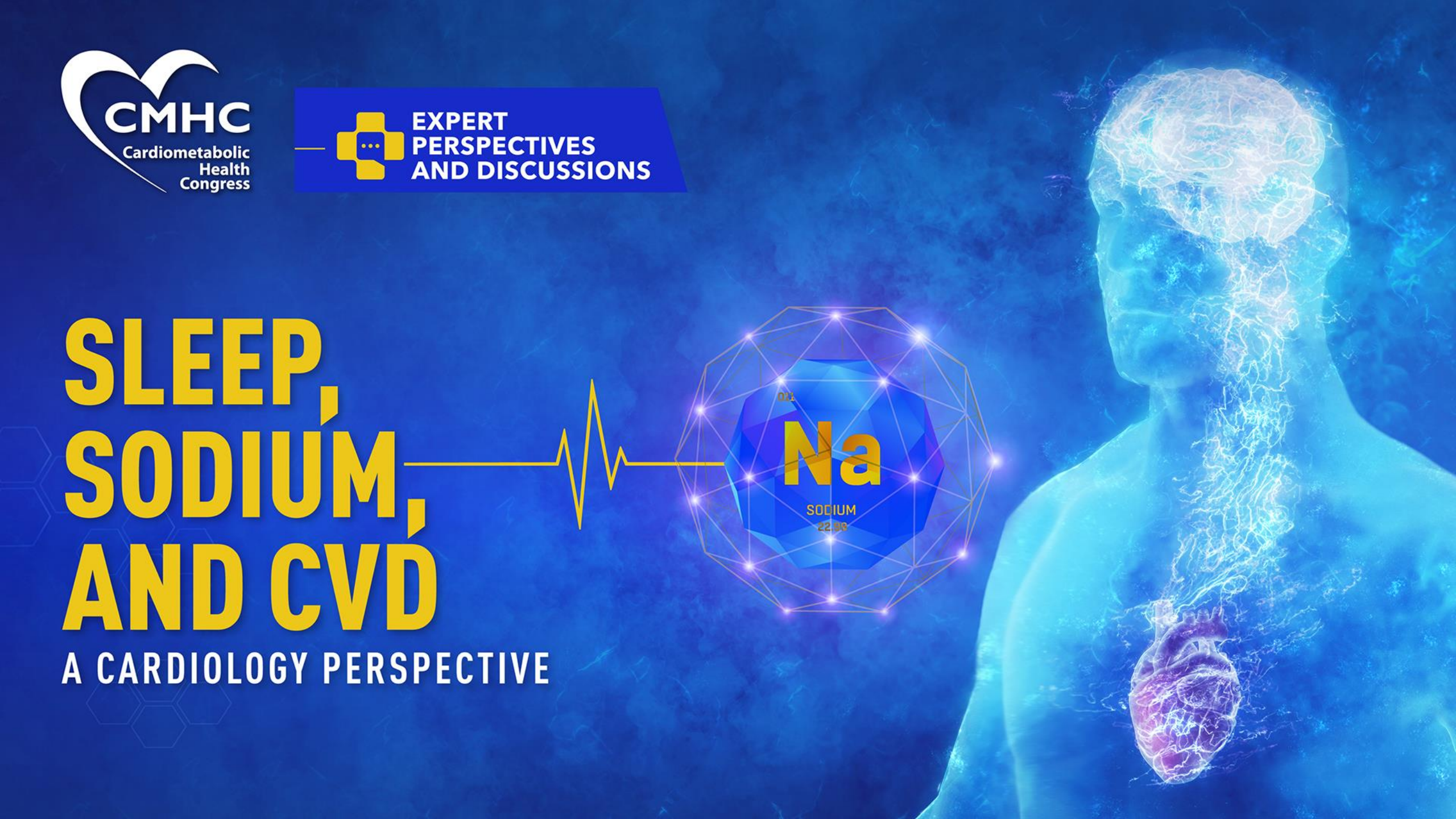
CMHC
Cardiometabolic Health Congress

EXPERT PERSPECTIVES AND DISCUSSIONS

SLEEP, SODIUM, AND CVD

A CARDIOLOGY PERSPECTIVE



Salt, Sleep and Cardiovascular Risk

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AGENDA

1 Salt and Blood Pressure

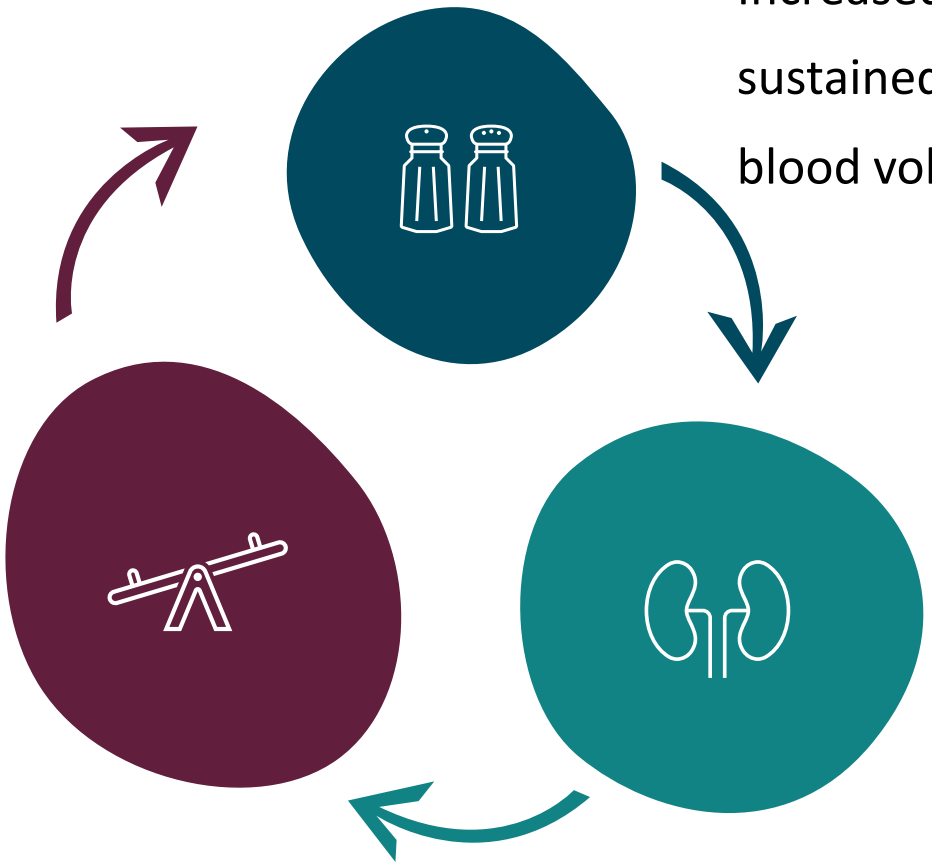
2 Salt Intake – Diets and Drugs

3 Sleep Disorders and CV Disease

4 Narcolepsy

How Does Salt Cause Hypertension

Increased salt intake is associated with sustained increases in plasma and blood volume



Increased salt intake may be accompanied by reduced ability of the kidney to excrete sodium

When the capacity of the kidneys to maintain Na+ balance and extracellular fluid volume within the appropriate range is compromised, increases in arterial pressure become necessary to re-establish normal balance – **Pressure Natriuresis**

Salt Sensitivity

- Some people can effectively excrete high dietary salt intake without an increase in arterial BP, and other people (salt sensitive) cannot excrete sodium effectively without an increase in arterial BP.
- This is a heterogeneous characteristic with a familial component
- Factors associated with heightened salt sensitivity (increased BP with sodium intake) include women, African Americans, post menopause and increased age
- 73% of black hypertensives are salt sensitive versus 56% of white hypertensives

Salt Sensitive Hypertension

Salt sensitive hypertension is defined as an increase in blood pressure associated with increased salt intake.

In response to a high salt diet, cardiac output increases. Salt resistant subjects respond with reciprocal decreases in systemic vascular resistance, while salt sensitive subjects have a paradoxical increase in vascular resistance associated with increased BP.

End organ structure and function damaged by salt may be the basis for the increased mortality among normotensive individuals with salt.

Approximately 50% of humans with hypertension have salt sensitivity with this number varying between sexes and influenced by age and race.

Among normotensives, approximately 26% are salt sensitive which has led to increased mortality - increased salt intake has effects apart from blood pressure and volume expansion that may contribute to tissue injury.

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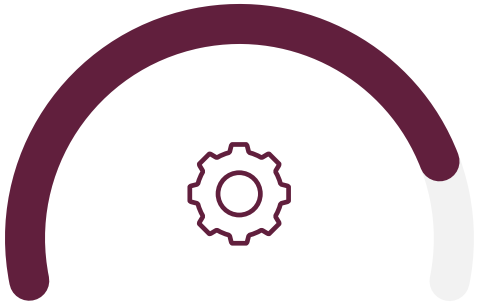
Salt, Diet and Drugs

1700 mg

How much sodium in effervescent paracetamol?

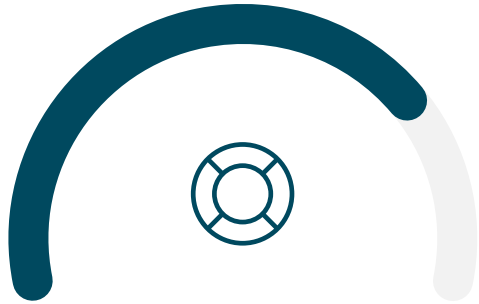
1640 mg

How much sodium in 9g of sodium oxybate?



3400 mg

Average US sodium intake



2300 mg

Recommended daily sodium intake

Sodium Loading

2300 mg/day increase in sodium excretion was associated with a 3.1–to 6.0–mmHg increase in SBP (INTERSALT Study, Elliott et al, 1996)

24-h SBP increased by 3.6 mm Hg with 3 weeks of effervescent paracetamol (1600 mg sodium/day) (Benitez-Camps et al, 2018)

Salt loading may blunt nocturnal BP decline (Higashi et al, 1997)

Elliott P et al. BMJ. 1996;312:1249-53.; Benitez-Camps M et al. J Hypertens. 2018;36:1656-62.
Higashi Y et al. Hypertension.1997;30:163-67.

Sodium Loading

Sodium-containing medications were associated with significantly increased odds of adverse cardiovascular events (George et al, 2013)

4 weeks after d/c effervescent paracetamol (1700 mg sodium), SBP was lower by 13 mmHg and DBP by 2.5 mmHg (Ubeda et al, 2009)

Sodium intake reduction of 1200mg/day is projected to reduce MI by 12%, stroke by 8%, and all-cause mortality by 4% (Bibbins-Domingo et al, 2010)

George J et al. BMJ. 2013;317:f6954. Ubeda A et al. Pharmacoepidemiol Drug Saf. 2009;18:417-9.
Bibbins-Domingo K et al. N Engl J Med. 2010;362:590-99.

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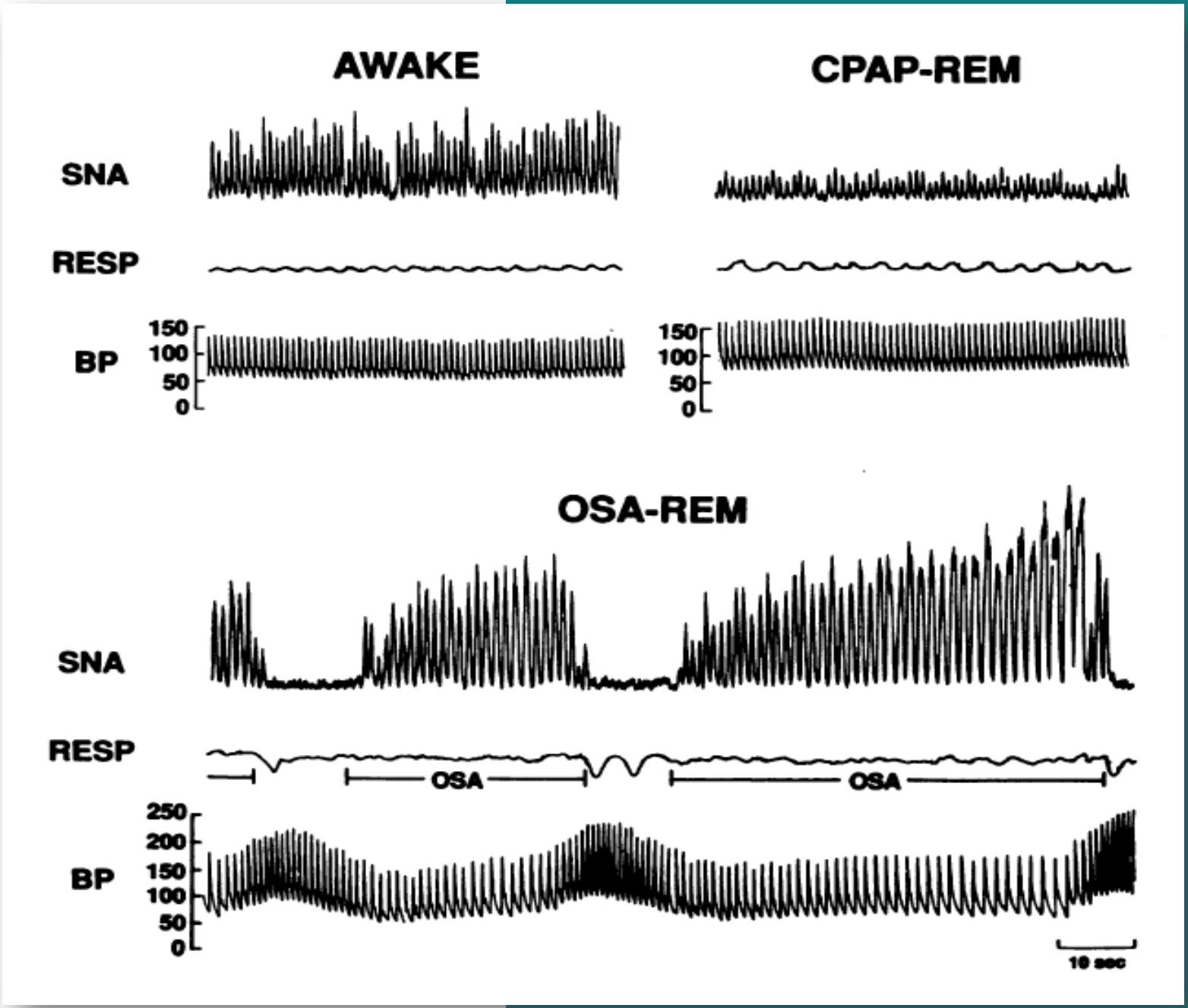
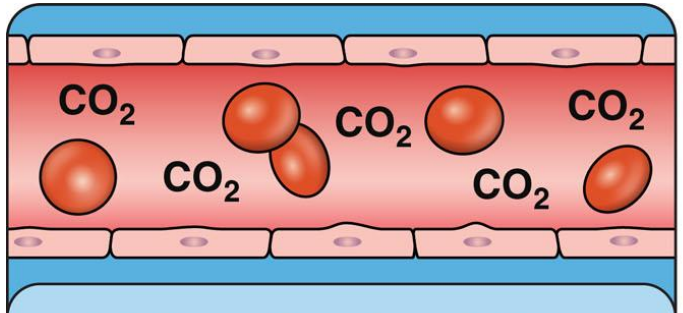


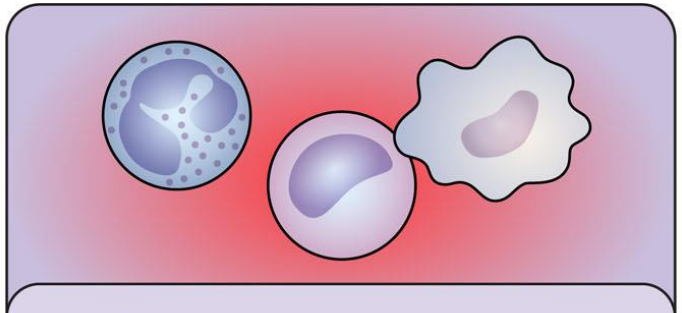
Somers et al., JCI 1995

Cardiovascular implications of OSA



OSA pathophysiology

- Hypoxemia/reoxygenation
- Autonomic dysfunction
- Arousals/sleep disruption
- Intrathoracic pressure changes
- Hypercapnia



Disease mechanisms

- Inflammation/atherosclerosis
- Endothelial dysfunction
- Hypercoagulability
- Metabolic dysregulation
- Hemodynamic changes
- Left atrial enlargement
- Sympathetic activation

Associated CVD

- Hypertension
- Atrial fibrillation and other arrhythmias
- Heart failure
- Coronary artery disease
- Stroke
- Pulmonary hypertension
- Metabolic syndrome/diabetes
- Mortality

Yeghiazarians Y et al. Circulation 2021;144:e56-e67.

Original Articles

Short Sleep Duration as a Risk Factor for Hypertension

Analyses of the First National Health and Nutrition Examination Survey

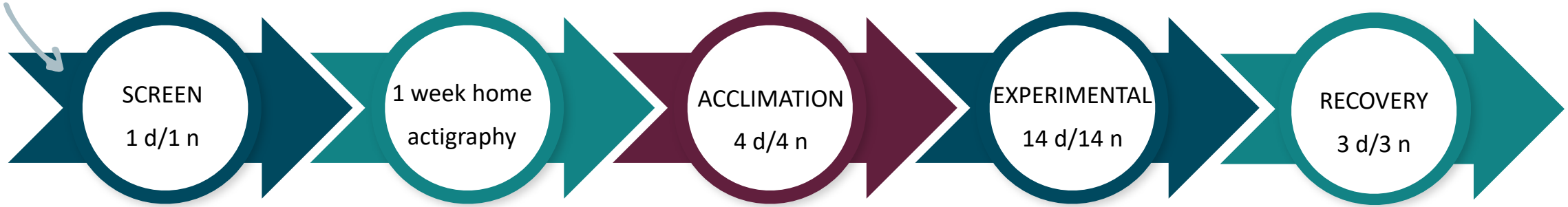
James E. Gangwisch, Steven B. Heymsfield, Bernadette Boden-Albala, Ruud M. Buijs, Felix Kreier, Thomas G. Pickering, Andrew G. Rundle, Gary K. Zammit, Dolores Malaspina

Sleep duration of five hours or less was associated with a two-fold increase in risk of hypertension

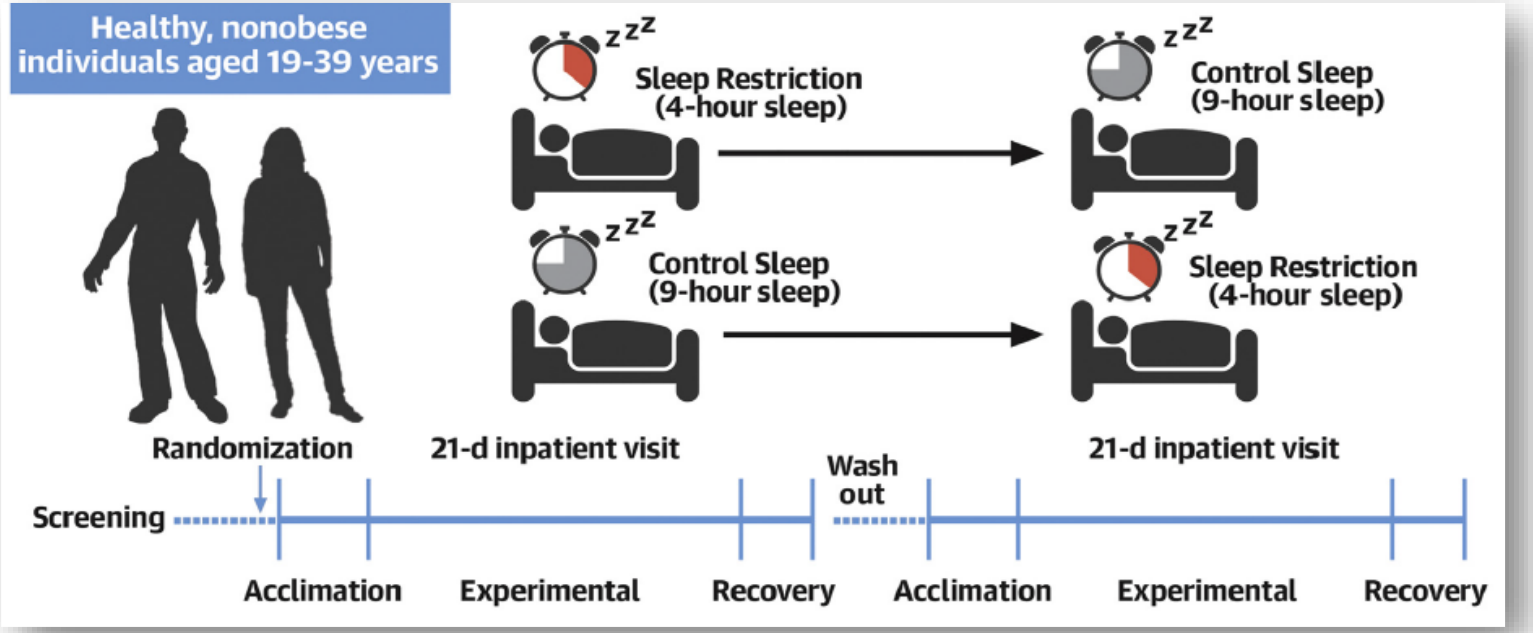
Hypertension. 2006; 47:833-839.

Design

Sleep Deprivation and Energy Balance



Simple crossover randomization to 9 hours vs 4 hours time in bed



Covassin et al, JACC 2022

Sleep and the Zeitgeist of Cardiovascular Medicine

The Most Talked About Articles From 2022

The following articles published in 2022 received the most attention online throughout the world during the year, according to Altmetrics. Altmetric attention scores include mainstream media coverage, mentions on social networks such as Twitter, discussions on research blogs, citations on Wikipedia, bookmarks on reference managers like Mendeley and more. Tap/click the donut to visit the article's details page to see the original mentions and references that have contributed to the attention score.

