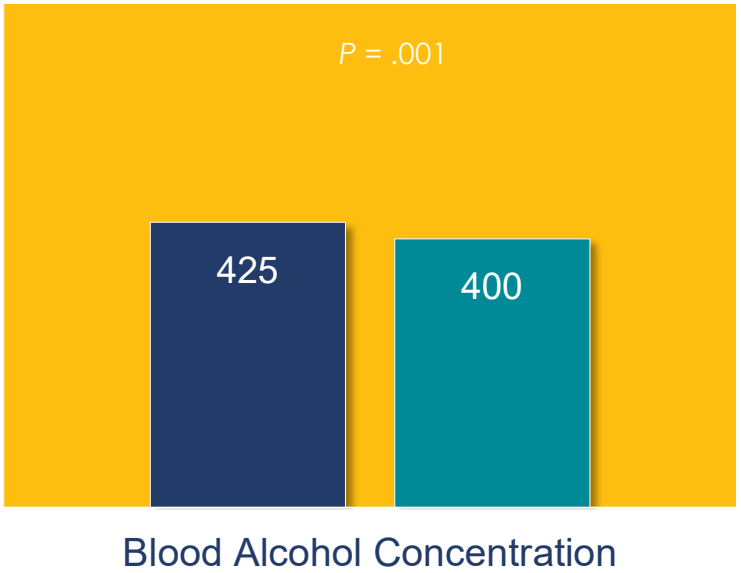
Renneboog B et al. *Am J Med.* 2006;119:71.e1-8. Reprinted with permission.

Attention Impairment in Patients With Hyponatremia vs Acute Alcohol Ingestion

Latency in HN Patients (n = 16)



Latency With Acute Alcohol Consumption in Healthy Subjects (n = 10)



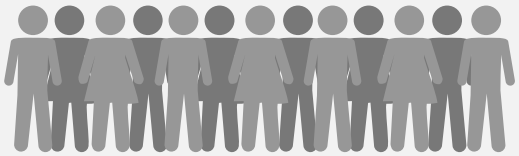
Latencies in response time are median values expressed in ms; *P* value between controls and patients with normal serum [Na^+] not significant; 4 selected attention tests: Go/No Go, intermodal comparison, Phasic Alert 1-4, and Phasic Alert 2-3.

Renneboog B et al. *Am J Med.* 2006;119:71.e1-8.

Mild Hyponatremia is Associated with Significant Cognitive Deficits and Propensity to Fall

Community-dwelling individuals with available serum sodium values were drawn from the Hunter Community Study, an Australian population-based prospective cohort study

Study participant characteristics



N = 2550

- Community-dwelling
- Elderly
- Cognitive function assessed using the ARCS*

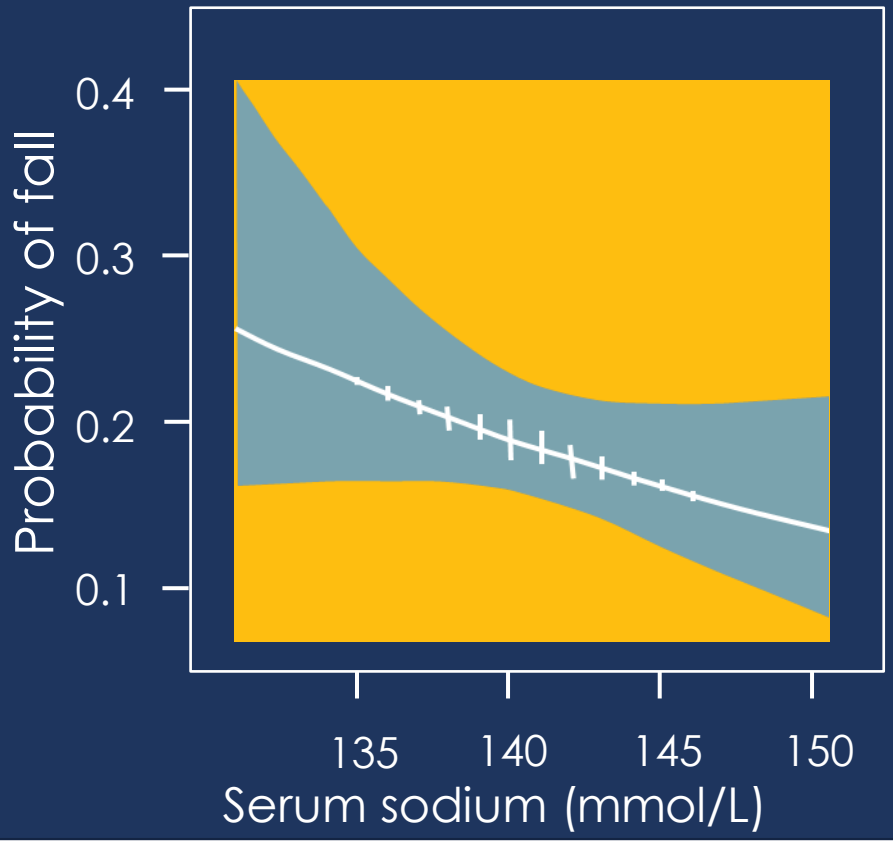
ARCS score for subjects with a serum sodium of 135 mmol/L was on average 4.67 units higher (CI=1.56 – 7.79, p = .01) out of a standardized score of 100 than for those with a sodium level of 130 mmol/L