Journal of the American College of Cardiology (JACC)

Effects of Experimental Sleep Restriction on Energy Intake, Energy Expenditure, and Visceral Obesity

J Am Coll Cardiol. 2022 Apr, 79 (13) 1254-1265

Consumption of Olive Oil and Risk of Total and Cause-Specific Mortality Among U.S. Adults

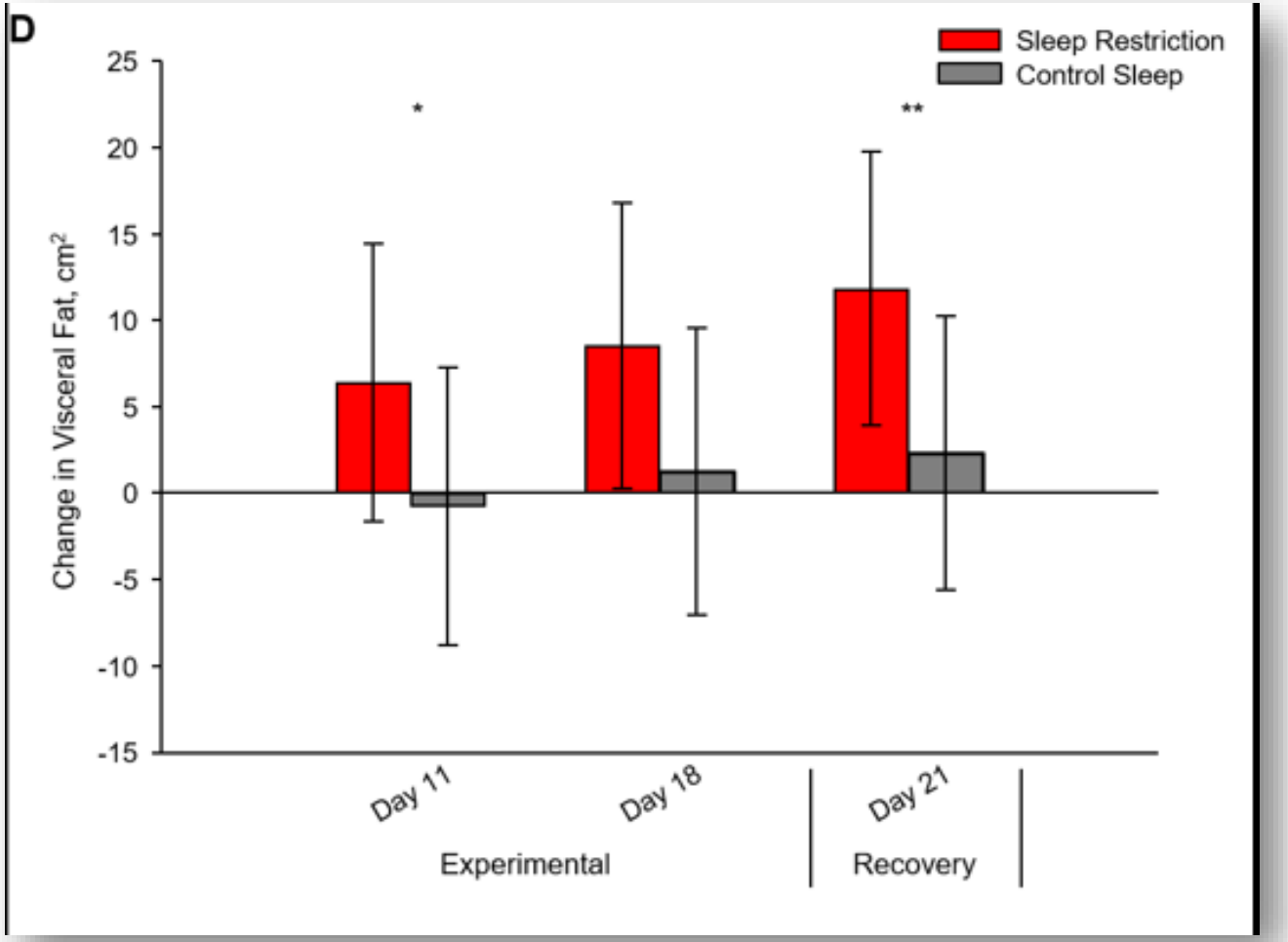
J Am Coll Cardiol. 2022 Jan, 79 (2) 101-112

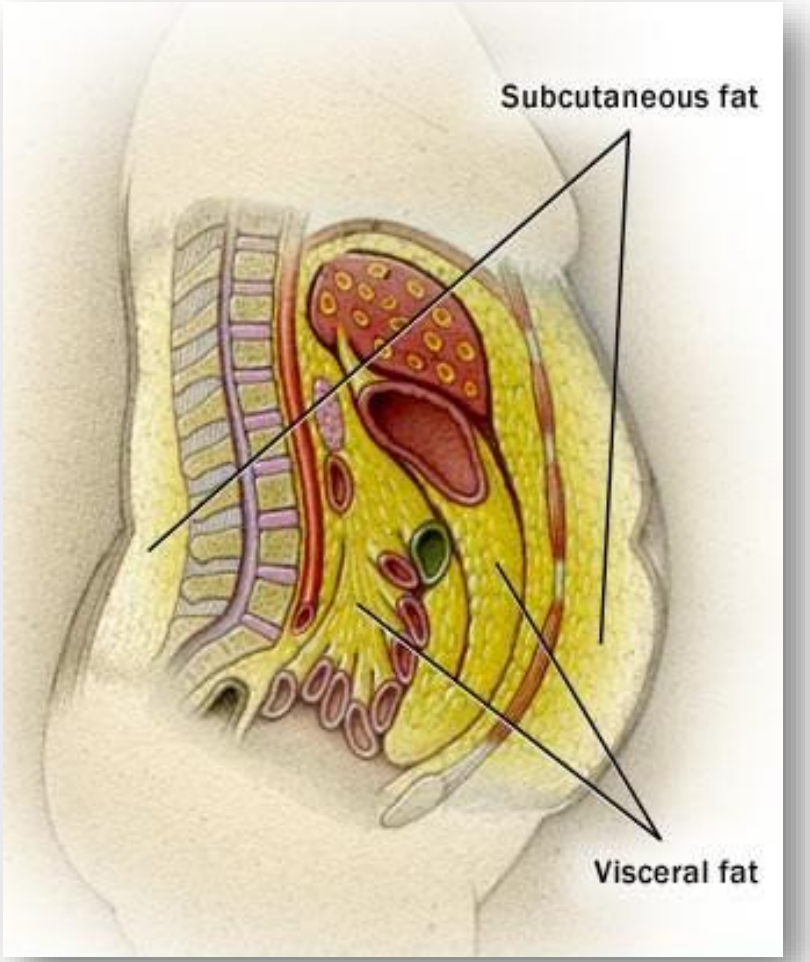
2022 ACC Expert Consensus Decision Pathway on Cardiovascular Sequelae of COVID-19 in Adults: Myocarditis and Other Myocardial Involvement, Post-Acute Sequelae of SARS-CoV-2 Infection, and Return to Play: A Report of the American College of Cardiology Solution Set Oversight Committee

J Am Coll Cardiol. 2022 May, 79 (17) 1717-1756

Visceral fat increases during Sleep Deprivation and further into Recovery

Calorie intake during sleep dep increased by more than 300kcal/day





Covassin et al, JACC 2022

Nurses Health Study

71617 women 45-65 years

10-year follow-up of Incident CHD

Sleep Duration	Relative Risk	Confidence Interval
5 Hours	1.82	1.34 – 2.41
6 Hours	1.30	1.08 – 1.57
7 Hours	1.06	0.89 – 1.26
8 Hours	1	1

(Ayas et al)

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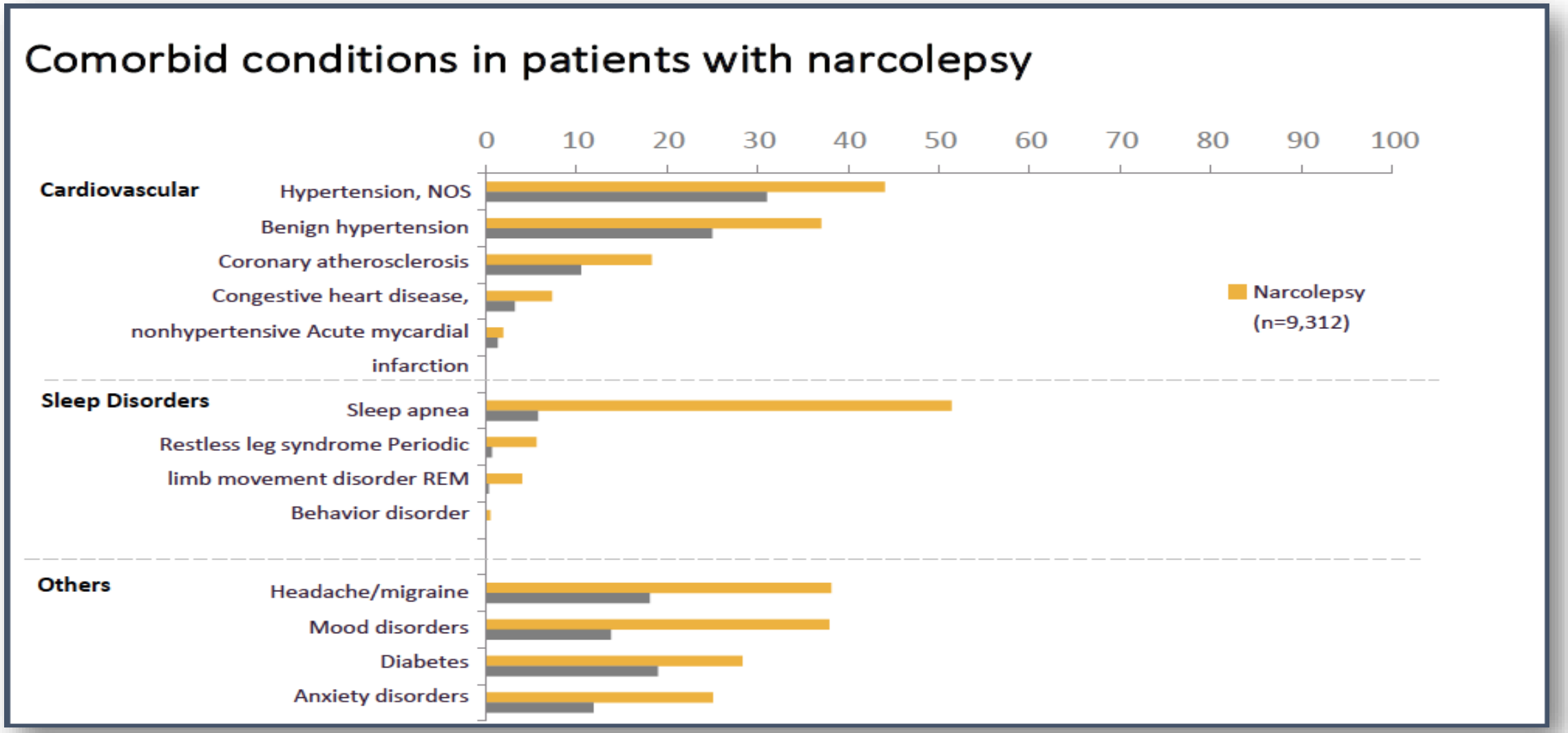
Narcolepsy – Clinical Characteristics

Narcolepsy is a chronic neurologic sleep disorder

Five predominant symptoms – excessive daytime sleepiness; cataplexy; disrupted nighttime sleep; sleep related hallucinations; and sleep paralysis

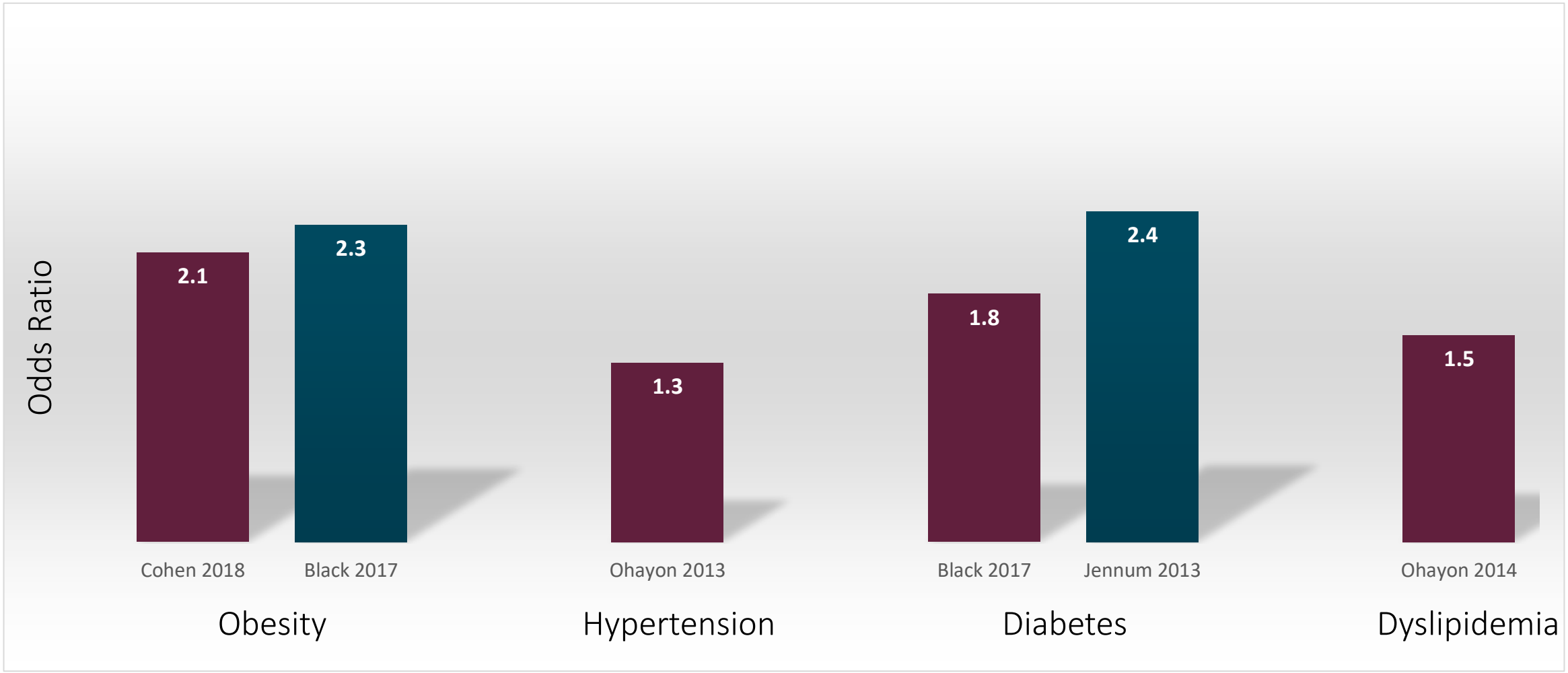
Onset of symptoms typically in childhood or adolescence

Narcolepsy and CV Disease: Bond Study

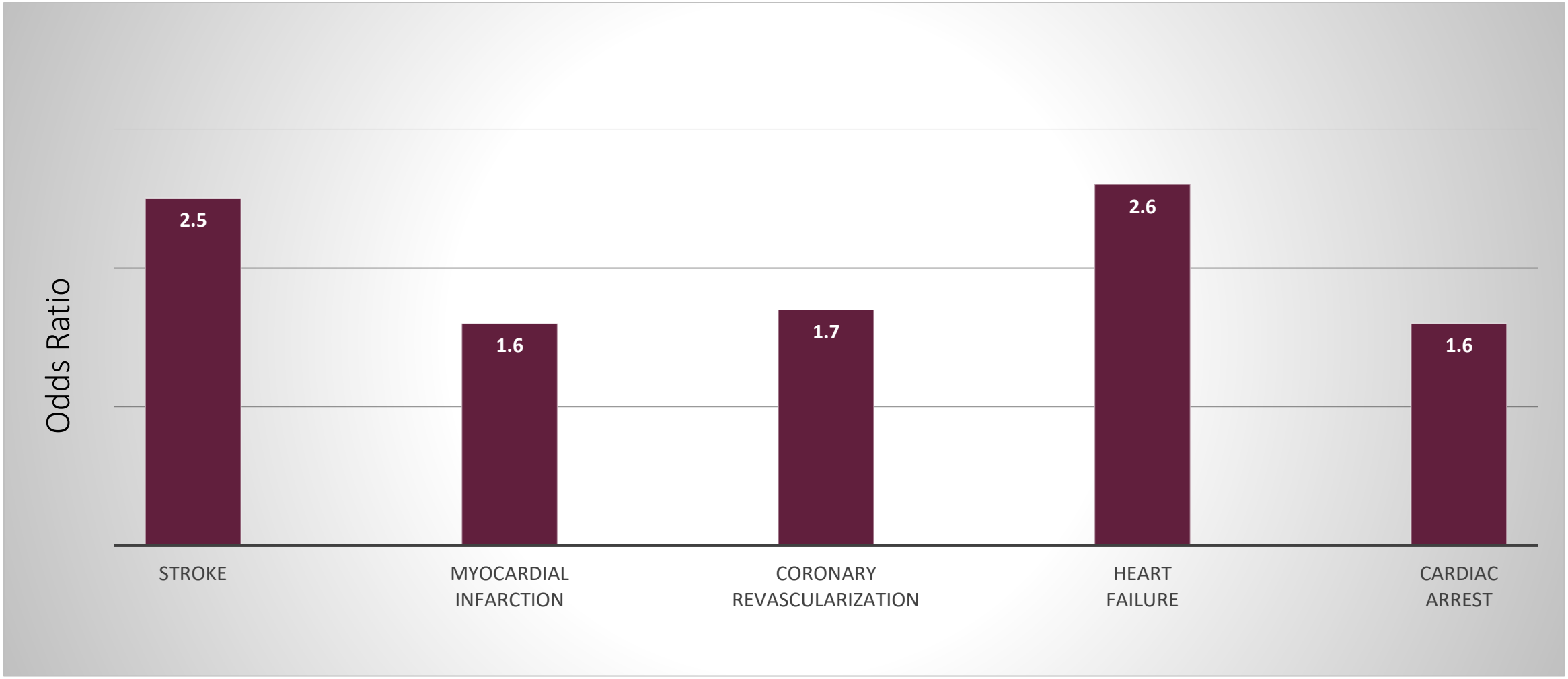


Black J, Reaven NH, Funk SE et al. Sleep Medicine 2017;33:15.

Cardiovascular and Cardiometabolic Comorbidities Associated With Narcolepsy



Narcolepsy and Cardiovascular Disease



BOND study 2017 (Black J et al)

Narcolepsy and Mortality

Mortality rates in patients with vs without narcolepsy were estimated using a longitudinal claims database, and compared to CDC general population data (Ohayon, 2014)

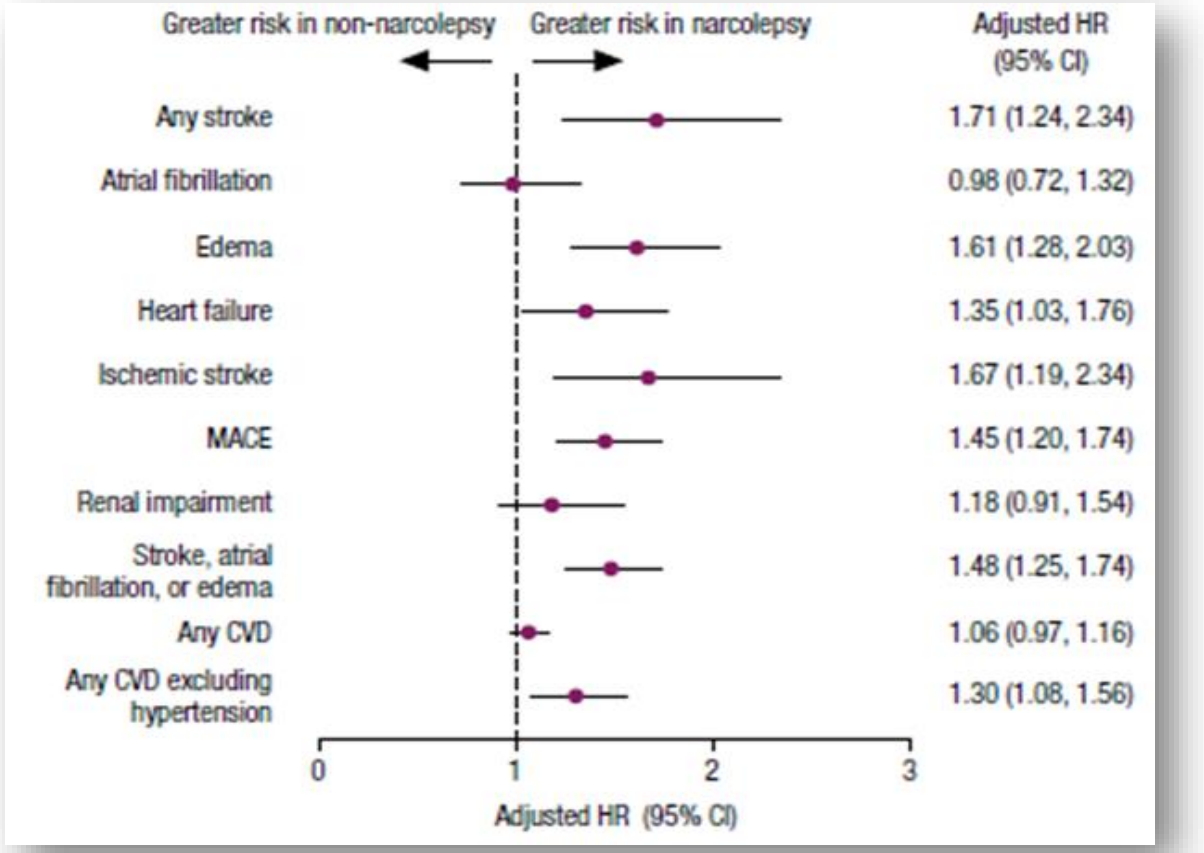
Patients with narcolepsy were at approx. 1.5-fold increased mortality risk

Ohayon M et al. Sleep. 2014;37:439-444.

CV Bond Study

Adjusted Hazard Ratios for Incidence of Newly-Diagnosed Cardiovascular/Renal Conditions in Patients with Narcolepsy and Matched Non-Narcolepsy Controls

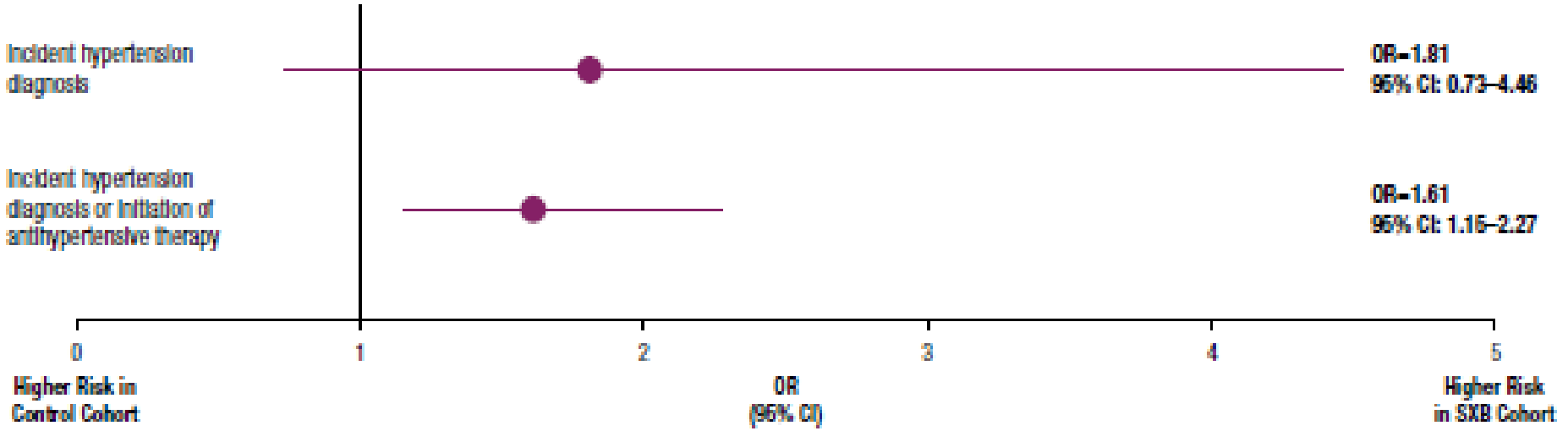
N=±38,000 N=±12,000



Ben-Joseph, Somers, et al Sleep 2023

Sodium Oxybate and Increased HTN Risk

Figure 1. Elevated Odds Ratio for New Onset of Hypertension in Patients With Narcolepsy Treated With Sodium Oxybate



A multivariable logistic regression model to estimate ORs and corresponding 95% CIs included all covariates used in the calculation of the PS as independent variables.

CI, confidence interval; OR, odds ratio; PS, propensity score; SXB, sodium oxybate.

- Risk of incident (new) hypertension diagnosis per 100 patients was numerically higher in the SXB cohort (0.94) than the control cohort (0.52; odds ratio [OR]=1.81; 95% confidence interval [CI]: 0.73–4.46)
- Risk of the composite endpoint of either diagnosis of hypertension or initiation of antihypertensive therapy per 100 patients was higher in the SXB cohort (6.60) than the control cohort (4.20; OR=1.61; 95% CI: 1.15–2.27)
- Results remained robust through a series of sensitivity analyses

Ben-Joseph, Somers et al, JACC (abstract) 2023

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The Effects of Sodium Intake on Blood Pressure and Cardiovascular Disease

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C. David Molina Professor of Medicine

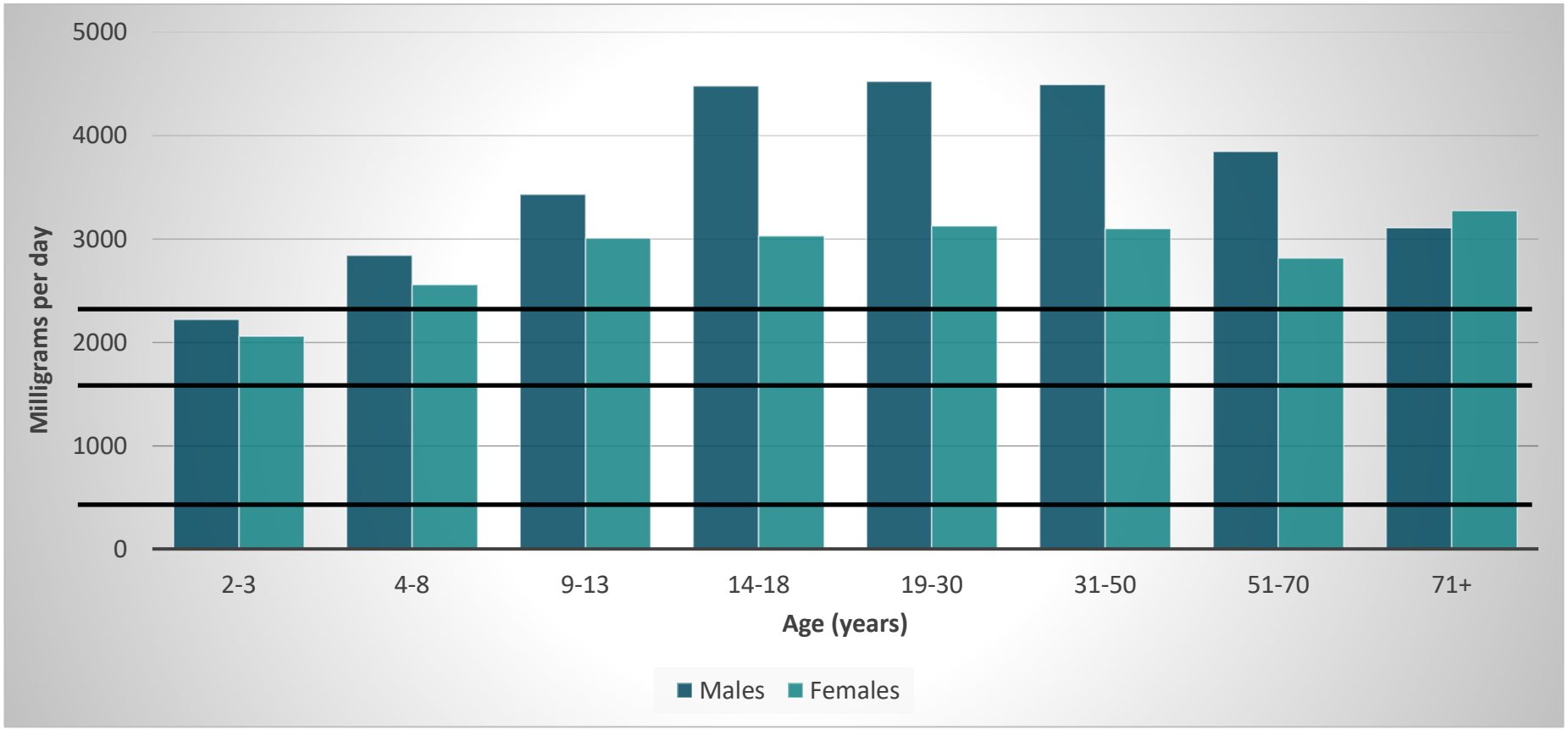
Director, Welch Center for Prevention, Epidemiology and Clinical Research

Johns Hopkins University School of Medicine

AGENDA

1. Dietary Intake of Sodium
   Hint – more than you think!
2. Blood Pressure Basics
3. Health Effects of Sodium Intake
   Blood pressure | Cardiovascular disease(CVD) | Other
4. Methodological Challenges
5. Recent Evidence

Estimated Mean Daily Sodium Intake in US, by age/sex Group, 2005-6



2300 mg+

1500 mg++

200 mg+++

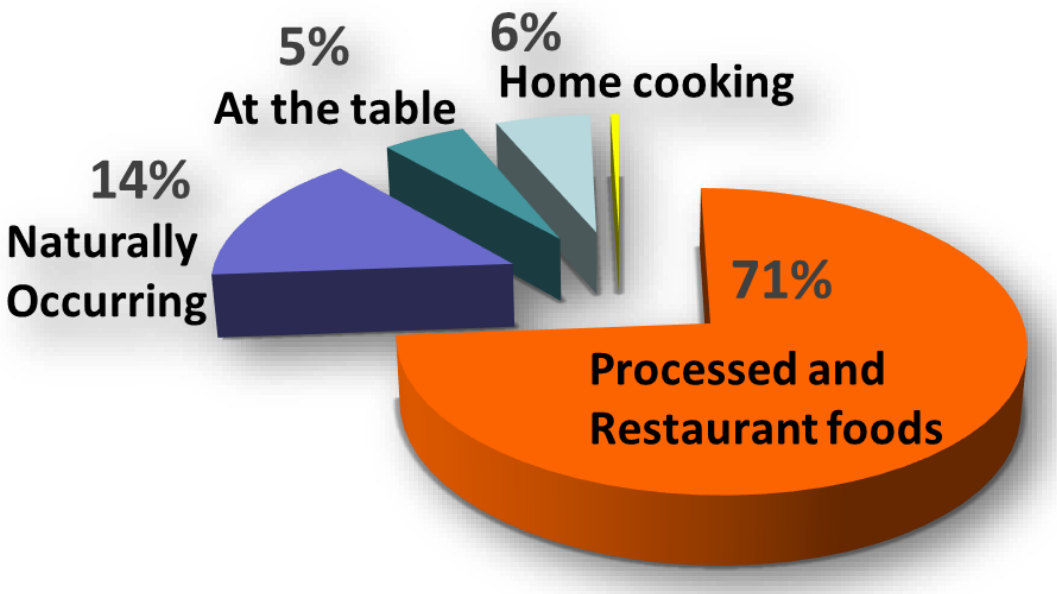
\+ Recommended upper limit of intake for adults

++ Recommended intake for blacks, hypertensives, and middle- and older-aged adults

+++ Needed to replace obligatory losses (Dahl, 1958)

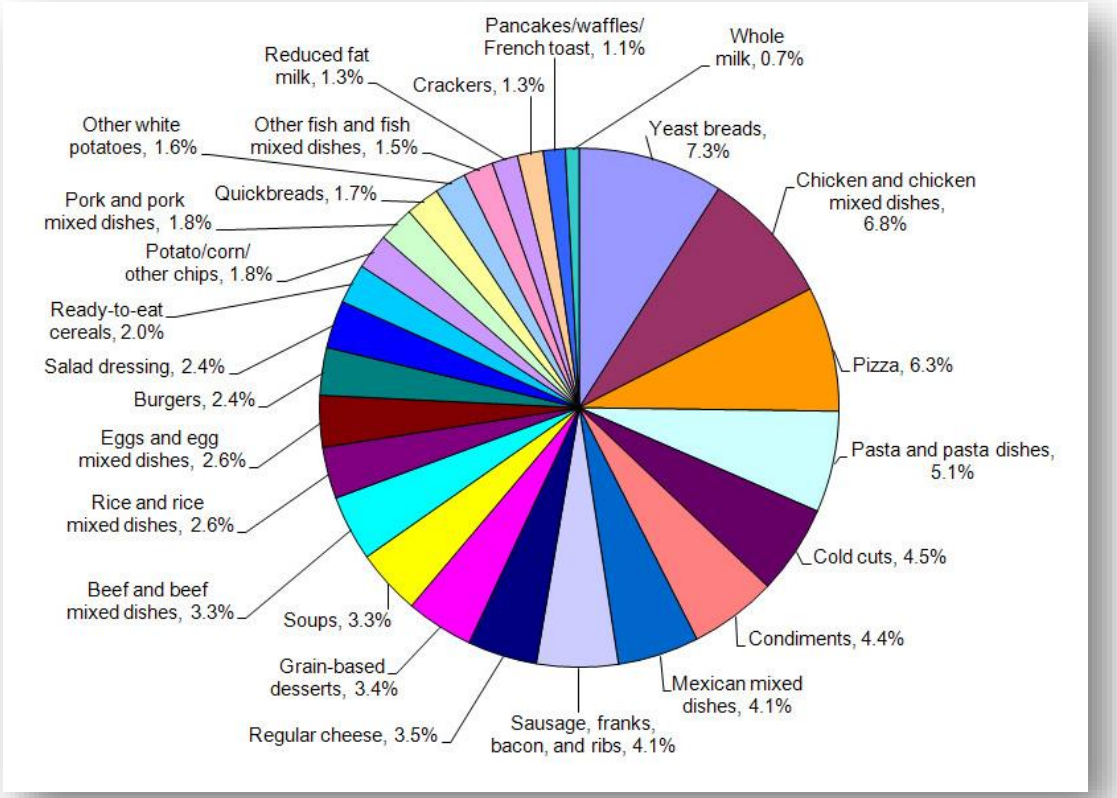
Dietary sources of sodium - US

In US, Most Sodium(>70%) Comes from Processed and Restaurant Food



Harnack LJ, et al. Sources of Sodium in US Adults from 3 Geographic Regions. Circulation. 2017;135:1775-1783.

Sources of Sodium Among the US Population, 2005-6



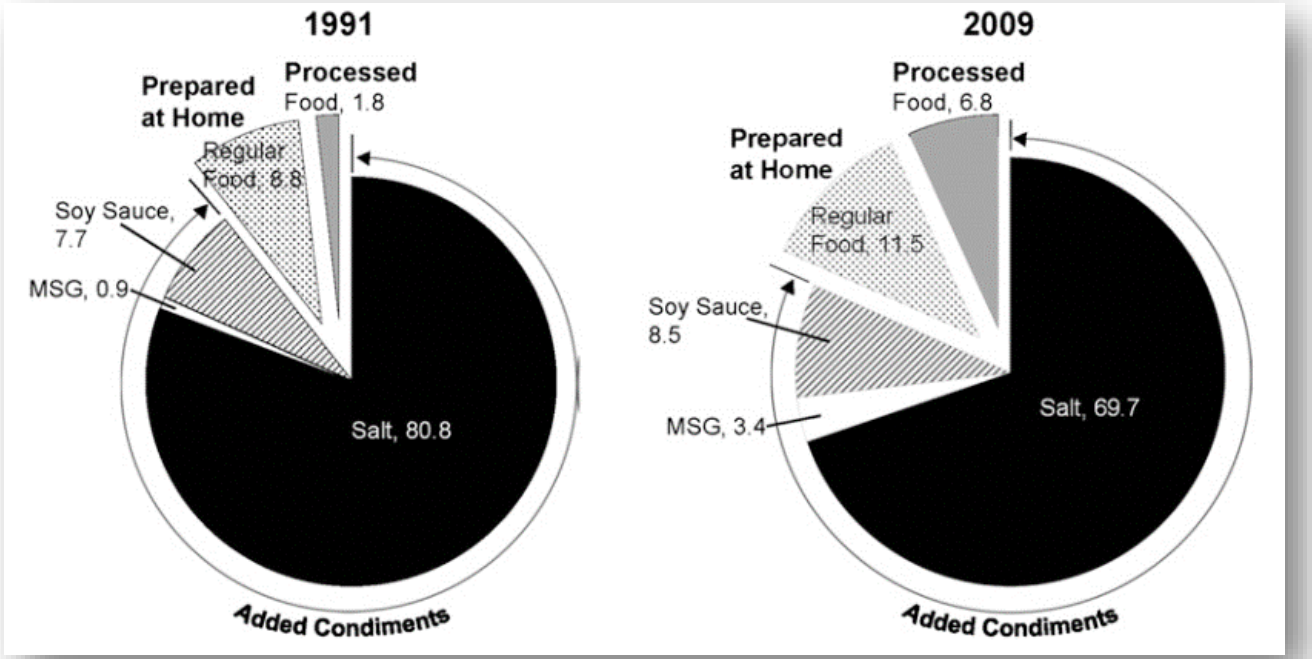
National Cancer Institute website http://riskfactor.cancer.gov/diet/foodsources/sodium/.

Dietary sources of sodium - China

In China, processed foods contributes to <10% of total sodium intake.

Most comes from added condiments, especially table salt (around 70% of all sodium)

However, the contribution of sodium from processed foods is rapidly increasing.



Du et al. Understanding the patterns and trends of sodium intake, potassium intake, and sodium to potassium ratio and their effect on hypertension in China. Am J Clin Nutr 2014;99:334–43.

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1 Dietary Intake of Sodium

Hint – more than you think!

2 Blood Pressure Basics

3 Health Effects of Sodium Intake

Blood pressure | Cardiovascular disease(CVD) | Other

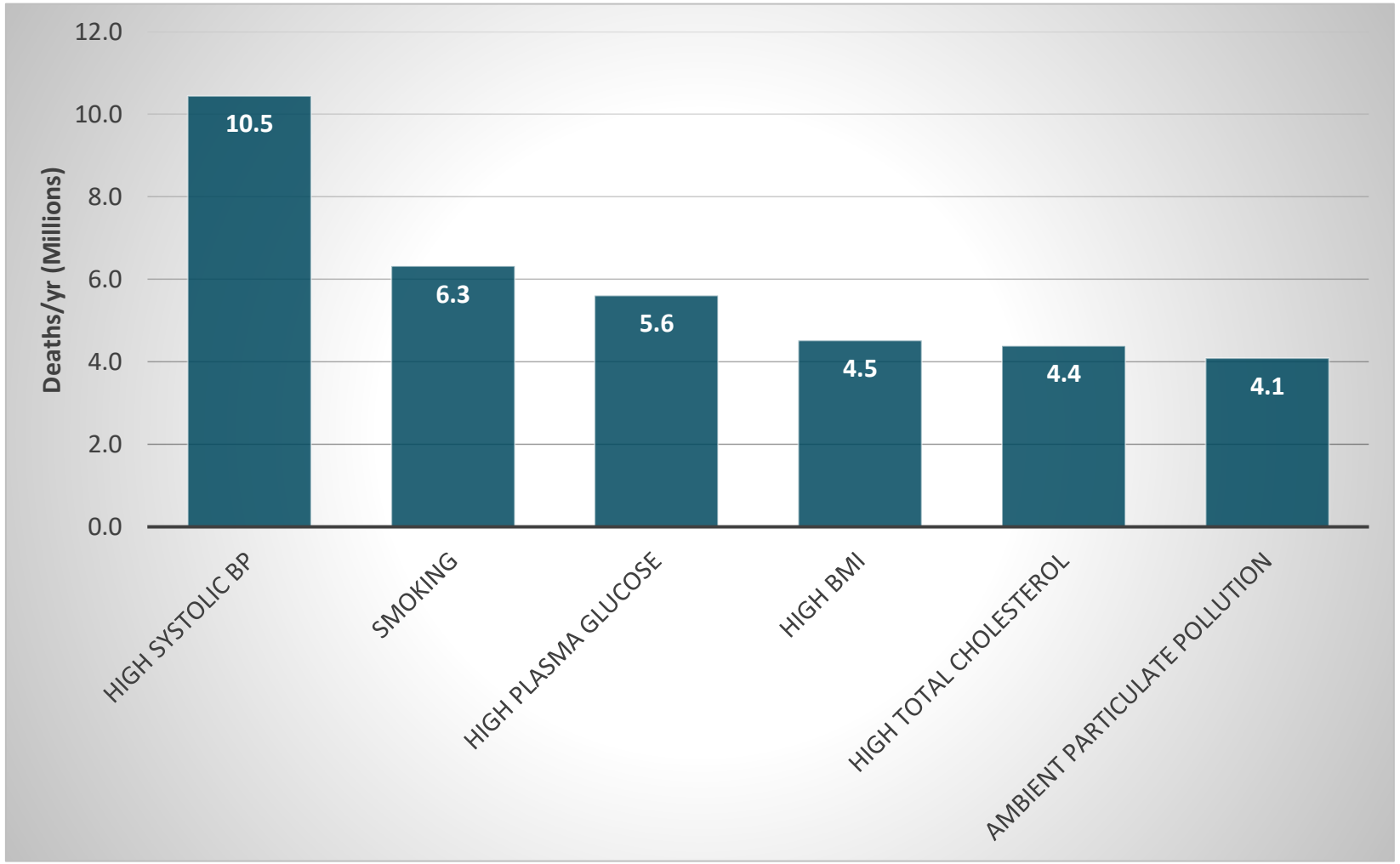
4 Methodological Challenges

5 Recent Evidence

Current Blood Pressure Classification

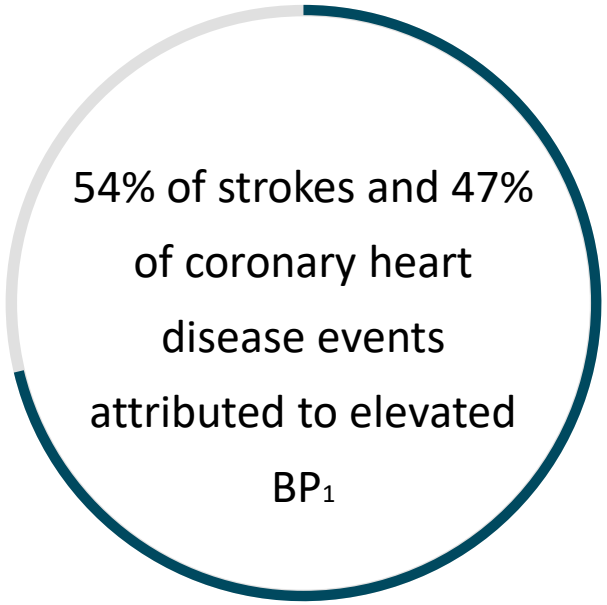
Category	Systolic BP		Diastolic BP
Normal	< 120	And	< 80
Elevated	120-129	Or	< 80
Hypertension Stage 1	130-139	Or	80-89
Hypertension Stage 2	≥140	Or	≥90

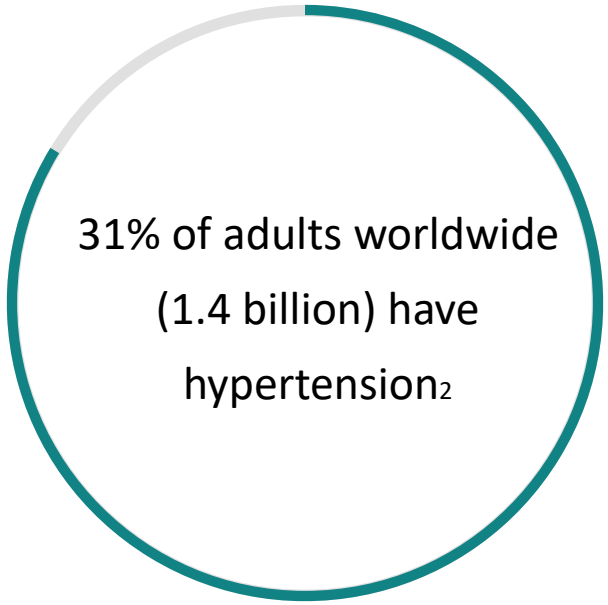
Big Picture: Elevated BP is the Leading Cause of Preventable Deaths Worldwide