This represents a 5% change in cognition, or a shift from 50th to the 37th centile in terms of cognition

*Audio Recorded Cognitive Screening tool (ARCS), a short cognitive battery that probes most cognitive domains traditionally assessed using conventional neuropsychological tests.

Gunathilake R et al. J Am Geriatric Soc 2013 61(10):1838-9

Mild Hyponatremia is Associated with Significant Cognitive Deficits and Propensity to Fall



- In the community dwelling elderly, mild hyponatremia is associated with an increased probability of falls
- A drop in serum sodium of 5 mmol from 135 to 130 mmol/L increased the risk of falling by 32% (OR = 1.32, 95% CI = 1.04–1.64)
- A change in age of 13 years, from 60 to 73, increased the risk of falling by 27% (OR = 1.27, 95% CI = 1.01–1.59)

A 5-mmol/L drop in sodium had about the same effect on falls as aging 13 years

Gunathilake et al. JAGS. 2013;61(10).1838-39.

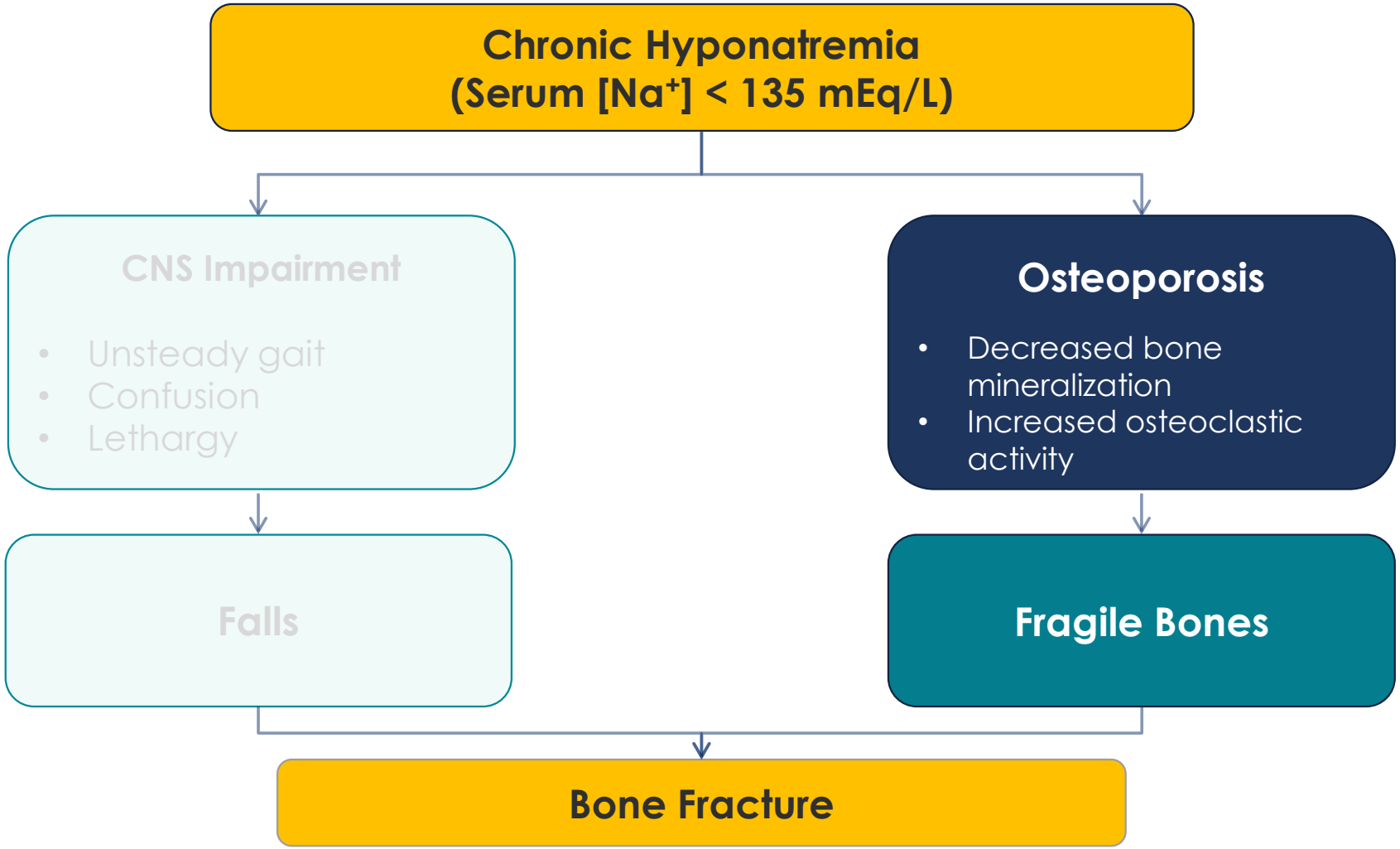
Mild Hyponatremia is an Independent Risk Factor for Patients Admitted with Falls