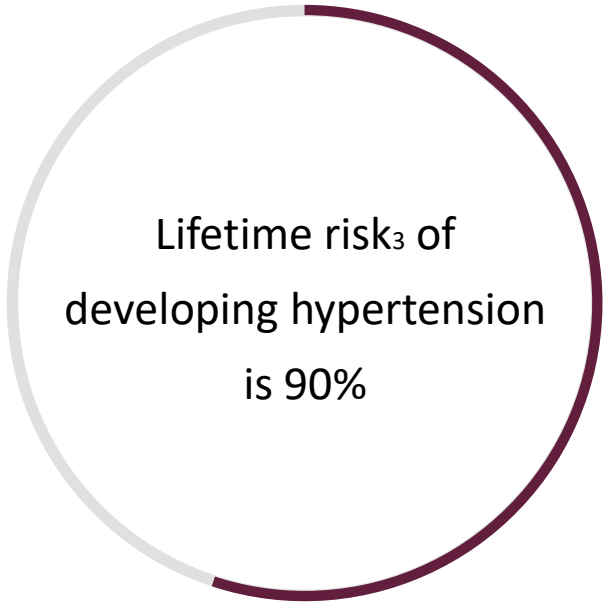


Source: http://ghdx.healthdata.org/gbd-results-tool, 2018

Magnitude of the BP Epidemic





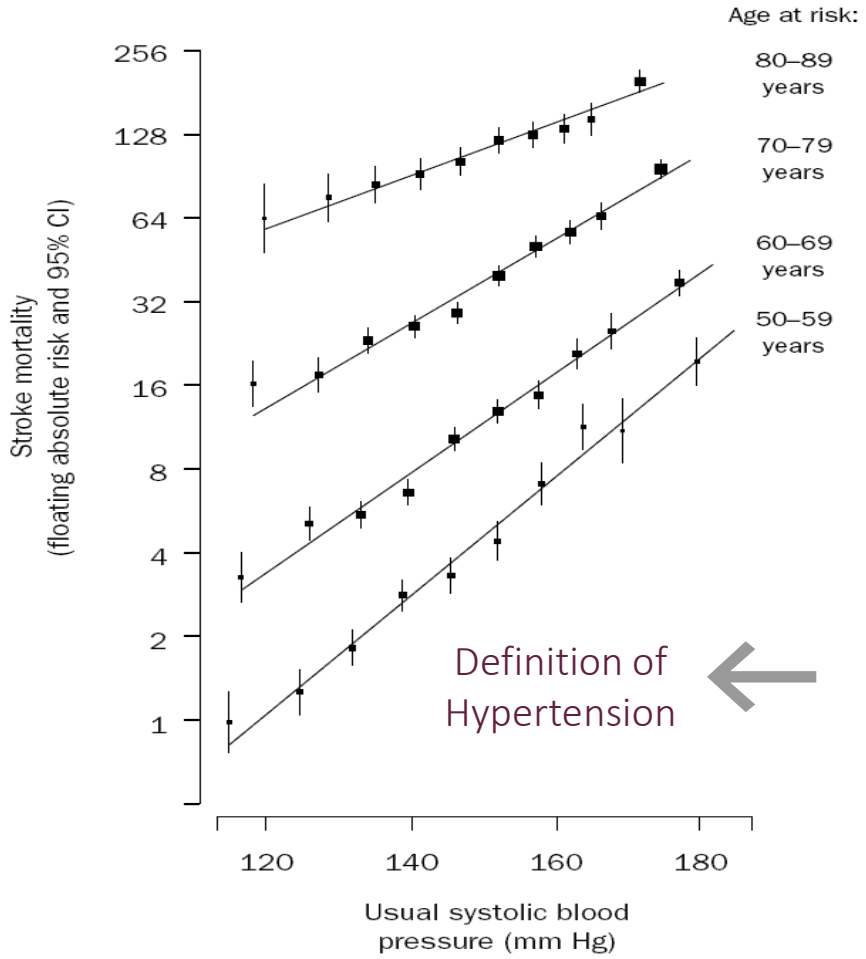


[1]Lawes CM Lancet 2008;371:1513

[2]Mills, Circulation 2016;134:4441

[3]Vasan JAMA 2002; 287:1003

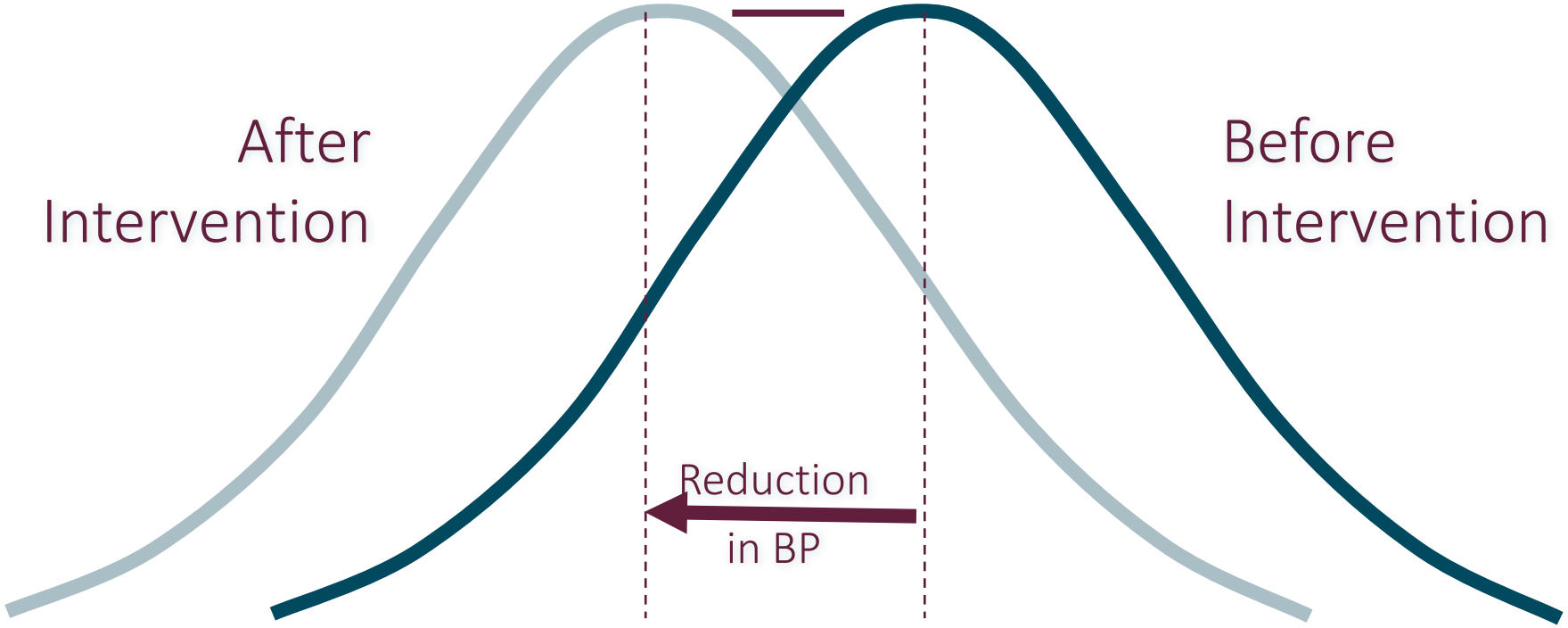
Stroke Mortality by Level of Usual Systolic BP*



Definition of Hypertension

*Source: Prospective Studies Collaboration, Lancet, 2002: Meta-analysis of 61 prospective studies with 2.7m person-yrs, 11.9k deaths

Effects of Population-Based BP Reduction (Favorably Shifting SBP Distribution)



Reduction in SBP mmHg	% Reduction in Mortality		
	Stroke	CHD	Total
2	-6	-4	-3
3	-8	-5	-4
5	-14	-9	-7

Stamler R. Hypertension 1991;17:I-16–I-20.

Adverse Effects of Excess Sodium Intake

Established Relationship

-Increased blood pressure

↓

CVD and Stroke

Probable Relationship

-Gastric cancer

-Increased protein excretion, CKD progression

-Headaches

Suggestive Relationship

-Increased risk of osteoporosis

-Increased left ventricular mass

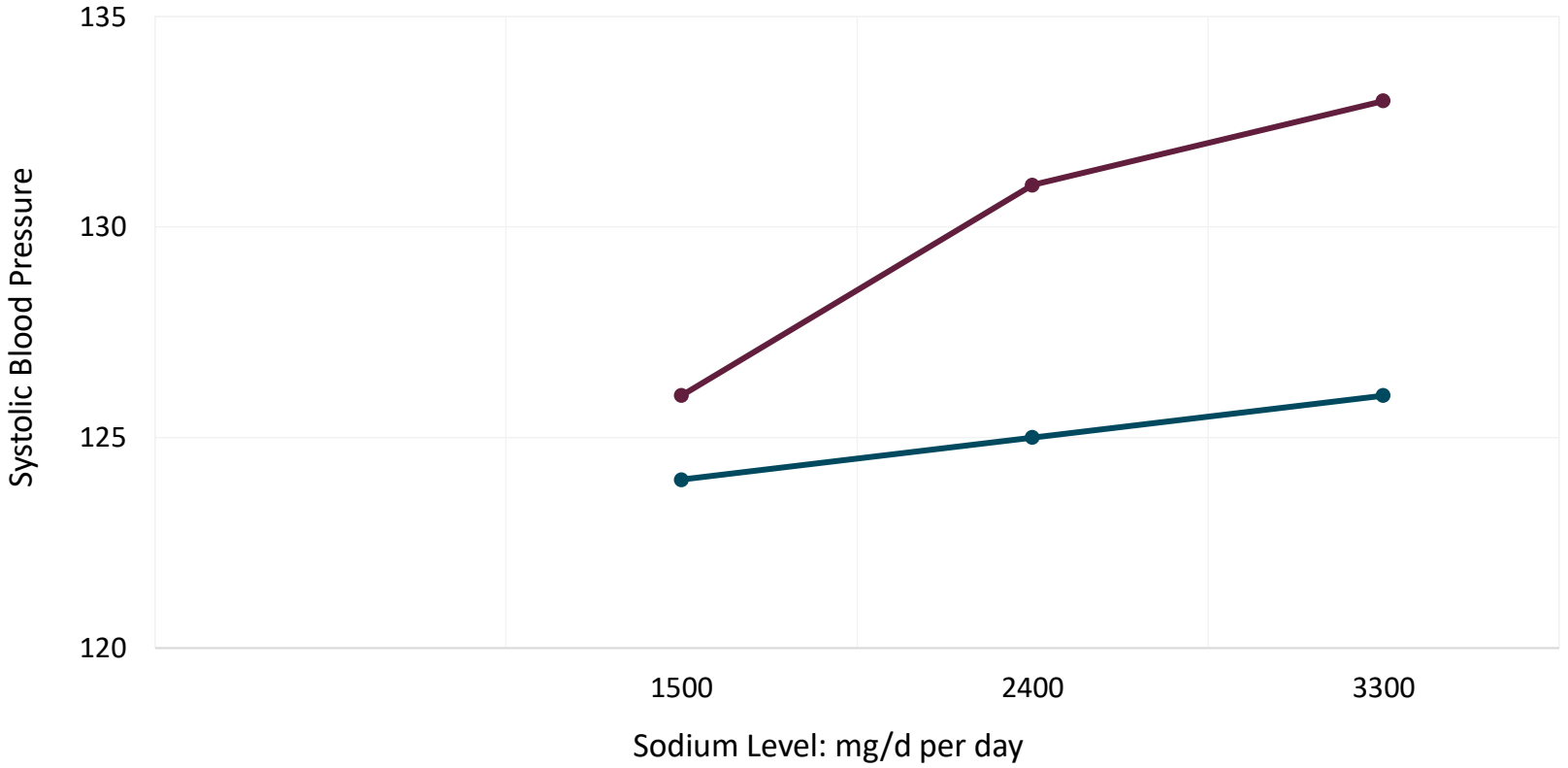
Hypothesized Relationship

-Overweight/obesity

Types of Evidence Linking Sodium Intake to Blood Pressure

Epidemiology	Over 50 population studies
Migration	Several, e.g. Kenya
Genetic	All defects identified so far impair the ability of the kidney to excrete salt.
Animal	All forms of hypertension are caused or aggravated by salt [rats, chimpanzees]
Trials	Children: ~10 trials, one trial in infants Adults: > 100 trials
Population	Northern Japan
Interventions	Portuguese villages

As Sodium Intake Is Reduced, So is Blood Pressure



Typical Diet

-6.7

P<.0001

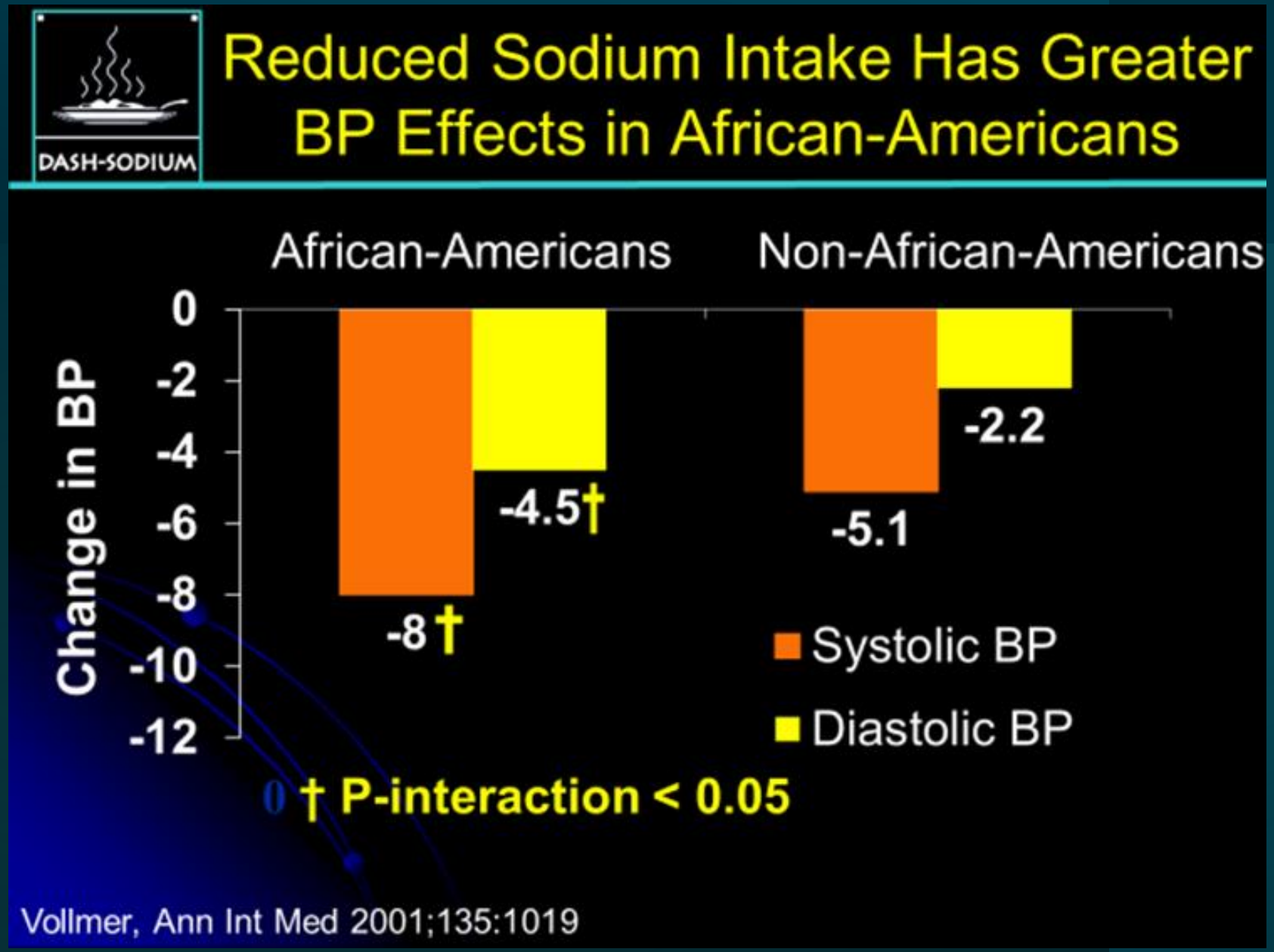
DASH Diet

-3.0

P<.0001

DASH-SODIUM

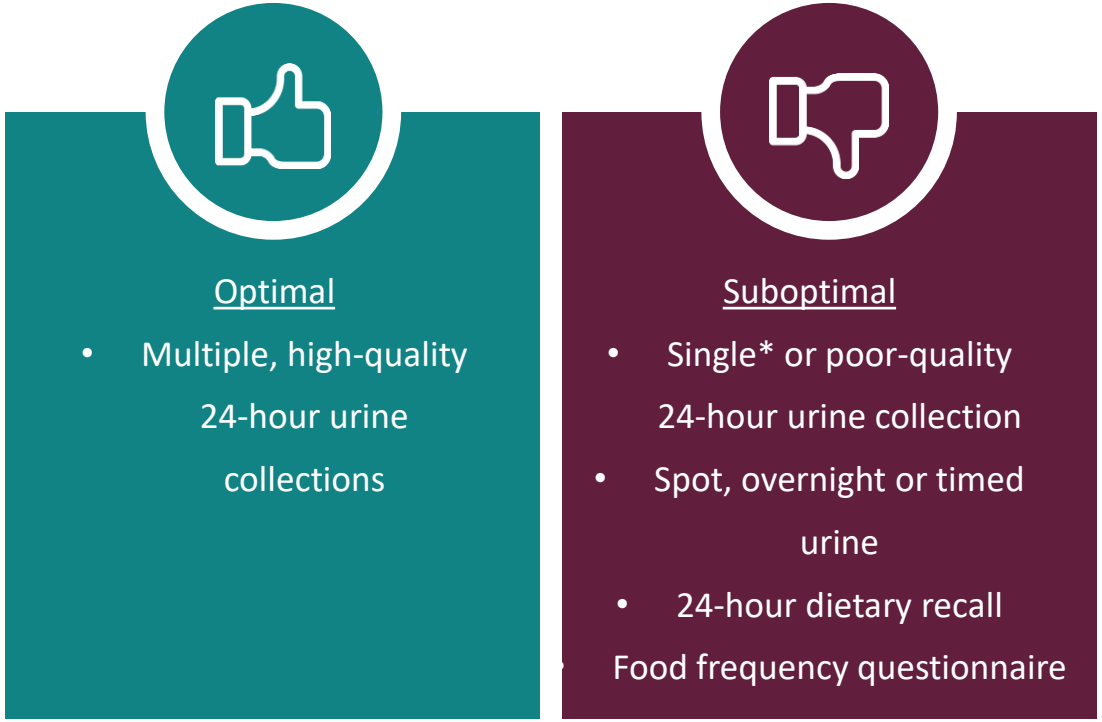
Sacks, NEJM 2001;344:3


DASH-SODIUM
Reduced Sodium Intake Has Greater BP Effects in African-Americans
African-Americans
Non-African-Americans
Change in BP
0
-2
-4
-6
-8
-10
-12
-8 †
-4.5†
-5.1
-2.2
Systolic BP
Diastolic BP
† P-interaction < 0.05
Vollmer, Ann Int Med 2001;135:1019

Why the fuss about sodium?

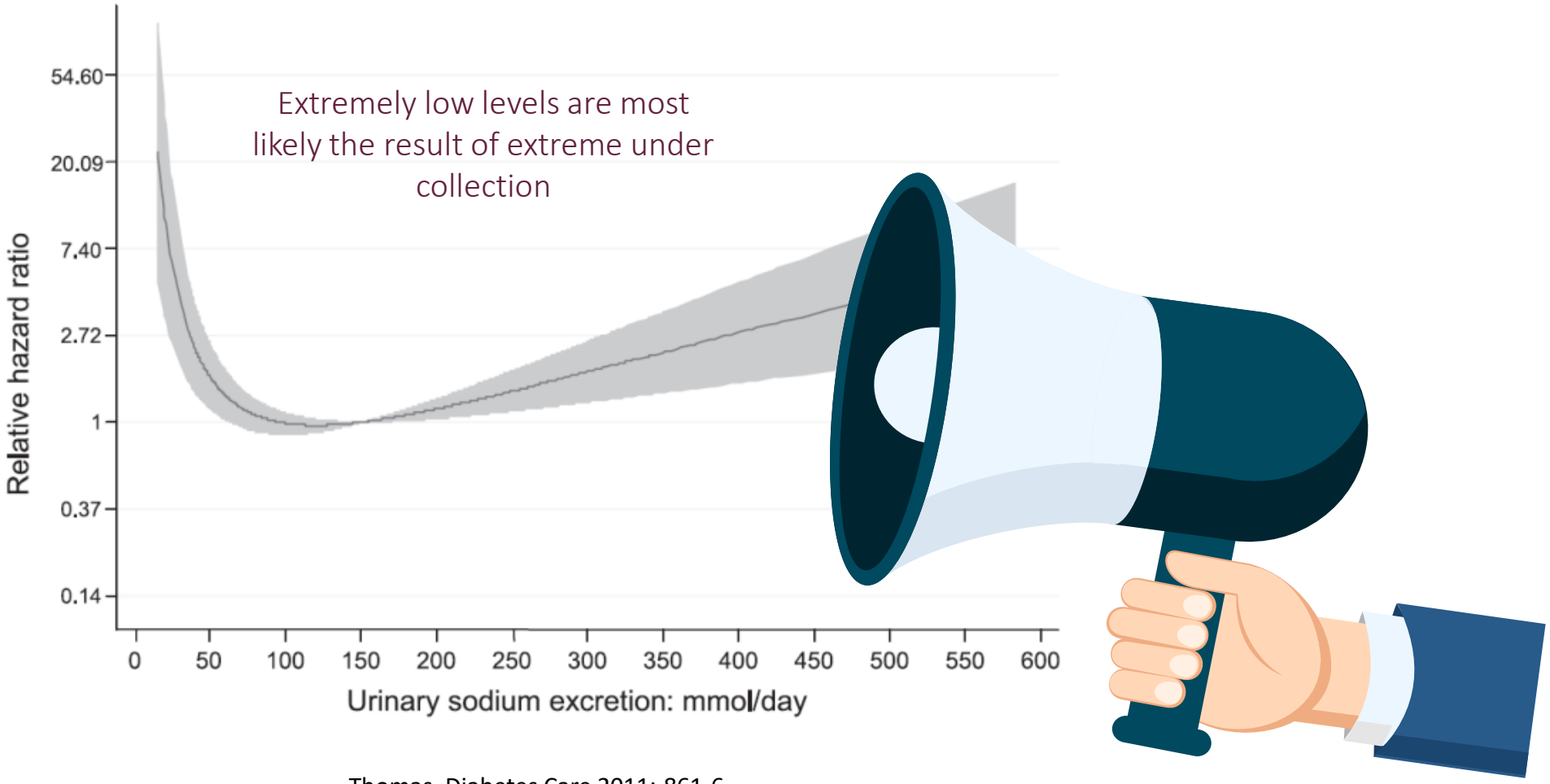
- Methodologic ‘landmines’
- Challenges of measuring sodium
- Interpretation of low diet and low urinary sodium excretion
- High cost of high-quality sodium research in humans

Options to Estimate Usual Sodium Intake of Individuals



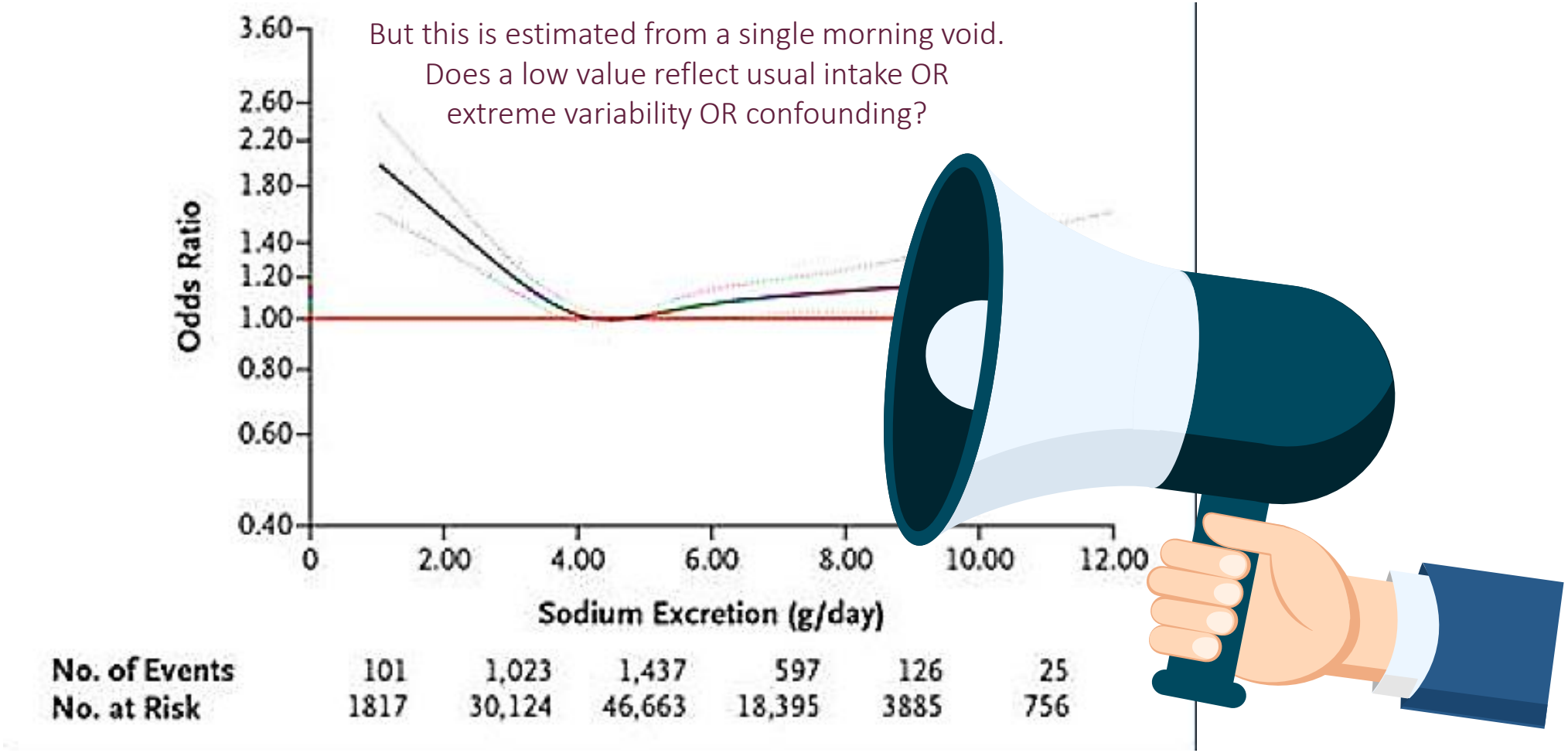
*Single 24-hour urine is fine for estimating group average