When adjusting for age, neurological disorder, and hematological disorder, patients with hyponatremia are significantly more likely to be admitted for a fall compared to non-hyponatremic patients

Variables	*Fall rate*	*Adjusted Odds Ratio (95% CI)*	*p-value*
Age			
65-74	**65.1%**	Reference	
75-84	**75.9%**	1.56 (1.25 - 1.95)	<0.001
≥85	**90.7%**	4.46 (3.31 – 6.00)	< 0.001
Gender			
Male	**70.9%**	Reference	
Female	**82.2%**	1.62 (1.32 - 1.99)	< 0.001
Pre-existing condition/ disorders			
Neurological	**84.6%**	1.68 (1.31 - 2.15))	< 0.001
Hematological	**82.2%**	1.41 (1.13 - 1.74)	0.002
Serum Sodium			
≥135 mmol/L	**76.5%**	Reference	
< 135 mmol/L	**86.4%**	1.81 (1.26 - 2.60)	0.001

Rittenhouse KJ. Injury, Int. J. Care Injured 46 (2015) 119–123

Chronic Hyponatremia and Osteoporosis



Adapted from Ayus et al. Nephrol Dial Transplant. 2012 Oct;27(10):3725-31.

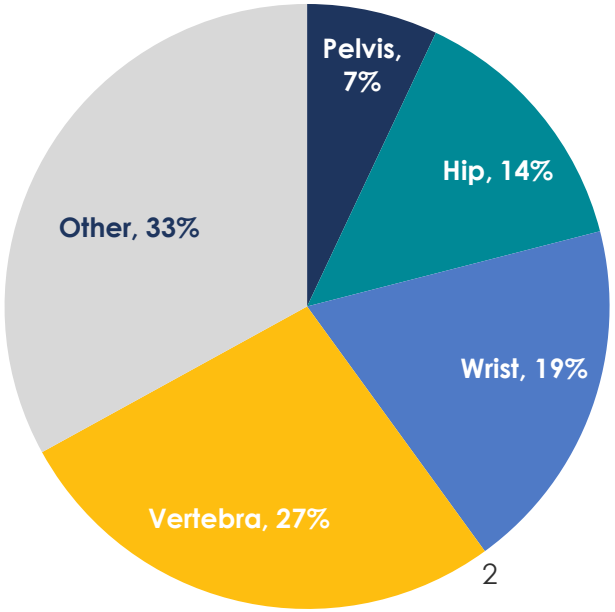
Osteoporosis: Definition and Epidemiology

Osteoporosis is a skeletal disorder characterized by:[1]

- Compromised bone strength
- Predisposition to fractures

Bone strength reflects the integration of:[1]

- Bone density
- Bone quality



2

Osteoporosis is a serious health issue in the Unites States[2]

- Affects 10 million Americans (71% women)
- 2 million fractures yearly
- Direct cost $17 billion

1. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy JAMA 2001; 285:785-795. 2. Burge, R et al. J. Bone. Miner. Res. 2007; 22:465-475

Normal Bone Remodeling: Balance Between Osteoblast and Osteoclast Activity

- Remodeling of adult bone is a continual process[1]
- It is the balance of opposing actions of bone removal through erosion, and bone building through mineralization[1]
- Osteoclasts are responsible for bone erosion and osteoblasts are responsible for bone building[1]
- In genetically modified mice it has been shown that vasopressin negatively regulates osteoblasts and stimulates osteoclasts, thereby contributing to bone loss in states of vasopressin excess[2]

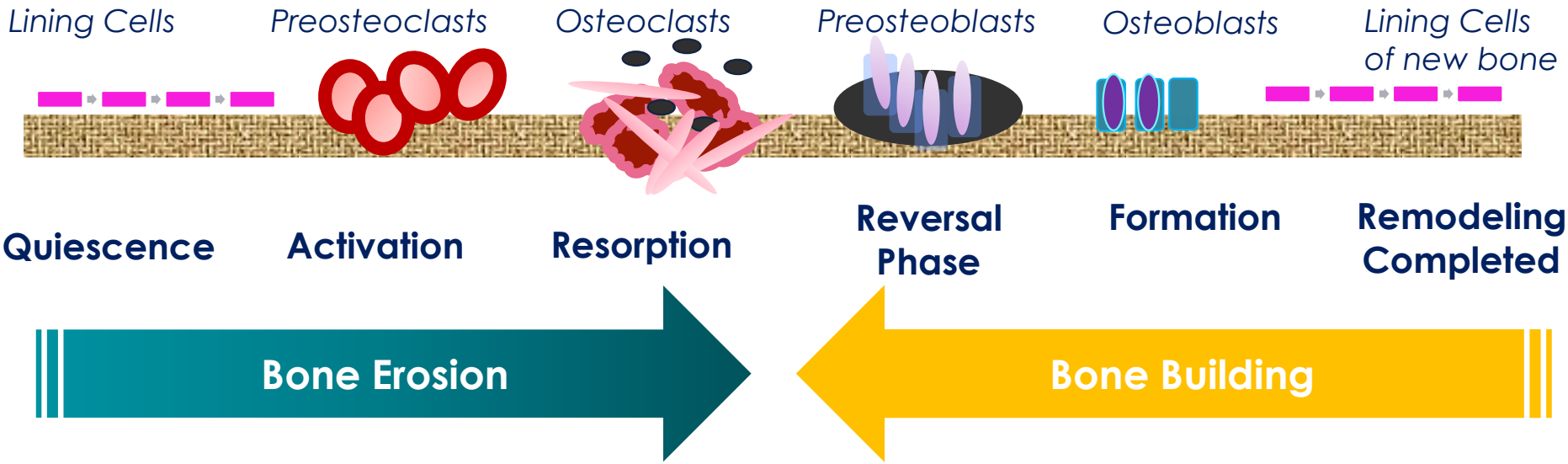


Figure adapted from Tanaka Y et al. Curr Drug Targets Inflamm Allergy 2005;4;325-328

1. Tanaka Y et al. Curr Drug Targets Inflamm Allergy 2005;4:325-328; 2. Tamma R et al. Proc Natl Acad Sci U S A. 2013 Nov 12;110(46):18644-9.

Significant Thinning of Rat Femurs After Chronic Hyponatremia

- Hyponatremia was induced in rats with desmopressin and maintained for 3 months
- DXA analysis of excised femurs of hyponatremic rats showed approximately 30% reduction in BMD compared to normonatremic controls
- Micro-computed tomography revealed reductions in both trabecular and cortical bone mass in hyponatremic rats compared to normonatremic controls

DXA: Dual energy X-ray Absorptiometry

Verbalis, JG et al. JBMR 2010; 25:554-663

Hyponatremia Increases Bone Resorption in Animals and Significantly Increases Odds of Osteoporosis in Humans

- NHANES III data analysis showed that among participants 50 years of age or older, a statistically significant positive linear association between serum sodium and femoral neck BMD in hyponatremic subjects ($p < .01$) but not in normonatremic subjects ($p = .99$)
- Among hyponatremic subjects, serum sodium explained 14.7% of the variation in total hip BMD
- At the femoral neck, the adjusted odds of osteoporosis was 2.87 times higher among hyponatremic adults (95% confidence interval (CI) = 1.41–5.81; $p = .003$)

Total hip BMD decreased by 0.037 g/cm^2 for every 1 mmol/L decrease in serum sodium

NAHNES III: The Third National Health and Nutrition Examination Survey

Verbalis JG et al. *JBMR 2010;* 25:554-563

Hyponatremia is a Risk Factor For Development of Both Osteoporosis and Fractures

- Large population-based study (>2.9mil)+ evaluating HN impact on osteoporosis and fragility fractures
- Case control matched Osteoporosis n=30,517* and Case control matched fragility fractures n=46,256*

Hyponatremia and Osteoporosis	Odds Ratio	Hyponatremia and Fragility Fractures	Odds Ratio
Recent	3.060	Recent	3.047
Chronic	3.970	Chronic	4.608
Prior	1.078	Prior	1.339
Chronic and Recent	12.092	Chronic and Recent	11.211
Only Recent	2.394	Only Recent	2.545
Only Chronic	2.991	Only Chronic	3.670

Definitions: **Recent**- at least ONE serum Na+ measurement <135mmol/L within 30 days before the end of the encounter window. **Chronic**- at least TWO serum Na+ measurements <135mmol/L at least ONE year apart during encounter window. **Prior**- at least ONE serum Na+ measurement <135mmol/L within encounter window.