J-Shaped Relationship of Total Mortality with Urine Sodium Excretion in Patients with Type 1 Diabetes

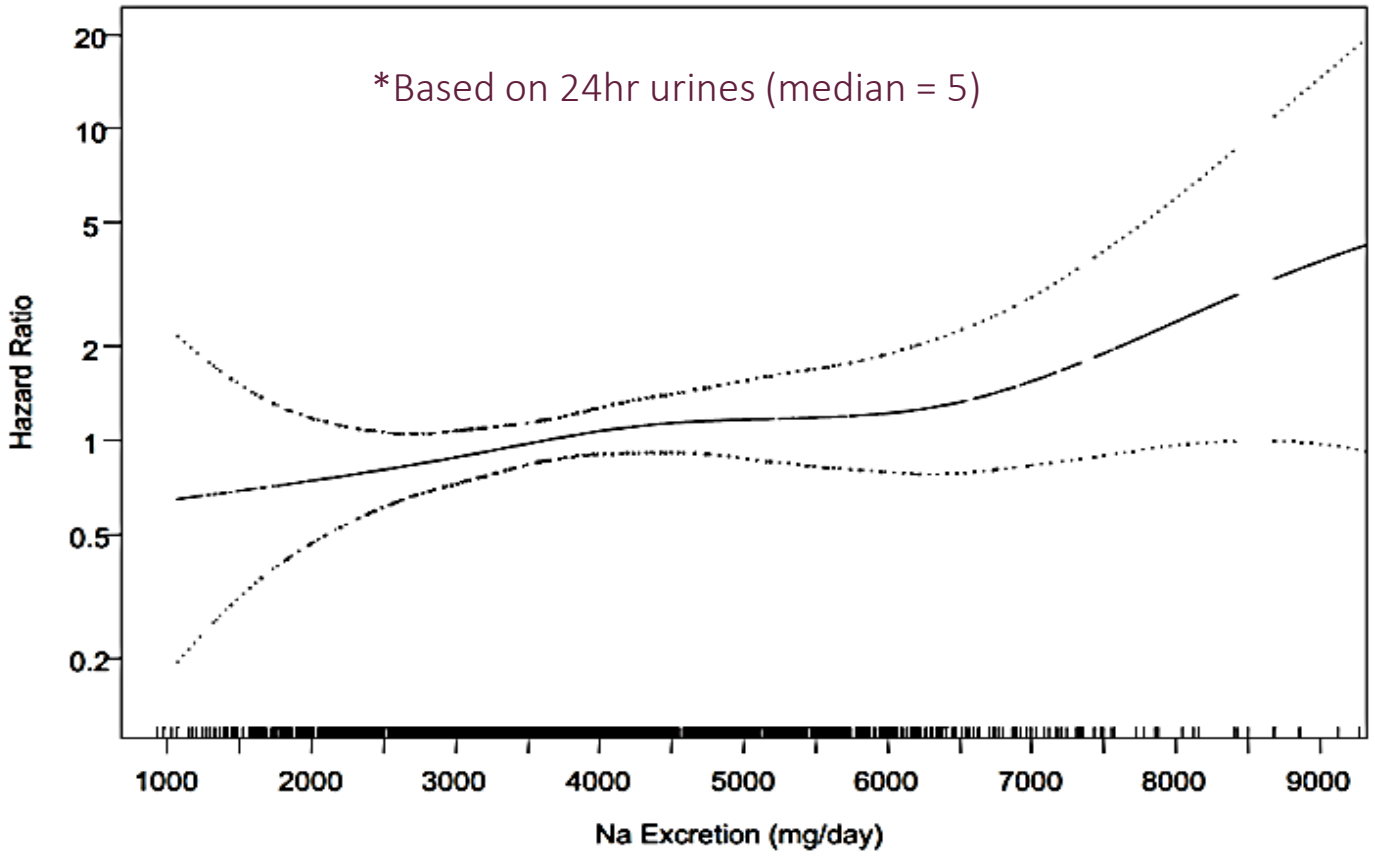


Thomas, Diabetes Care 2011: 861-6

Estimated Sodium Excretion (from early morning void) and Risk of Death or CVD Events in PURE Study (n=101,945)

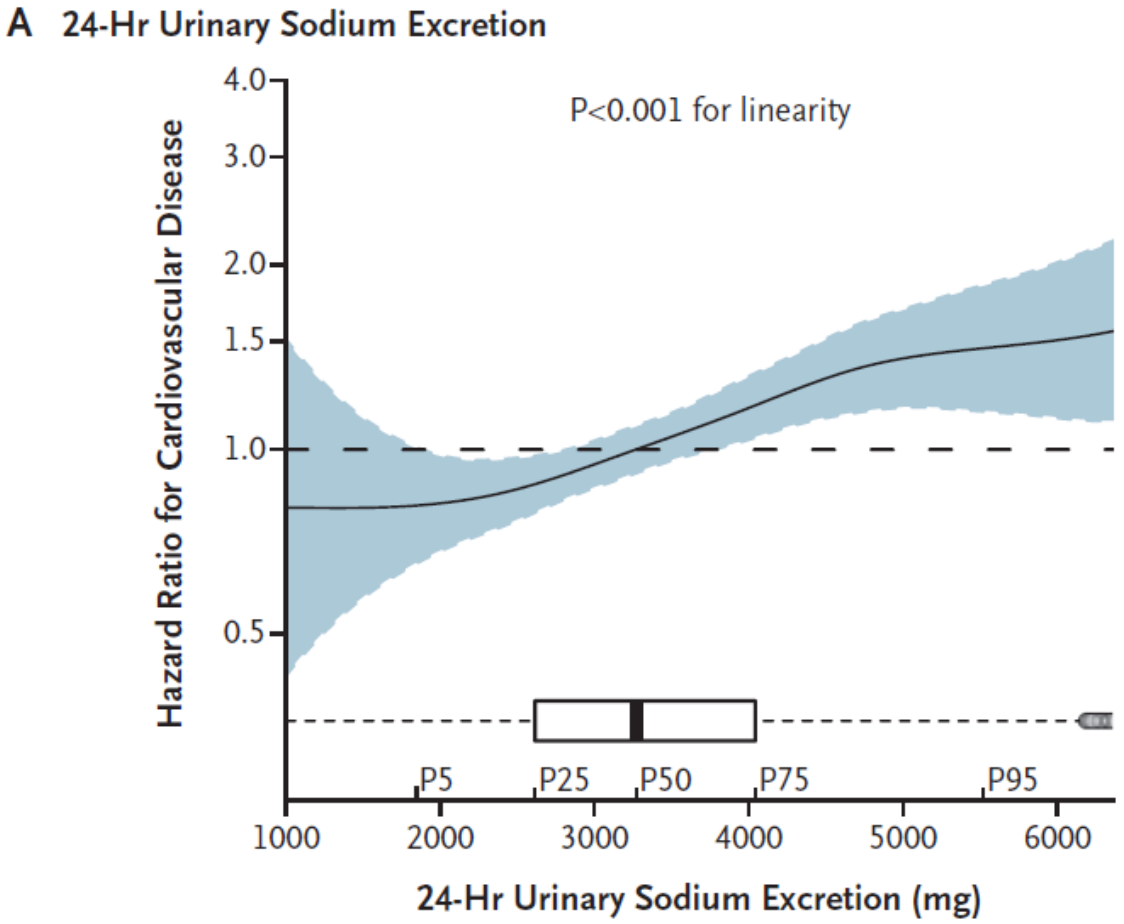


Direct Relationship of CVD with Urinary Sodium Excretion* in 2,275 Individuals with Prehypertension



Cook, Circ 2014:129:981

Direct Association of CVD with Urinary Sodium Excretion: Meta-Analysis of Cohort Studies with > two 24 Hr Urine Collections



Source: Ma, NEJM 2021

AGENDA

1 Dietary Intake of Sodium

Hint – more than you think!

2 Blood Pressure Basics

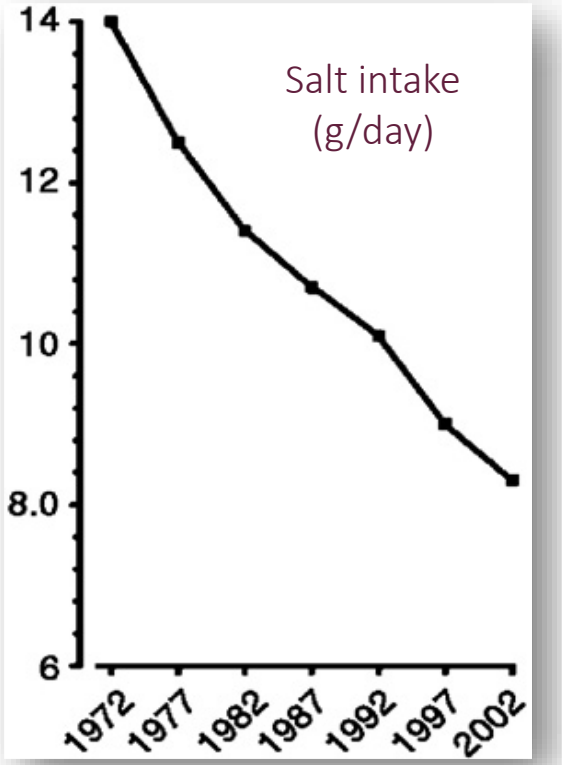
3 Health Effects of Sodium Intake

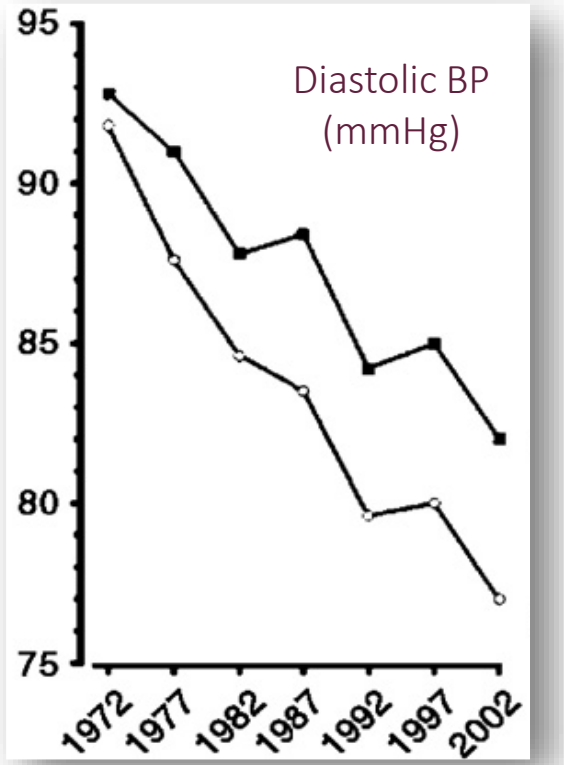
Blood pressure | Cardiovascular disease(CVD) | Other

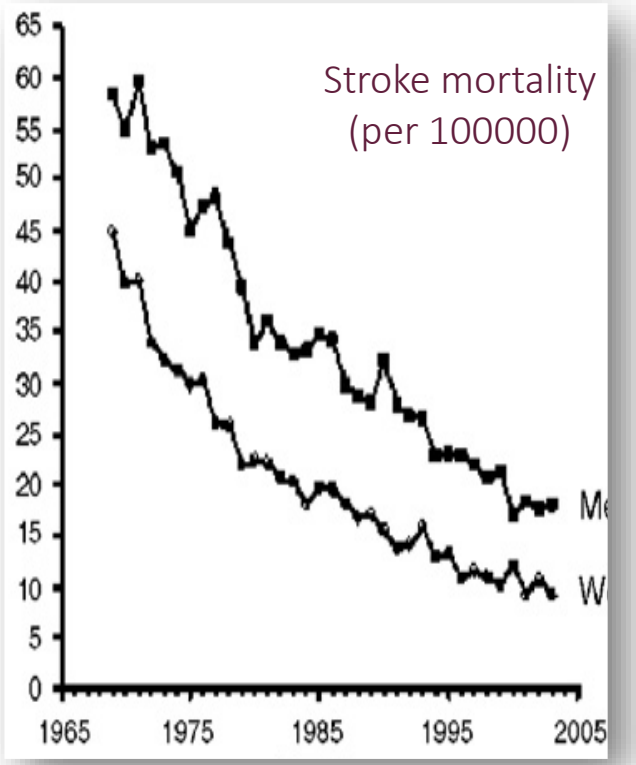
4 Methodological Challenges

5 Recent Evidence

Finland: Salt Intake, BP and Stroke Mortality Over Three Decades

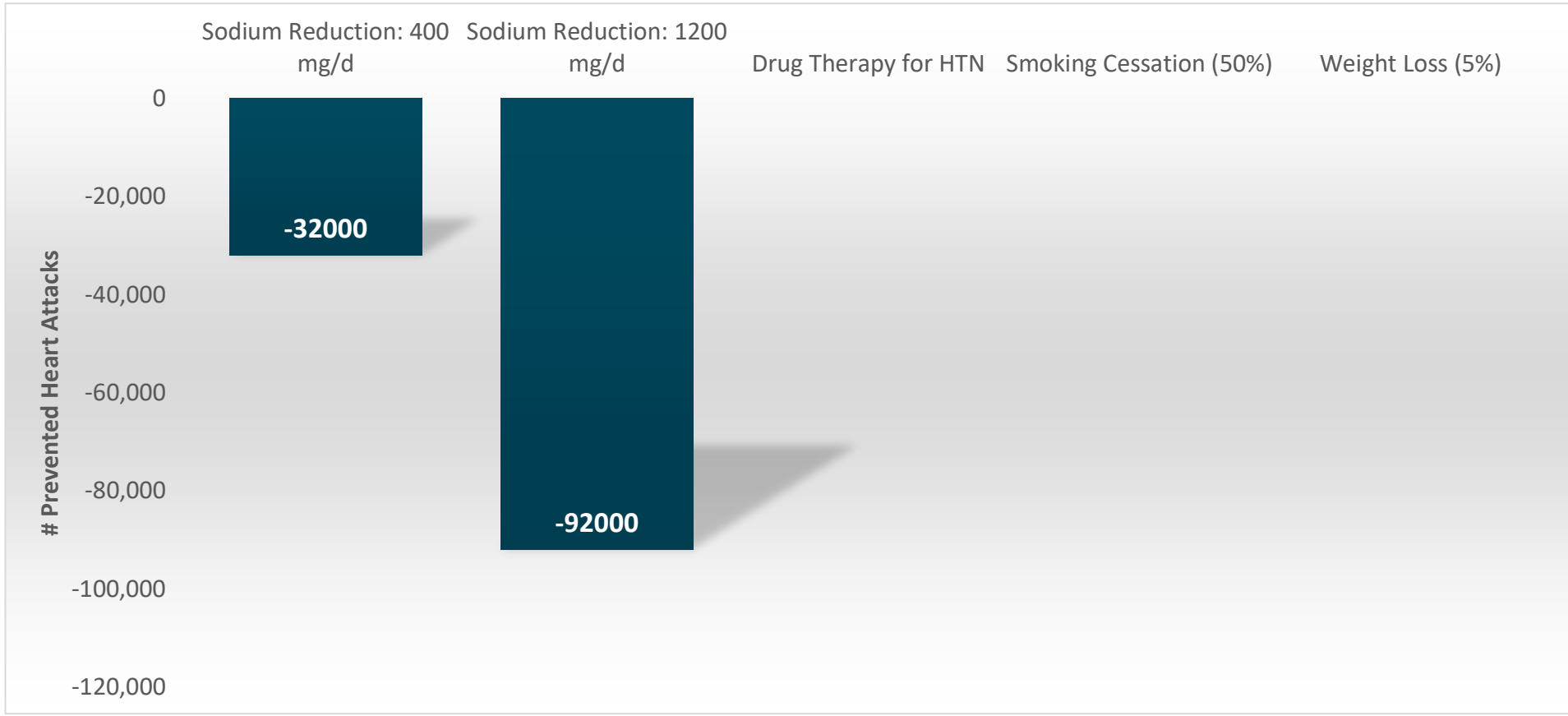






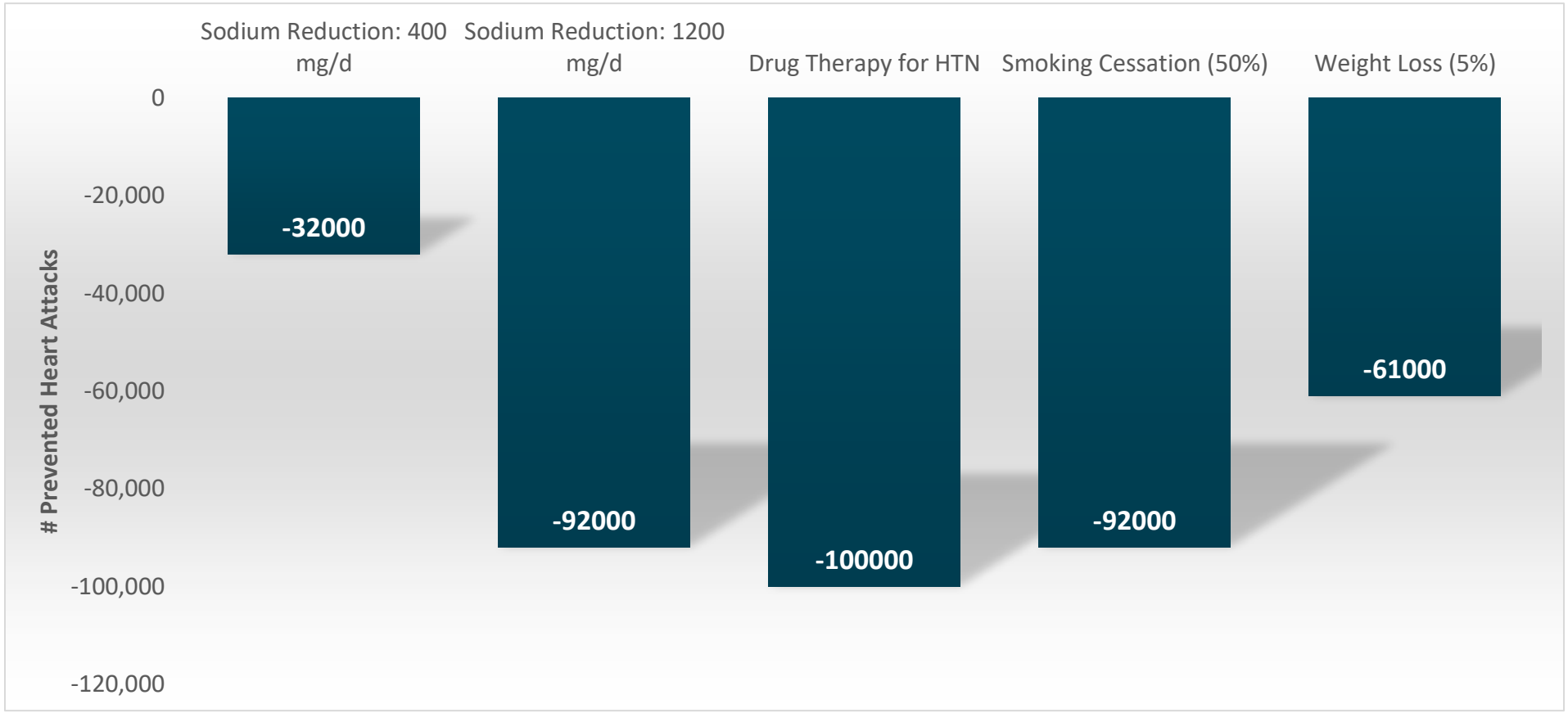
Karppanen & Mervaala. Prog Cardiovasc Dis 2006;49:59-75.