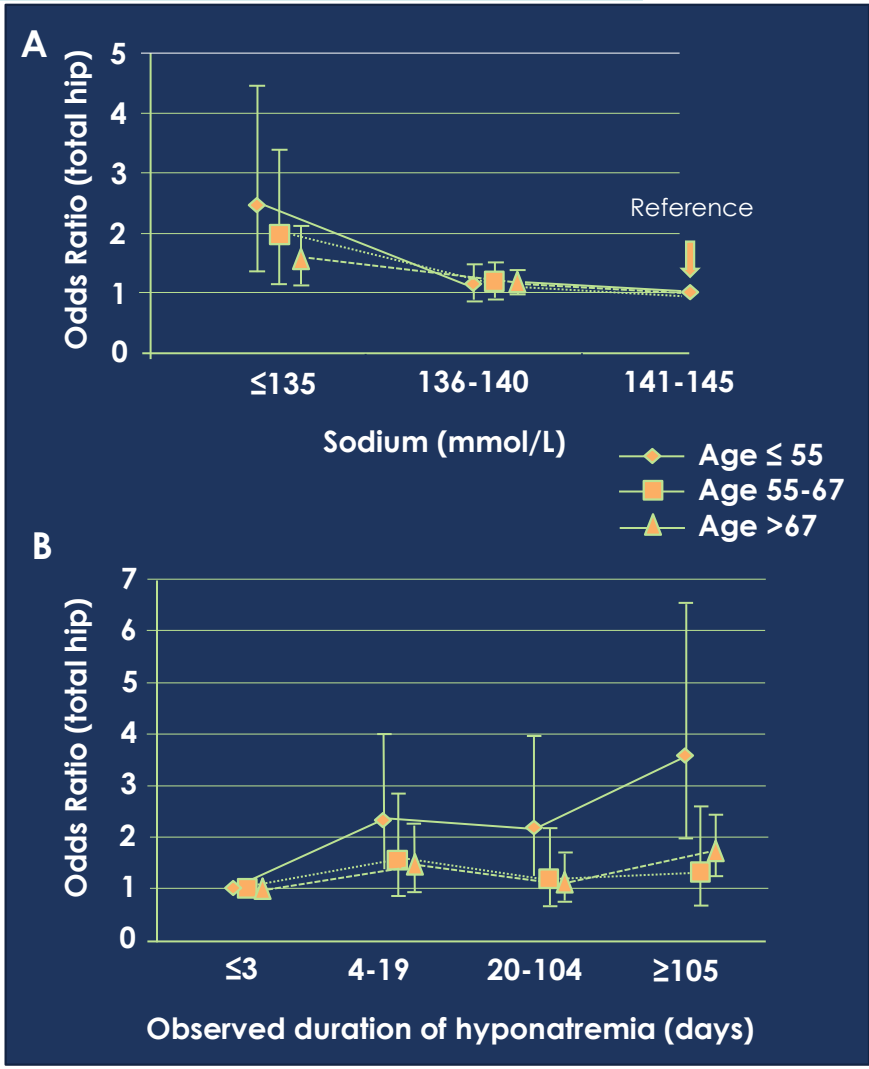
+MedStar Health database and matched for age, sex, race, and duration of record & HN defined as <135mmol/L

Usala RL et al. J Clin Endocrinol Metab. 2015 Aug;100(8):3021-31.

Chronic Hyponatremia May Lead to Early Aging of Bone in Young Individuals

- Cross sectional study of 24,784 patients with available bone densitometry to test the effect of age on the association between hyponatremia and osteoporosis
- Osteoporosis was most prevalent in patients with serum sodium of ≤135 mmol/L in all anatomical sites (lumbar, femoral neck, total hip) compared with normonatremic ($p<0.001$)
- Rate of osteoporosis in hyponatremic patients < 55 years of age was comparable to the rate of osteoporosis in normonatremic patients age > 67 years
- The odds ratio (OR) of osteoporosis associated with hyponatremia was the highest at the youngest age group (<55 years) with a trend toward null in the older age groups in all anatomical sites in fully adjusted models ($p \leq 0.015$) (A)
- The highest odds of osteoporosis belonged to the longest observed duration of hyponatremia in the youngest age group declining toward no increased risk of OP in the older groups ($p \leq 0.029$ for total hip) (B)

Chronic hyponatremia may contribute to early aging of the bone in younger individuals



Afshinnia F et al. Osteoporos Int. 2015 Sep;26(9):2291-8.

Cumulative Burden of Chronic Hyponatremia and Association with Osteoporosis

- In a large study (>340,000) of a racially and ethnically diverse population in a routine clinical practice environment in the United States,
  - Chronic hyponatremia was associated with an increased risk of osteoporosis
  - There was a graded association where people with incrementally higher serum sodium levels had lower risk for osteoporosis
  - 89% of the study population had three or more sodium measurements- the results appear consistent with previous findings and provide new insights into the potential cumulative burden of hyponatremia on bone modeling

A time-weighted mean sodium increase of 3 mEq/L was associated with a lower risk of osteoporosis [adjusted RR (95% CI) 0.95 (0.93, 0.96)].

Adams AL, et al. *Osteoporos Int*. 2019;30(4):853-861.

Mild Hyponatremia Is a Risk Factor for Falls and Fractures, Independent of BMD

- Baseline serum sodium measured in 5208 elderly subjects from the **prospective** population-based Rotterdam Study (Netherlands)
- Hyponatremic patients (399) were older, had more recent falls, higher type 2 diabetes prevalence, and used diuretics more often
- Hyponatremia (HN) was not associated with lower BMD but was associated with increased risk of incident non-vertebral fractures and all-cause mortality
- The increased risk of falls with HN remained after adjusting for age, sex, BMI, disability index, use of diuretics or psycholeptics, and prevalent diabetes (OR) = 1.35, 95% confidence interval1.03–1.75, p = .029)
- Increased fracture risk in HN was independent of recent falls, pointing toward an effect on bone quality.

Characteristic	Normonatremia (n = 4809)	Hyponatremia (n = 399)	p value (adjusted for age and sex)
Recent fall (%)	16.4	23.8	.006
Disability index (%)	0.62 (1.39)	0.97 (1.76)	.031
Disability index ≥ 0.5 (%)	32.4	44.9	.037
Nonvertebral Fracture (%)	17.3	23.3	.004*[a]
Femoral neck BMD (g/cm²)	0.861 ± 0.14	0.873 ± 0.15	.105
All-cause mortality	32.6	51.6	.00017*[b]

*Adjusted for age, sex and body mass index.
[a] Hazard ratio 1.39, 95% CI (1.11-1.73)
[b] Hazard ratio 1.35, 95% CI (1.15–1.57)

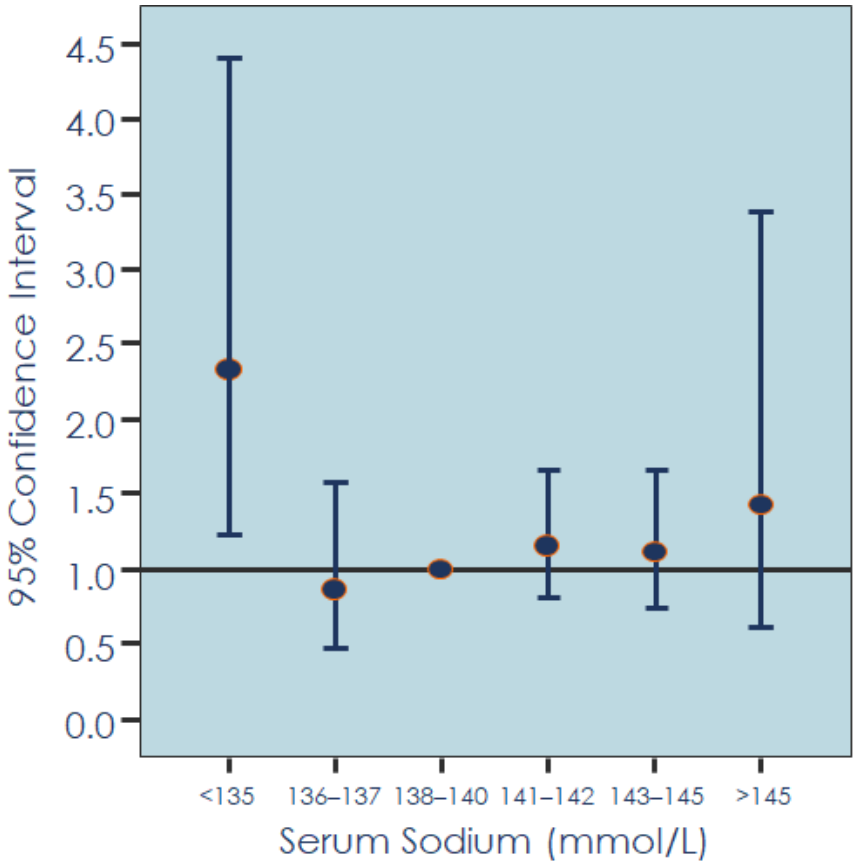
Hoorn et al. *J Bone Miner Res 26(8):* 1822-1828, 2011