Estimated Annual Number of Prevented Heart Attacks from Population-Wide Sodium Reduction



Bibbins-Domingo, NEJM 2010;362:590

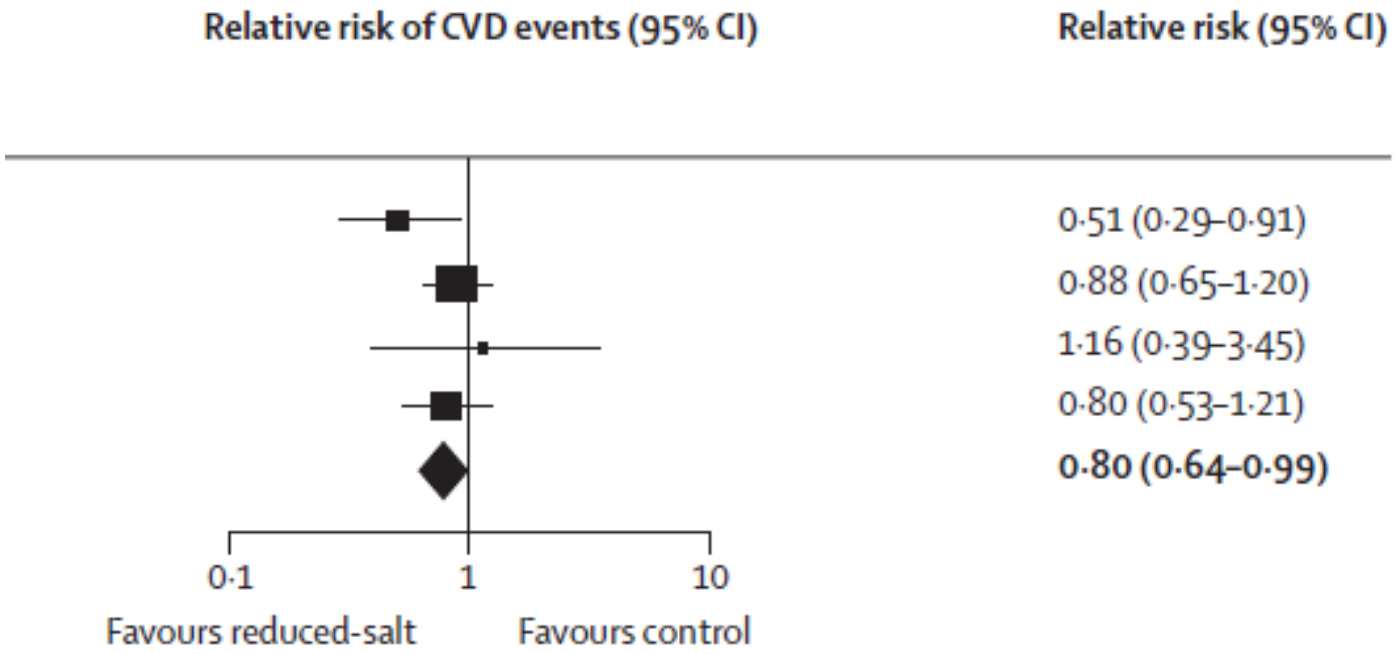
Estimated Annual Number of Prevented Heart Attacks from Population-Wide Sodium Reduction



Bibbins-Domingo, NEJM 2010;362:590

Effects of Population-Based BP Reduction (Favorably Shifting SBP Distribution)

Events	
Trial	Na/Cntl
TOHP I	17 / 32
TOHP II	71 / 80
Morgan	6 / 5
TONE	36 / 46
Total	130 / 163



He FJ, MacGregor GA. Lancet. 2011;378:380–382

AGENDA

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Salt substitution: Replacement of regular salt with potassium-enriched low-sodium salt substitutes (LSSS)

Most common to partially replace sodium chloride (NaCl) with potassium chloride (KCl)

- Regular salt: 100% NaCl
- LSSS: 75% NaCl + 25% KCl

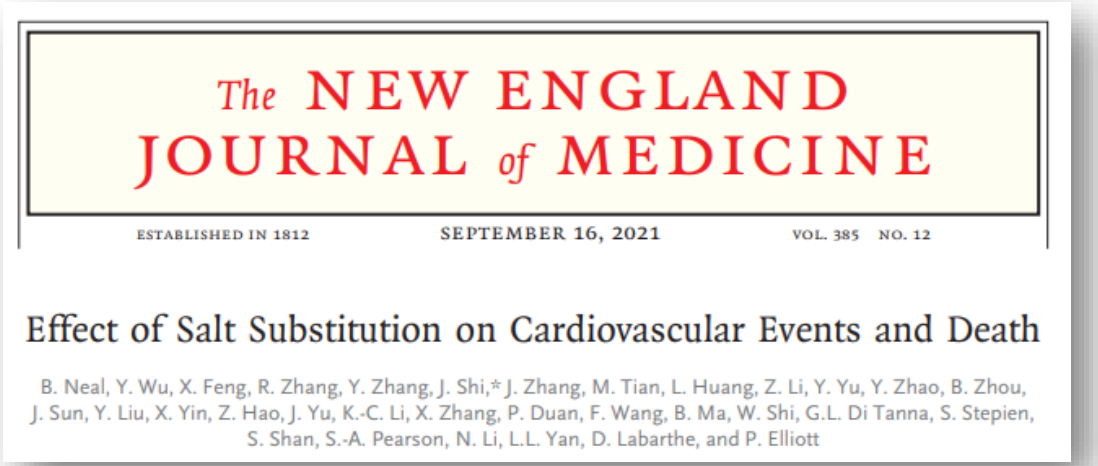
Known under many names

- Low-or reduced-sodium salts
- Potassium salts

*Single 24-hour urine is fine for estimating group average

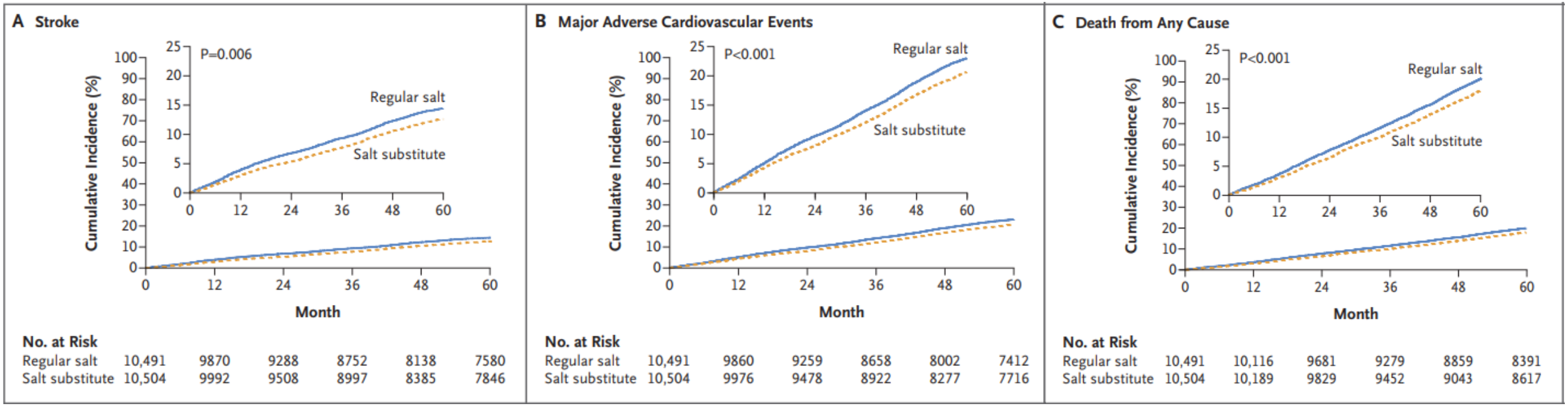
The Salt Substitute and Stroke Study (SSaSS)

Design	Cluster-randomized trial involving 20,995 persons from 600 villages in rural China
Participants	A) had a history of stroke or B) were ≥60 y and had high blood pressure.
Intervention	Villages randomized to intervention group received LSSS free-of-charge to cover household use.
Outcomes	Primary: Stroke Secondary: Major adverse CVD events and death from any cause Safety: Clinical hyperkalemia
Mean Follow-Up	4.7 y



Neal et al. Effect of Salt Substitution on Cardiovascular Events and Death. N Engl J Med 2021;385:1067-77.

12-14% reduction of stroke, CVD, and all-cause mortality



Outcomes	Salt Substitute	Regular Salt	Rate Ratio	P Value
	No. of events per 1000 person-yr		(95% CI)	
Stroke	29.14	33.65	0.86 (0.77-0.96)	P=0.006
Major Adverse CV Events	49.09	56.29	0.87 (0.80-0.94)	P<0.001
Death from Any Cause	39.28	44.61	0.88 (0.82-0.95)	P<0.001

Neal et al. Effect of Salt Substitution on Cardiovascular Events and Death. N Engl J Med 2021;385:1067-77.

Summary

01

Current dietary intakes of sodium greatly exceed dietary recommendations

02

As sodium intake rises, so does blood pressure and the risk of cardiovascular disease

03

Best available evidence indicates that reducing sodium intake will have major beneficial effects on blood pressure and cardiovascular disease

The Sleep Specialist's Perspective: Sleep and Cardiovascular Risk

Richard K. Bogan, MD, FCCP, FAASM

Associate Clinical Professor

Medical University of South Carolina, Charleston, SC

University of South Carolina, Columbia, SC

Principal, Bogan Sleep Consultants, LLC

Sleep Homeostasis: Survival

Decreased Alertness

Microsleeps

Automatic Activity

Apathy

Fatigue

Memory Loss

Mood Changes

Accidents

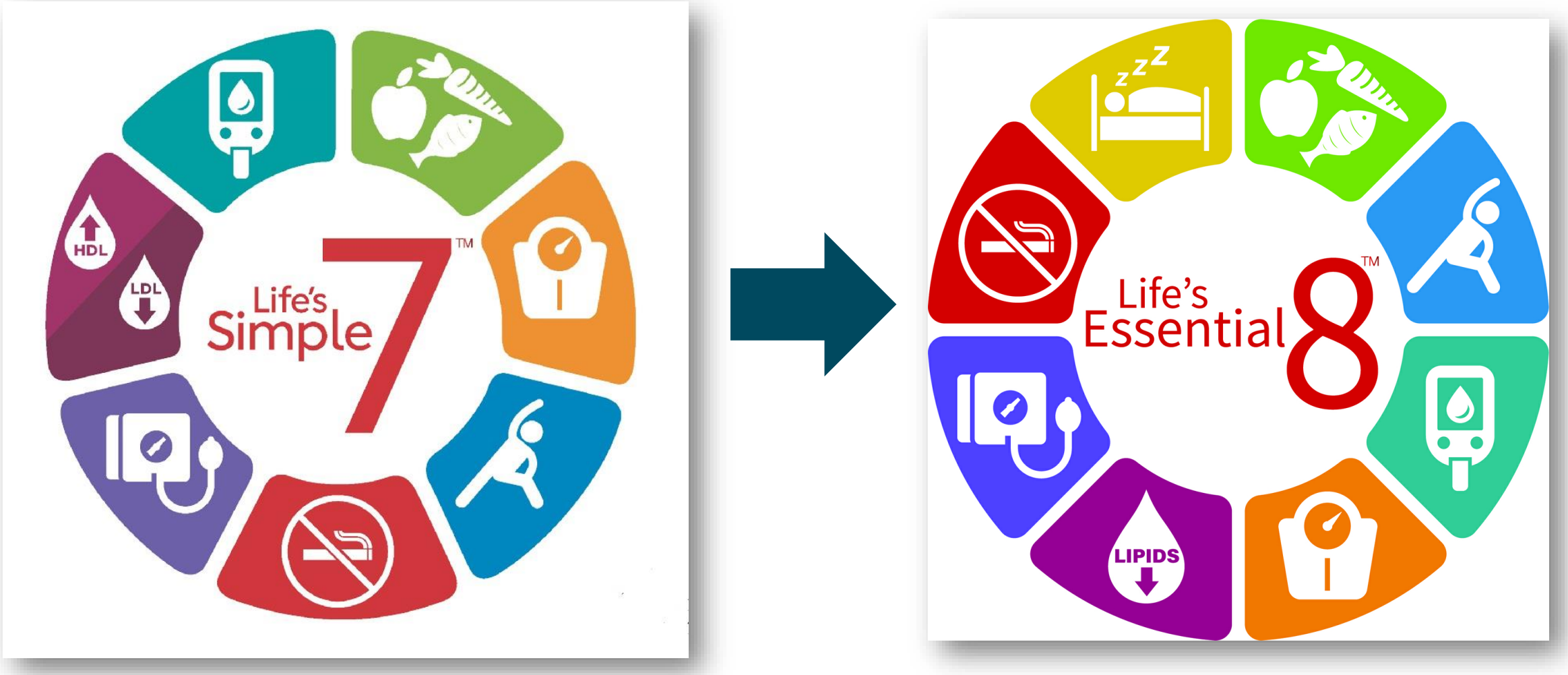
Productivity Impairment

Metabolic Changes

Autonomic Tone Changes

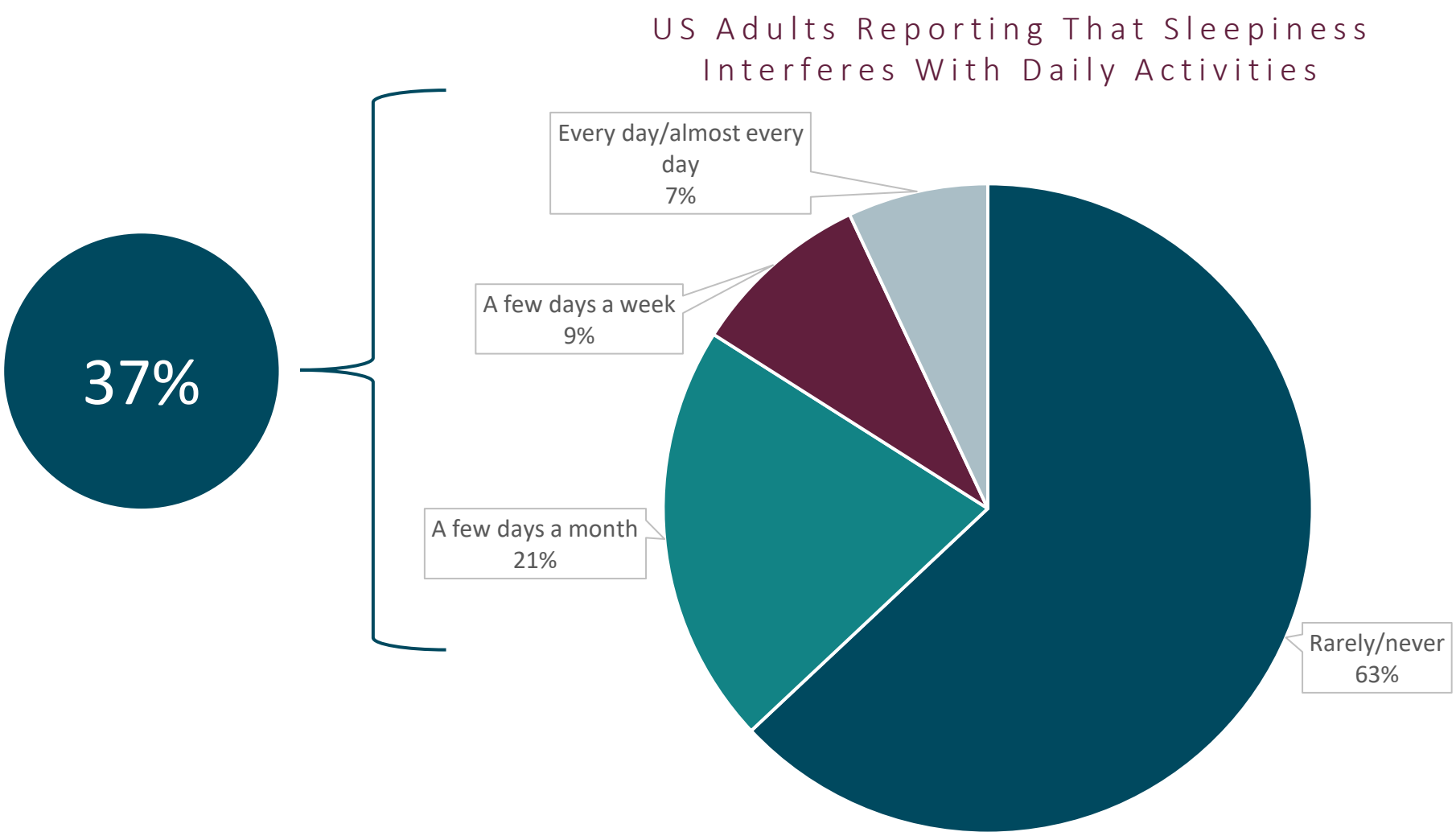
Immune Response

Sleep: AHA's Essential 8 Factors Affecting CV Health



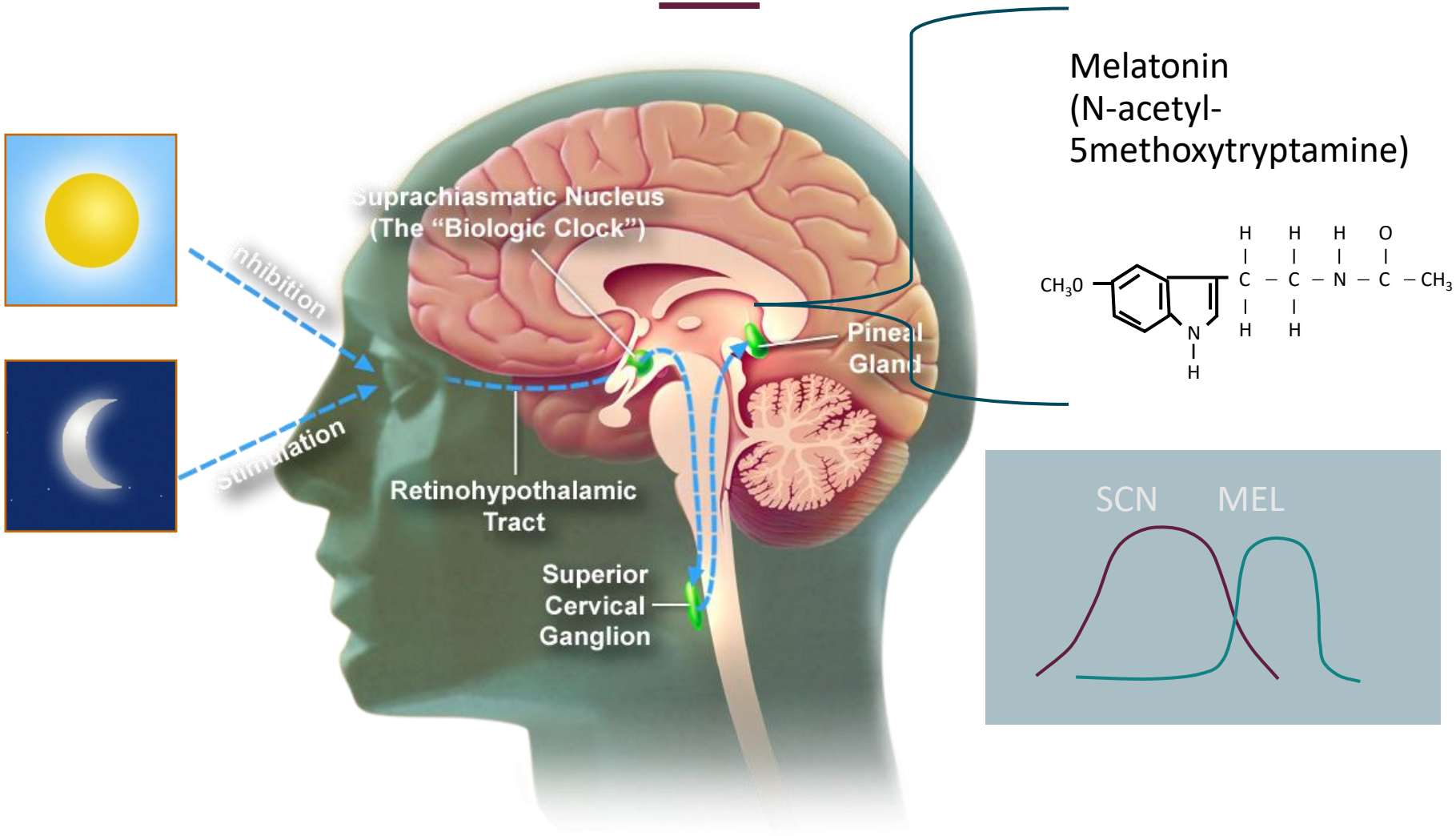
American Heart Association – Life's Essential 8. Available at https://www.heart.org/en/healthy-living/healthy-lifestyle/lifes-essential-8, accessed June 1, 2023.

Sleepiness: Impact on Daily Activities



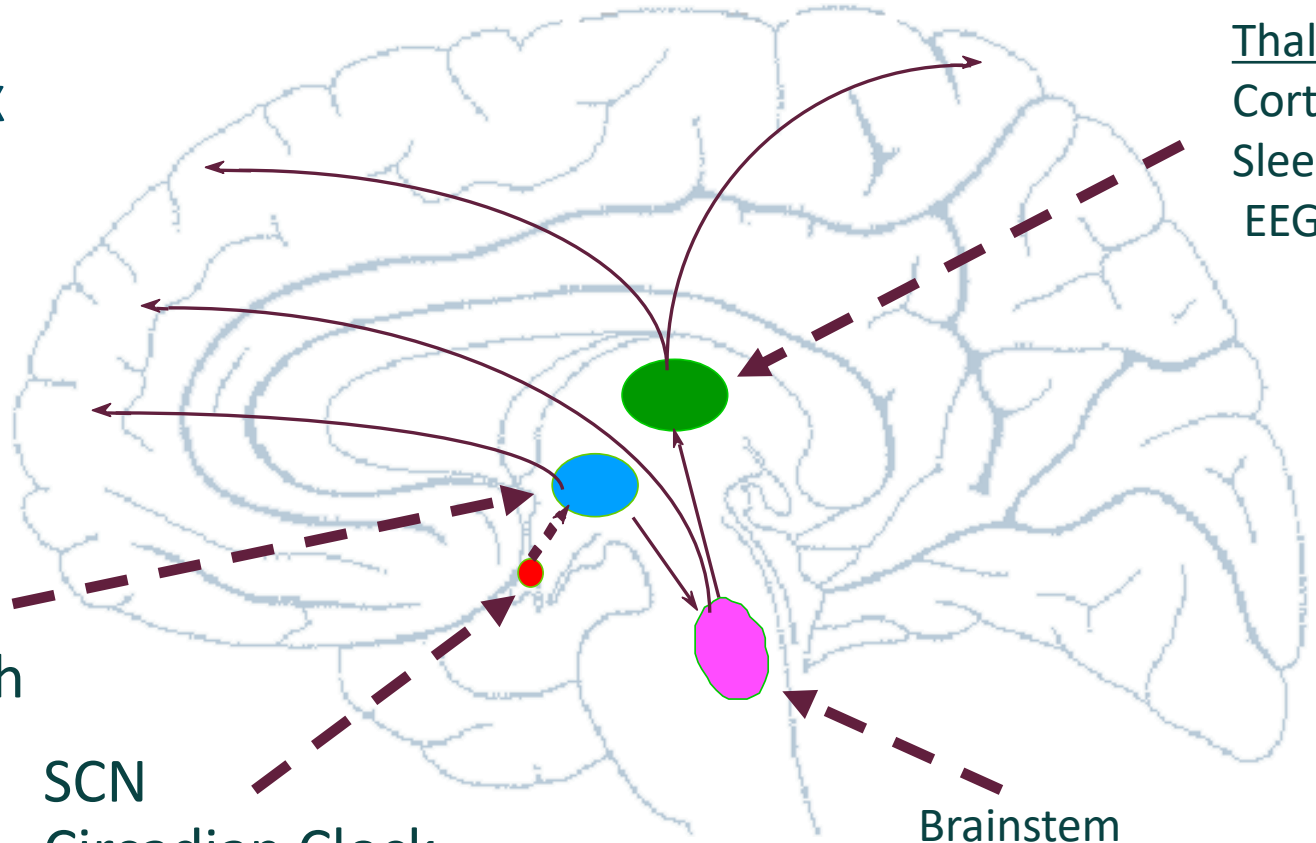
National Sleep Foundation. 2002 Sleep in America Poll. At: http://www.sleepfoundation.org/2002poll.html.