Hyponatremia Increased the Risk of Fracture in CKD Independent of Osteoporosis

Association of hyponatremia with fracture occurrence in 1,408 female patients

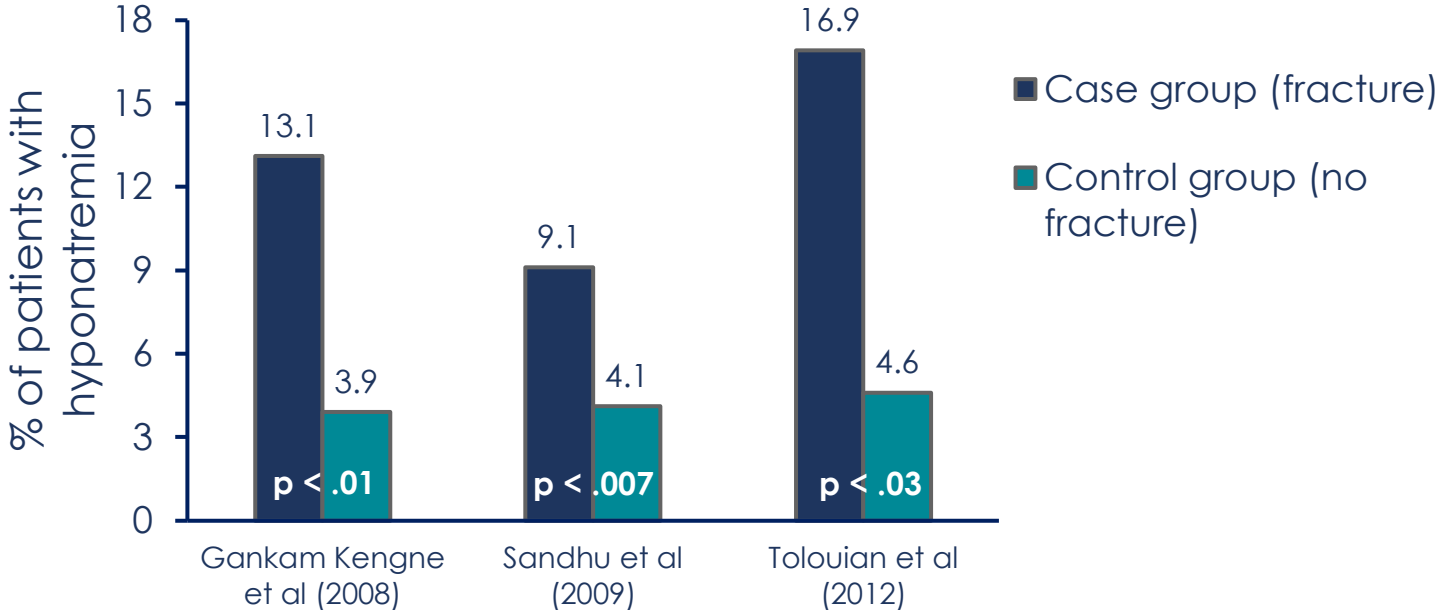
	OR (CI)	p
Unadjusted	2.86 (1.66 - 4.95)	<0.001
Adjusted	2.25 (1.24 - 4.09)	0.01

Adjusted for age, T-score, amenorrhea, steroid use, liver disease, smoking and alcohol use, liver disease and osteoporosis treatments



Kinsella et al. *Clin J Am Soc Nephrol* 5:275-280, 2010

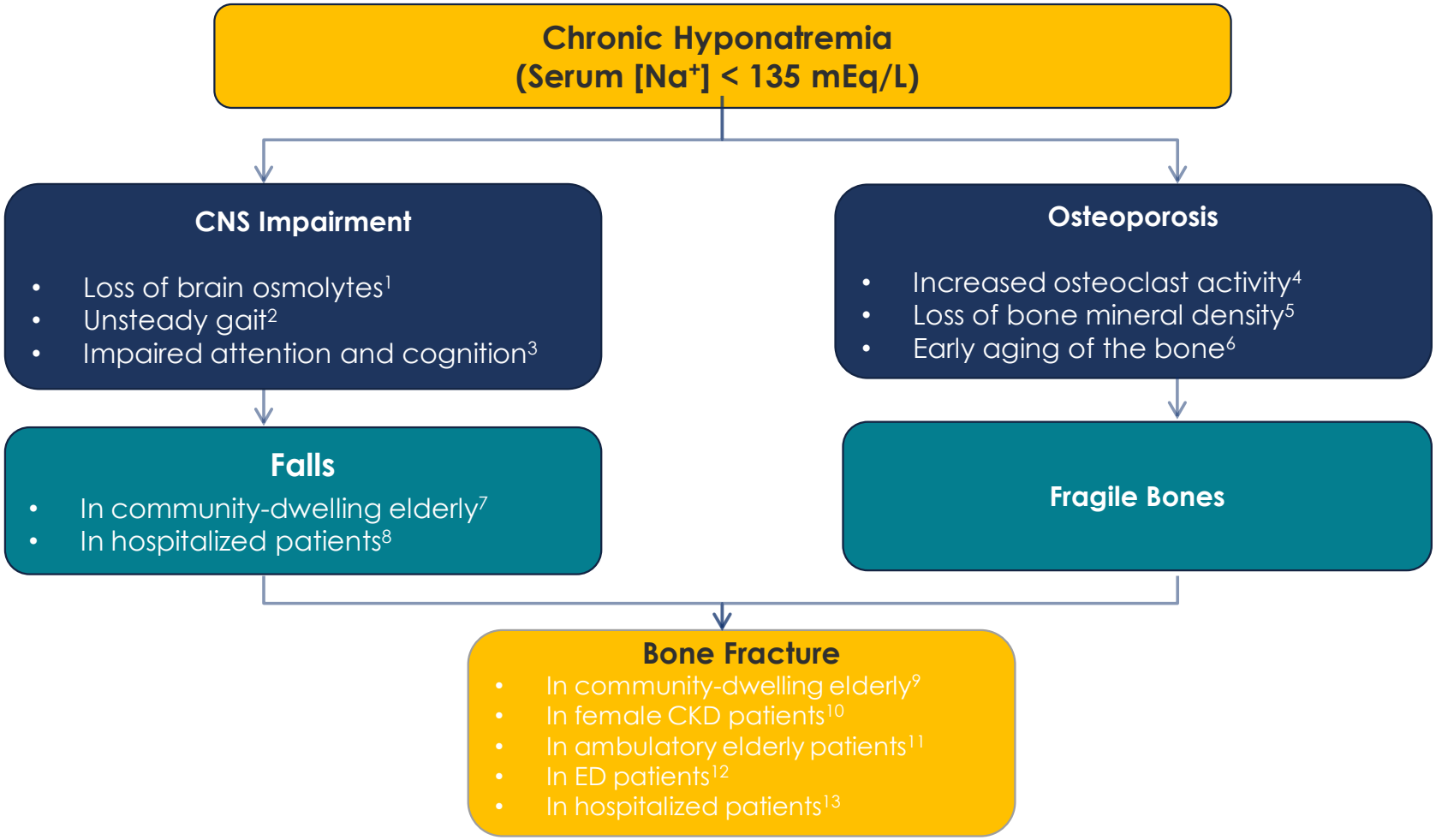
Prevalence of Hyponatremia in Patients with Bone Fracture



- Three case-control studies of individuals aged 65 years or over compared the prevalence of hyponatremia where the case group had a verified bone fracture and the control group had no history of bone fracture[1]
- Gankam Kengne et al found **mild asymptomatic hyponatremia** to be associated with bone fracture after incidental fall in ambulatory elderly (adjusted OR: 4.16, 95% CI: 2.24–7.71)[2]
- Tolouian et al found that fracture cases were almost 5 times as likely as controls to be hyponatremic (OR=4.80, 95% CI:1.06–21.67)[3]

1. Soiza RL et al. J Clin Med. 2014 Aug 18;3(3):944-58. 2. Gankam Kengne F et al. QJM. 2008 Jul;101(7):583-8. 3. Tolouian R et al. J Nephrol. 2012 Sep-Oct;25(5):789-93.

Hyponatremia in Falls and Fractures: Summary



1. Videen JS, Michaelis T, Pinto P, Ross BD. J Clin Invest. 1995 Feb;95(2):788-93. 2. Renneboog B et al. *Am J Med.* 2006;119:71.e1-8. 3. Gunathilake et al. JAGS. 2013;61(10).1838-39. 2013;61(10).1838-39.
4. Tamma R et al. Proc Natl Acad Sci U S A. 2013 Nov 12;110(46):18644-9. 5. Usala RL et al. J Clin Endocrinol Metab. 2015 Aug;100(8):3021-31. 6. Afshinnia F et al. Osteoporos Int. 2015 Sep;26(9):2291-8.
7. Gunathilake et al. JAGS. 2013;61(10).1838-39. 8. Rittenhouse KJ. Injury, Int. J. Care Injured 46 (2015) 119–123. 9. Hoorn et al. *J Bone Miner Res 26(8):* 1822-1828, 2011. 10. Kinsella et al. *Clin J Am Soc Nephrol* 5:275-280, 2010. 11. Gankam Kengne F et al. QJM. 2008 Jul;101(7):583-8. 12. Soiza RL et al. J Clin Med. 2014 Aug 18;3(3):944-58. 13. Tolouian R et al. J Nephrol. 2012 Sep-Oct;25(5):789-93.

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