Circadian Rhythms and the Suprachiasmatic Nucleus (SCN)



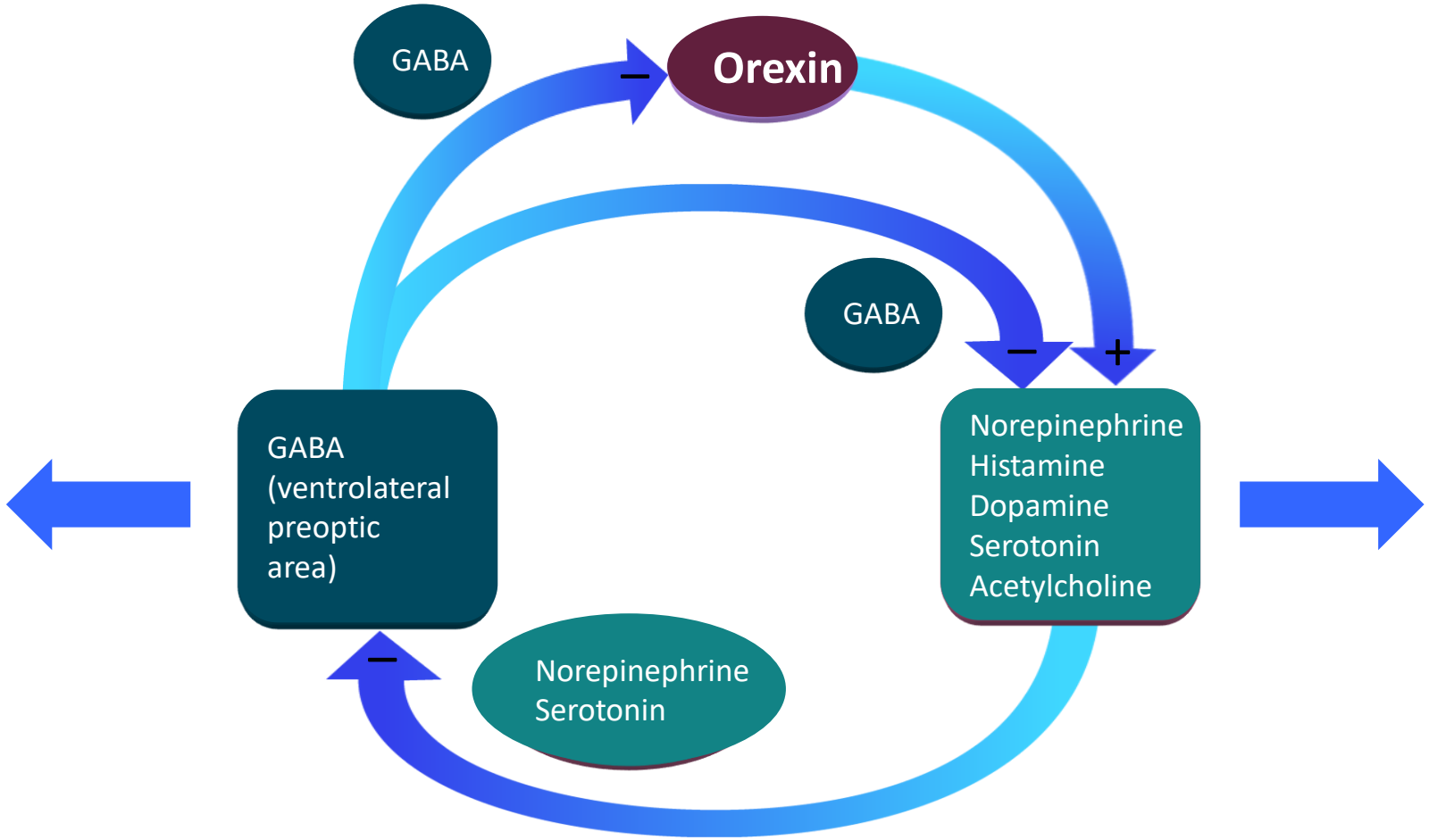
Adapted from Brzezinski A. N Engl J Med. 1997;336:186-195.

Sleep: Neurophysiology



Courtesy of E. Mignot, MD. Stanford University.

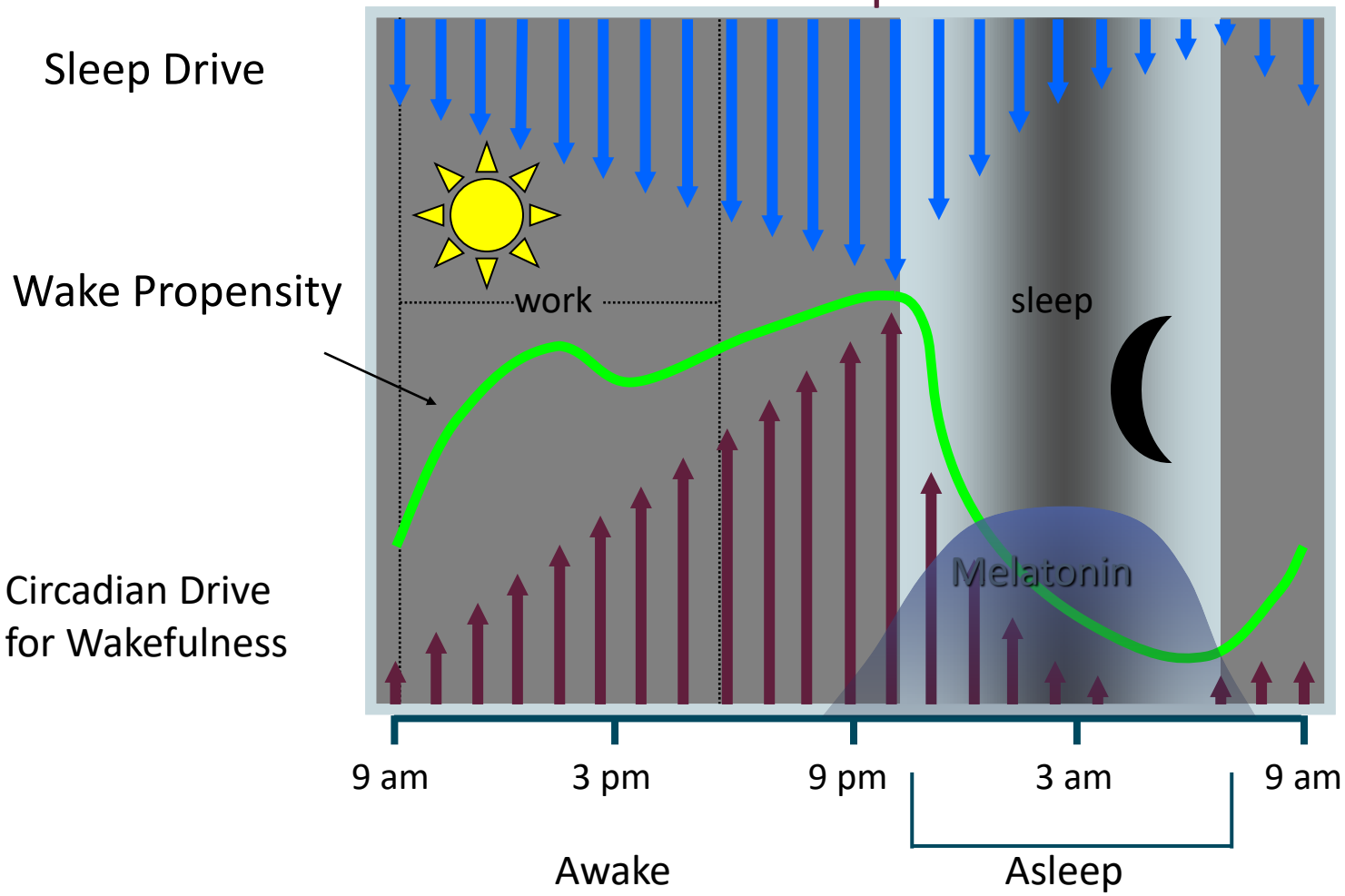
Hypocretin Stabilizes The Sleep/Wake Switch



Adapted from Saper et al. Trends Neurosci. 2001;24:726.

Physiologic Determinants of Sleepiness

Normal Sleepiness



Courtesy of Michael Thorpy, MD.

Common Causes of Sleepiness

Sleep-wake disorders

Disorders of sleep-wake regulation

- Idiopathic hypersomnia
- Insomnia
- Kleine-Levin syndrome
- Narcolepsy

Disorders of sleep disruption

- OSA
- Periodic limb movement disorder
- Restless legs syndrome

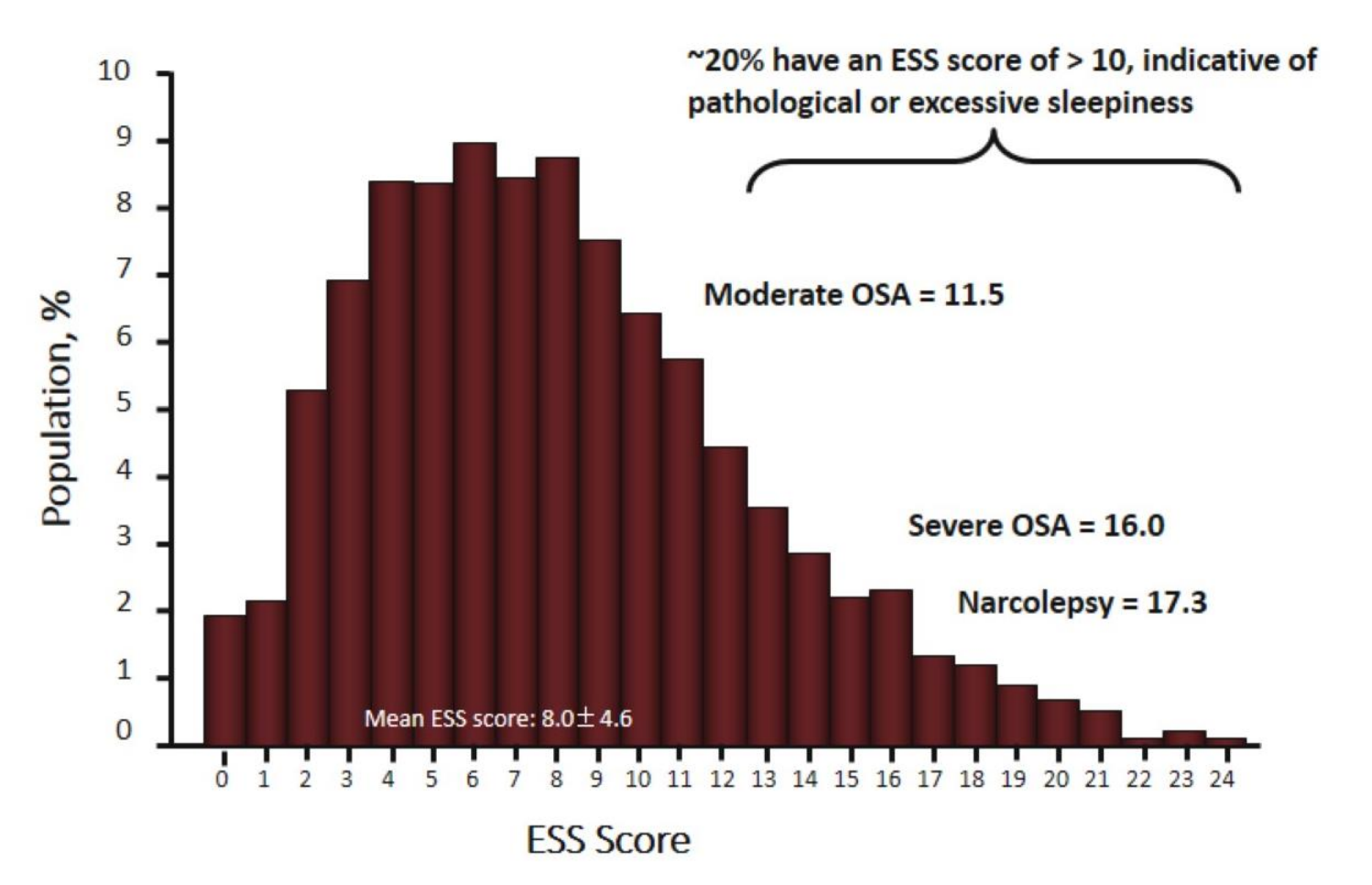
Disorders of circadian rhythm

- Shift-work sleep disorder
- Delayed or advanced sleep phase syndrome
- Non-24-hour sleep-wake rhythm disorder

Insufficient Sleep

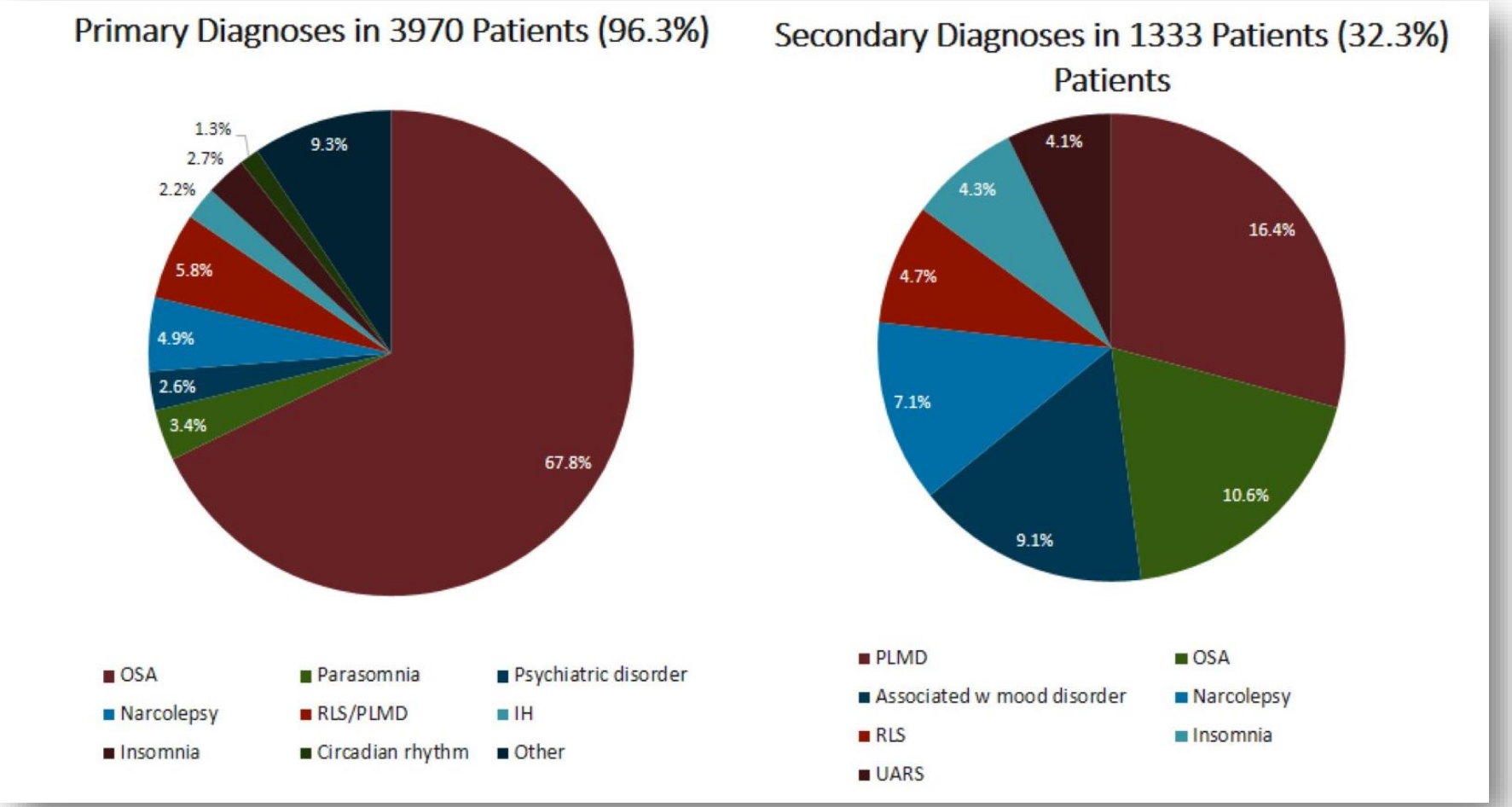
Medication Effects

ESS Scores Among a Population-Based Sample of 3283 Adults



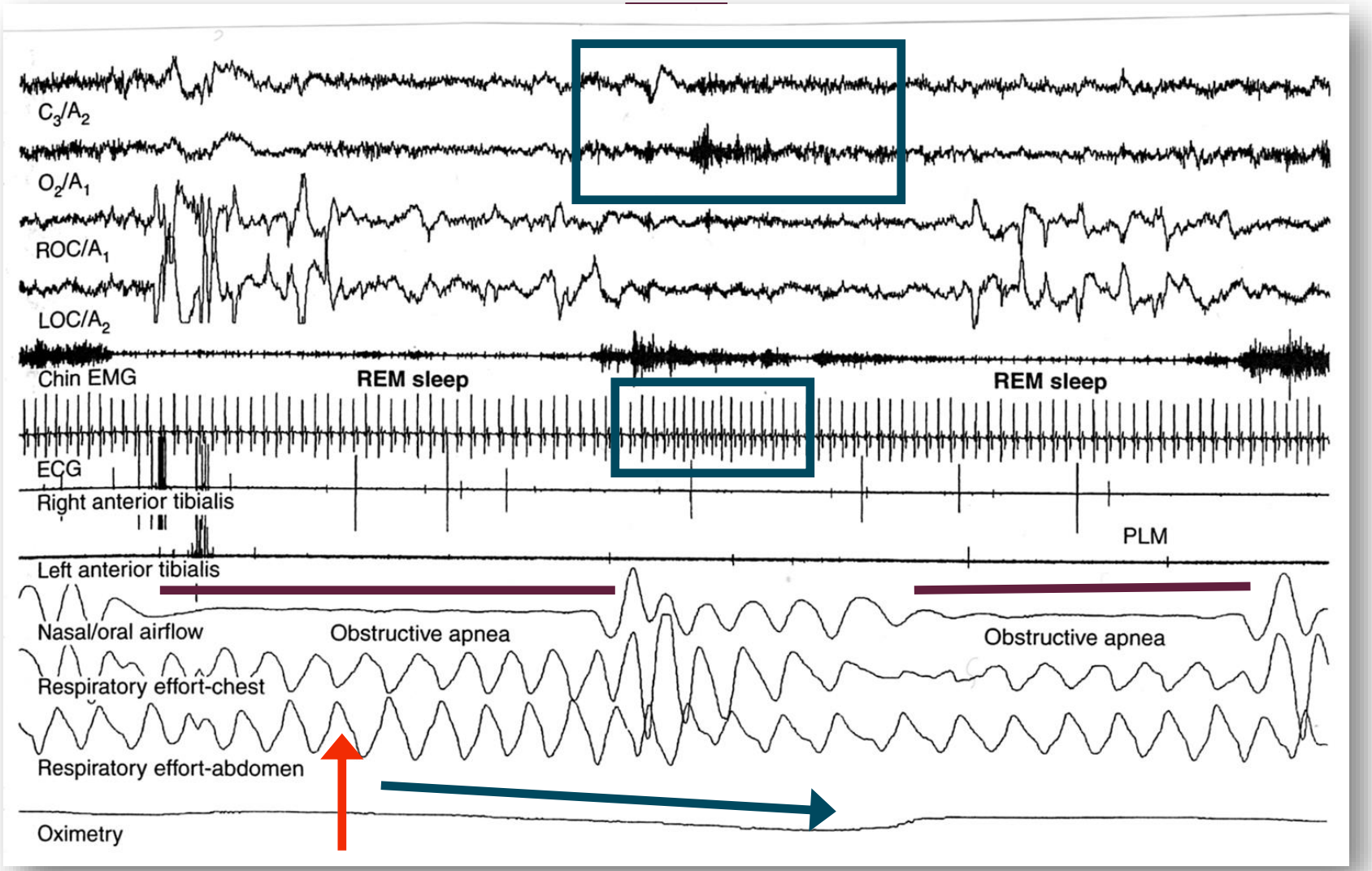
Myers EJ, et al. *Sleep.* 2003;26(suppl):A194

Point Prevalence of Sleep Disorders Among 4122 Patients in 19 Regional Sleep Centers

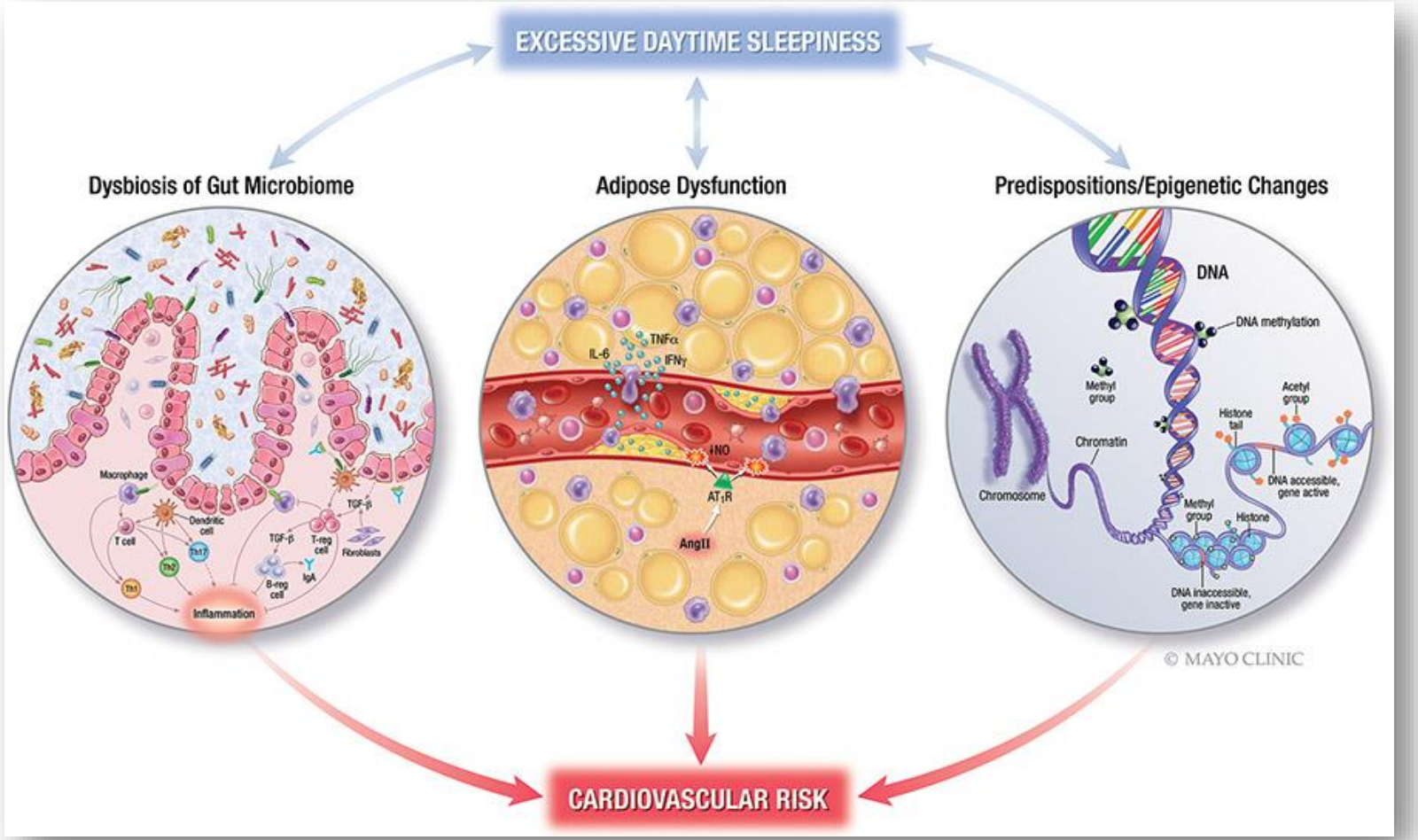


Punjabi NM, et al. *Sleep.* 2000;23:471-480.

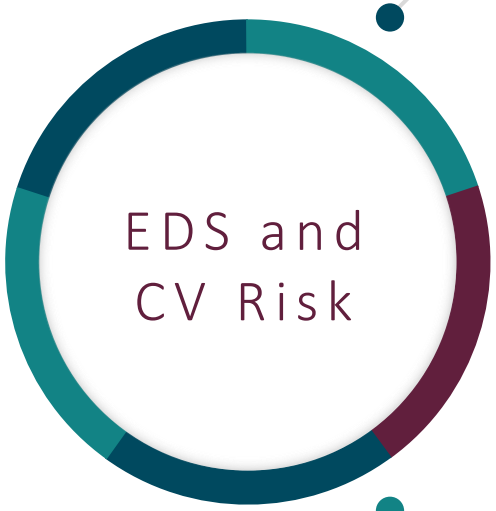
EEG Arousals and Desaturations on Polysomnogram



How EDS may contribute to increased CV risk



Bock J, Covassin N, Somers V. Excessive daytime sleepiness: an emerging marker of cardiovascular risk. Heart. 2022;108(22):1761-1766. Published 2022 Oct 28. doi:10.1136/heartjnl-2021-319596



EDS is also associated with increased cardiovascular risk and mortality in the general population, mainly elderly.

In a population-based prospective study, elderly (65 years of age) with no history of coronary heart disease or stroke with EDS frequently had an increased risk of coronary heart disease and stroke over a median follow-up of 5.1 years .

In the same study, EDS was associated with an increased risk of cardiovascular mortality but not cancer-related mortality, over six years of follow-up.

In a different study, the relationship between EDS and increased cardiovascular risk was independent of any history of CVD.

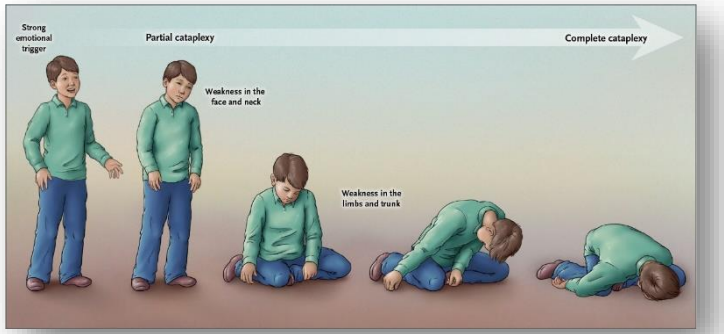
Studies of younger adult participants with EDS have shown increased risk of vascular death, ischemic stroke, and myocardial infarction; ischemic heart disease; and incident stroke and incident coronary heart disease.

Jennum, et al., Sleep Medicine Reviews,Volume 58, 2021, 101440, 1087-0792. M. Blachier, et al. Excessive daytime sleepiness and vascular events: the Three City Study Ann Neurol, 71 (2012), pp. 661-667

Characteristics of Narcolepsy

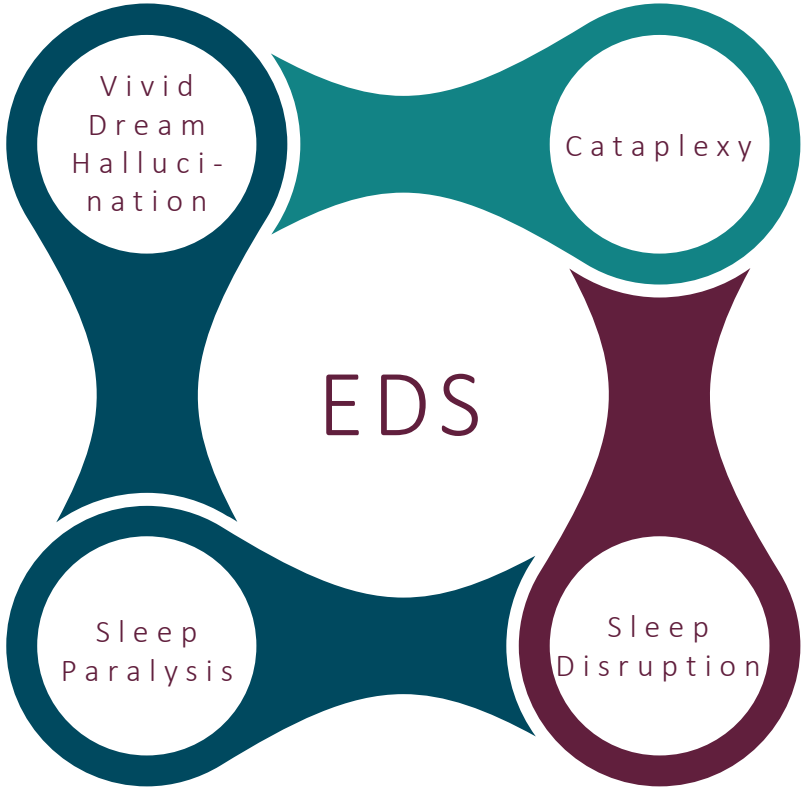
Excessive daytime sleepiness

Cataplexy: - Brief, emotionally-triggered episodes of muscle weakness in ~50%



Other REM sleep-like phenomena

- Sleep paralysis: inability to move when dozing off or upon awakening
  - Occurs in 40-80% of patients
- Hypnagogic and hypnopompic hallucinations: vivid dream-like hallucinations at beginning or end of sleep
  - Can be visual, auditory or tactile
  - Occurs in in 40-80% of patients



Narcolepsy: Symptoms. Harvard Medical School Division of Sleep Medicine. http://healthysleep.med.harvard.edu/narcolepsy/what-is-narcolepsy/narcolepsy_symptoms. Published 2013. Accessed December 2018.

Scammell, TE, NEJM, 2017

Two Types of Narcolepsy

Narcolepsy Type I (NT1; Narcolepsy with Cataplexy)

- Sleepiness
- At least one of the following:
  -Cataplexy and a positive Multiple Sleep Latency Test (MSLT)*
  -Low CSF orexin-A concentrations
- Hypnagogic hallucinations, sleep paralysis, and fragmented sleep are more common in Type 1 narcolepsy.

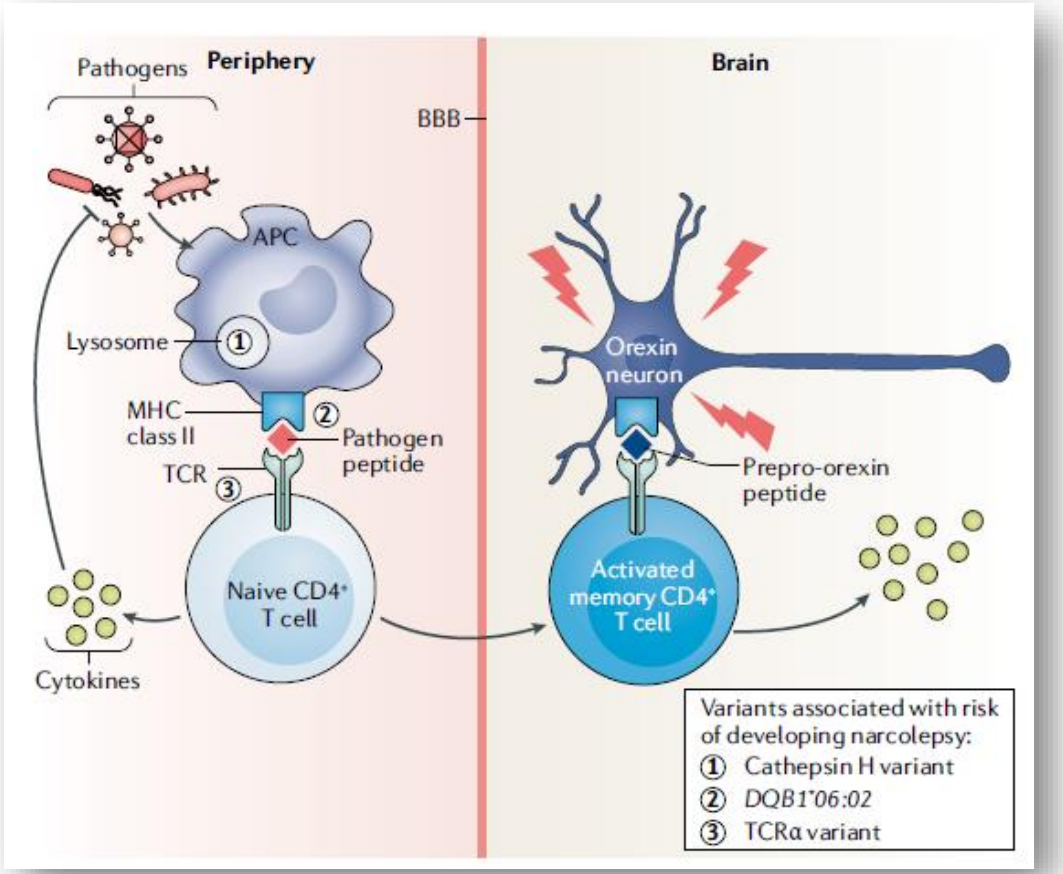
Narcolepsy Type 2 (NT2; Narcolepsy without Cataplexy)

- Sleepiness
- Positive MSLT
- Positive MSLT : mean sleep latency of ≤8 minutes and ≥2 sleep-onset REM periods. REM sleep latency < 15min on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT.

Pathophysiology and Mechanisms of Narcolepsy

- Disorder of both sleep and wake: Brain state instability
- Role of hypocretin /orexin
  - decreased levels
  - receptor mutation (rare)
- Genetic Contributions
- Acquired autoimmune disorder

T-Cell Mediated Model

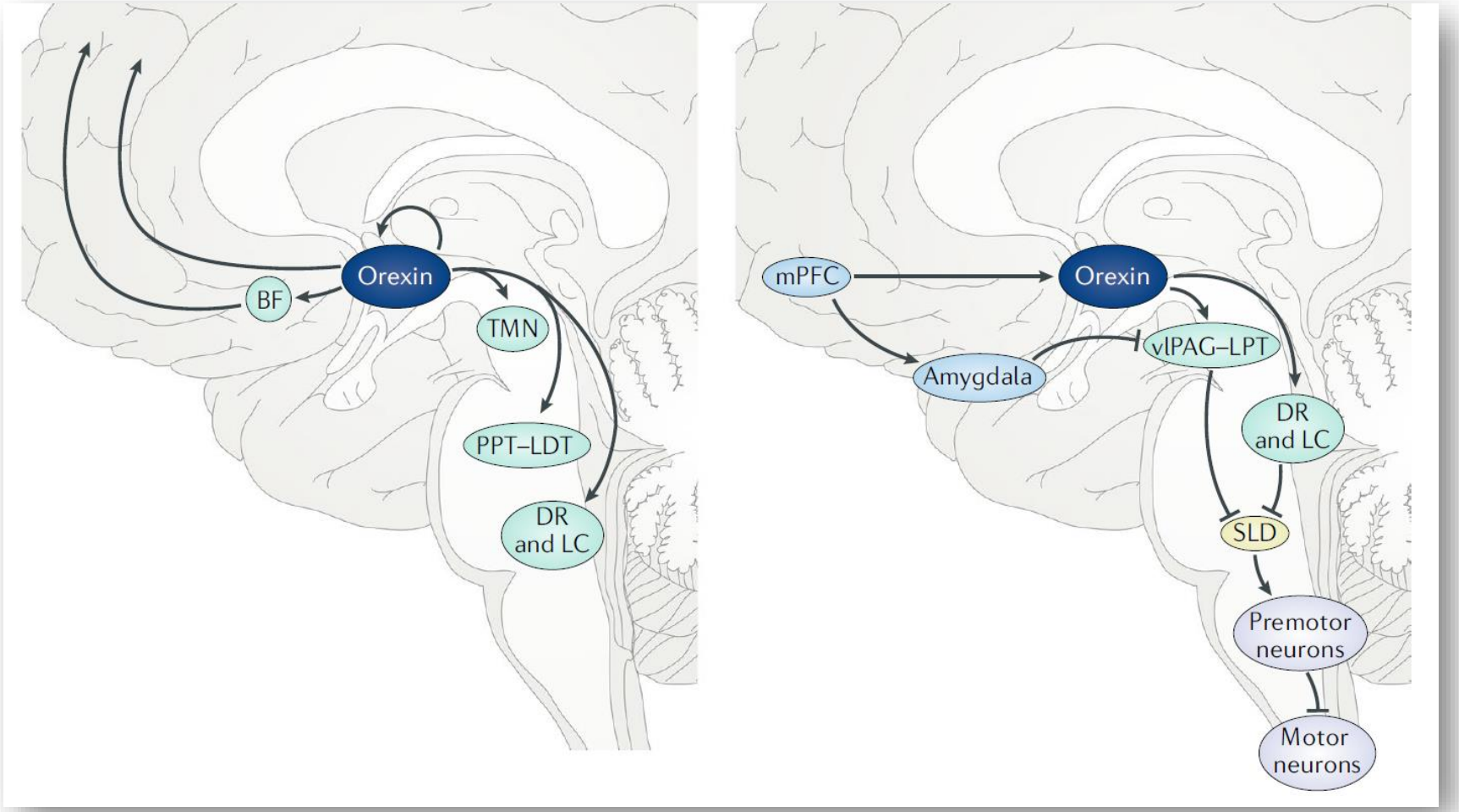


Mahoney et al, Nature Rev, 2019

Projections of Hypocretin/Orexin Neurons

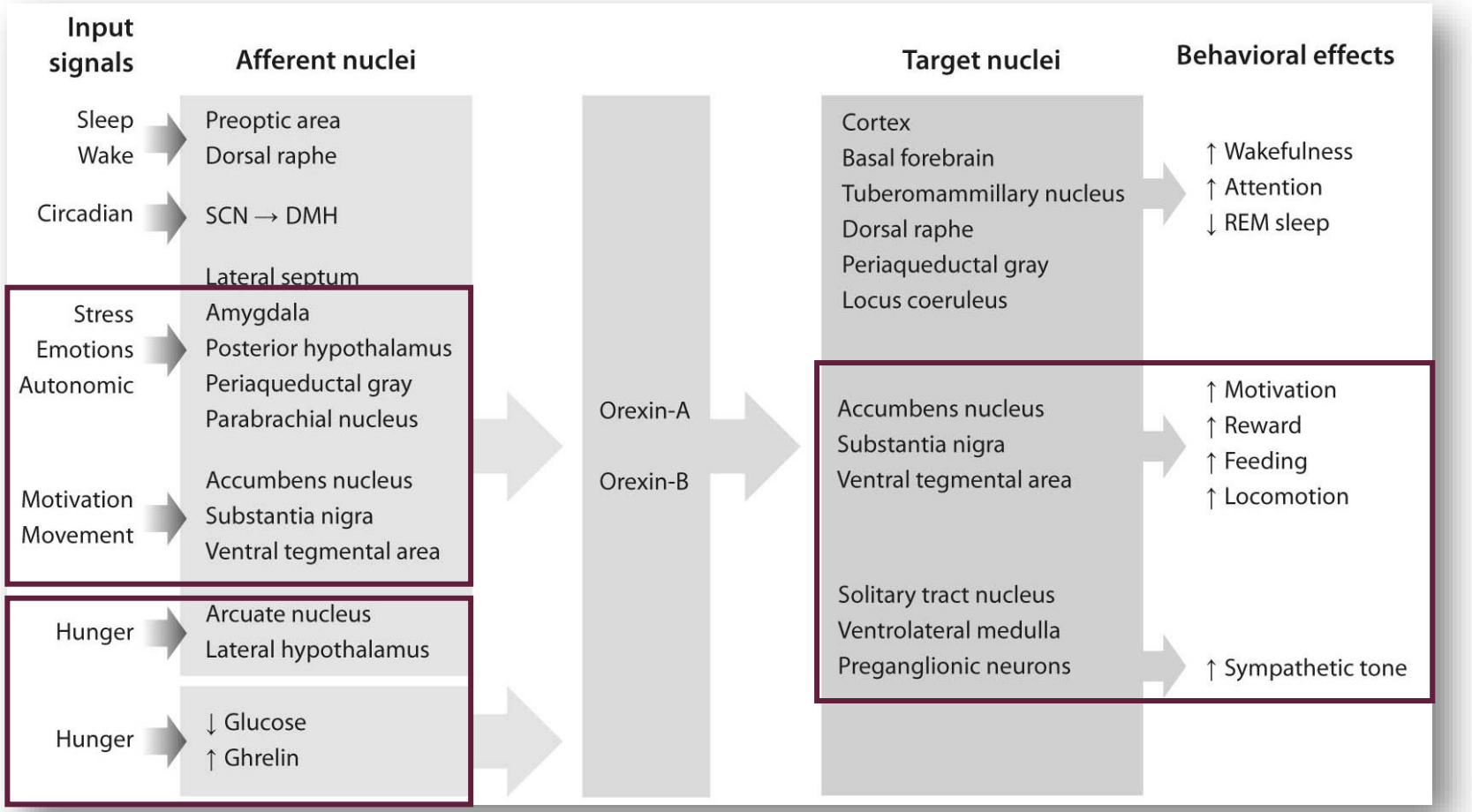
Maintain wake/alertness

Maintain muscle activity during wake



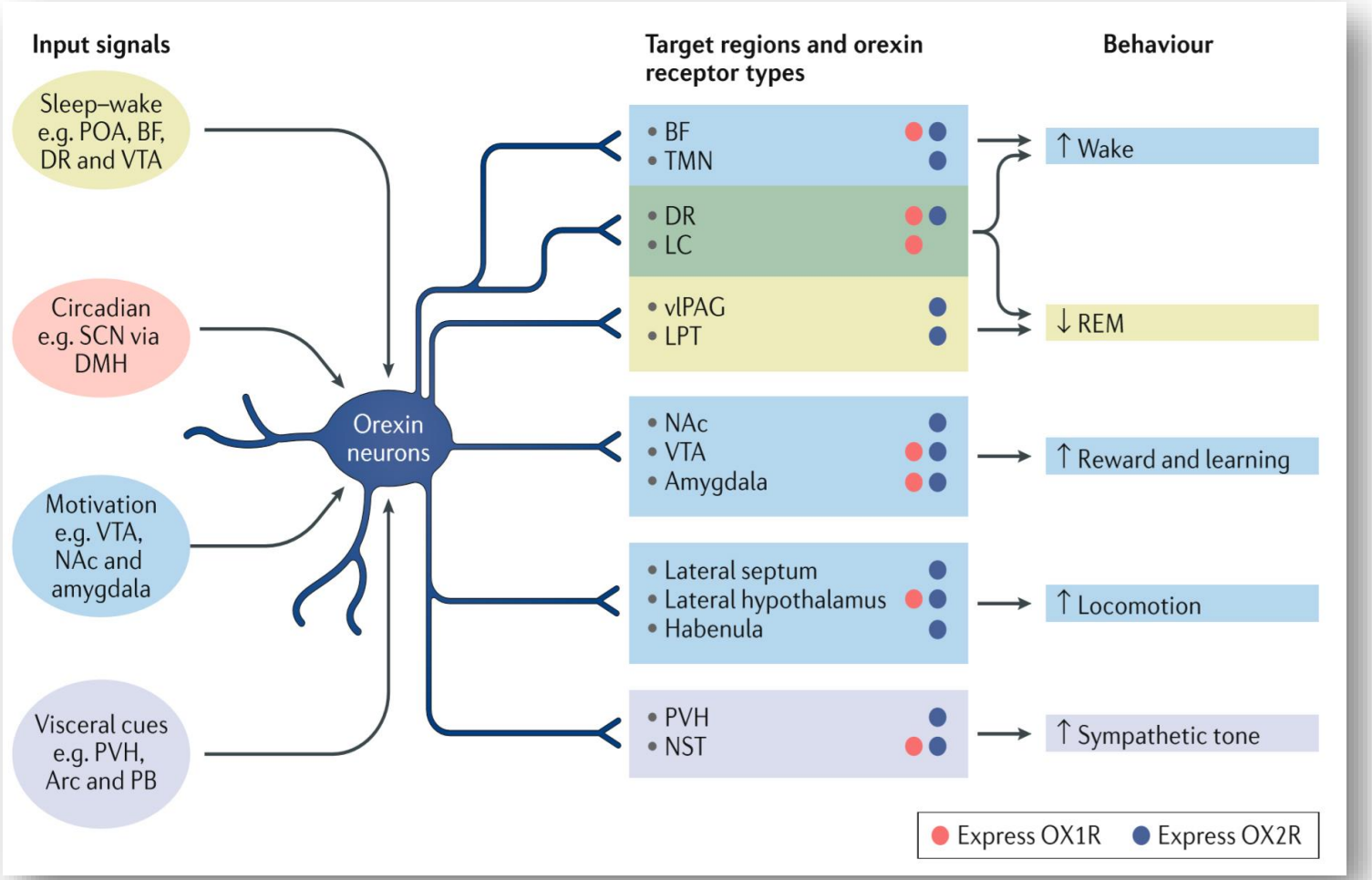
Mahoney et al, Nature Rev, 2019

Orexin System: Beyond Sleep and Wake Regulation



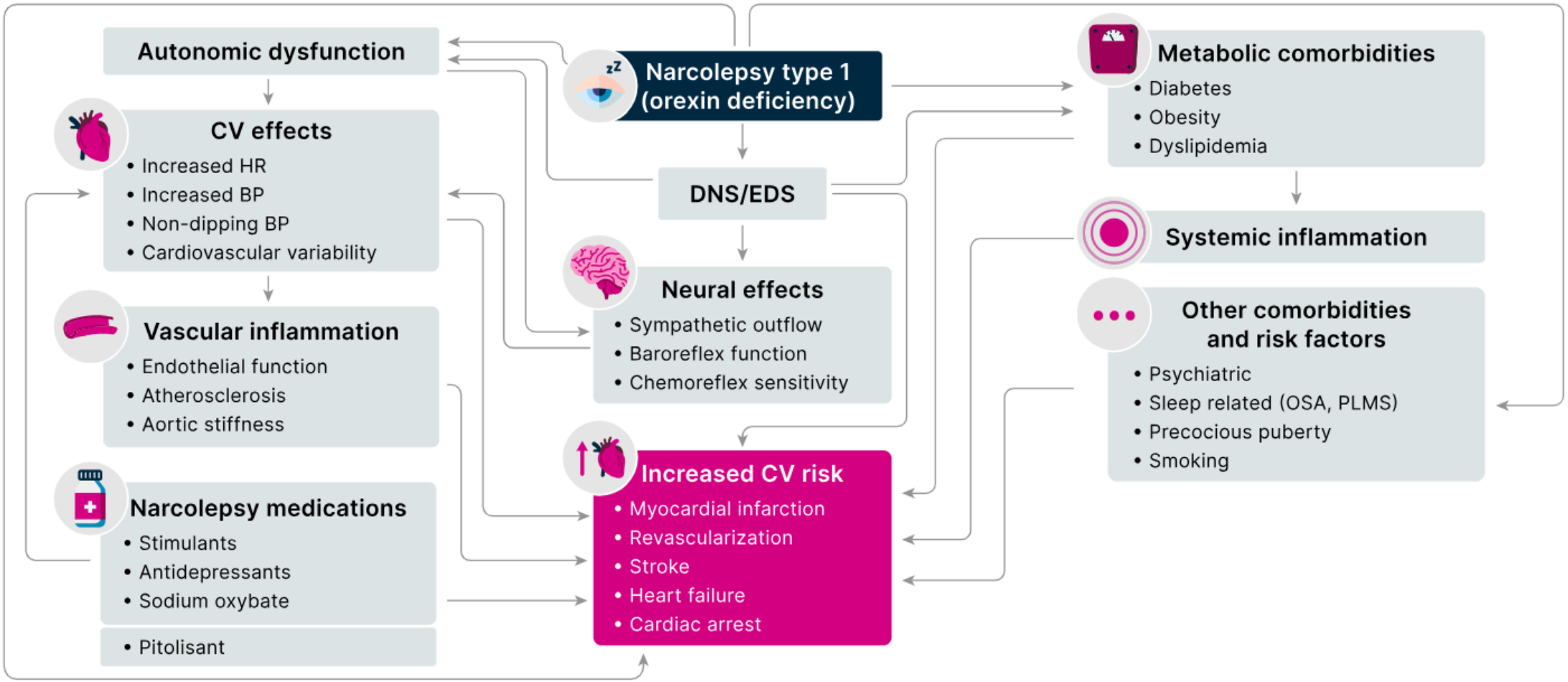
Krystal AD, et al. J Clin Psychiatry. 2013;74(suppl 1):3–20.

Orexin Neuron Connections



PVH = Paraventricular nucleus NTS = Nucleus tractus solitarius

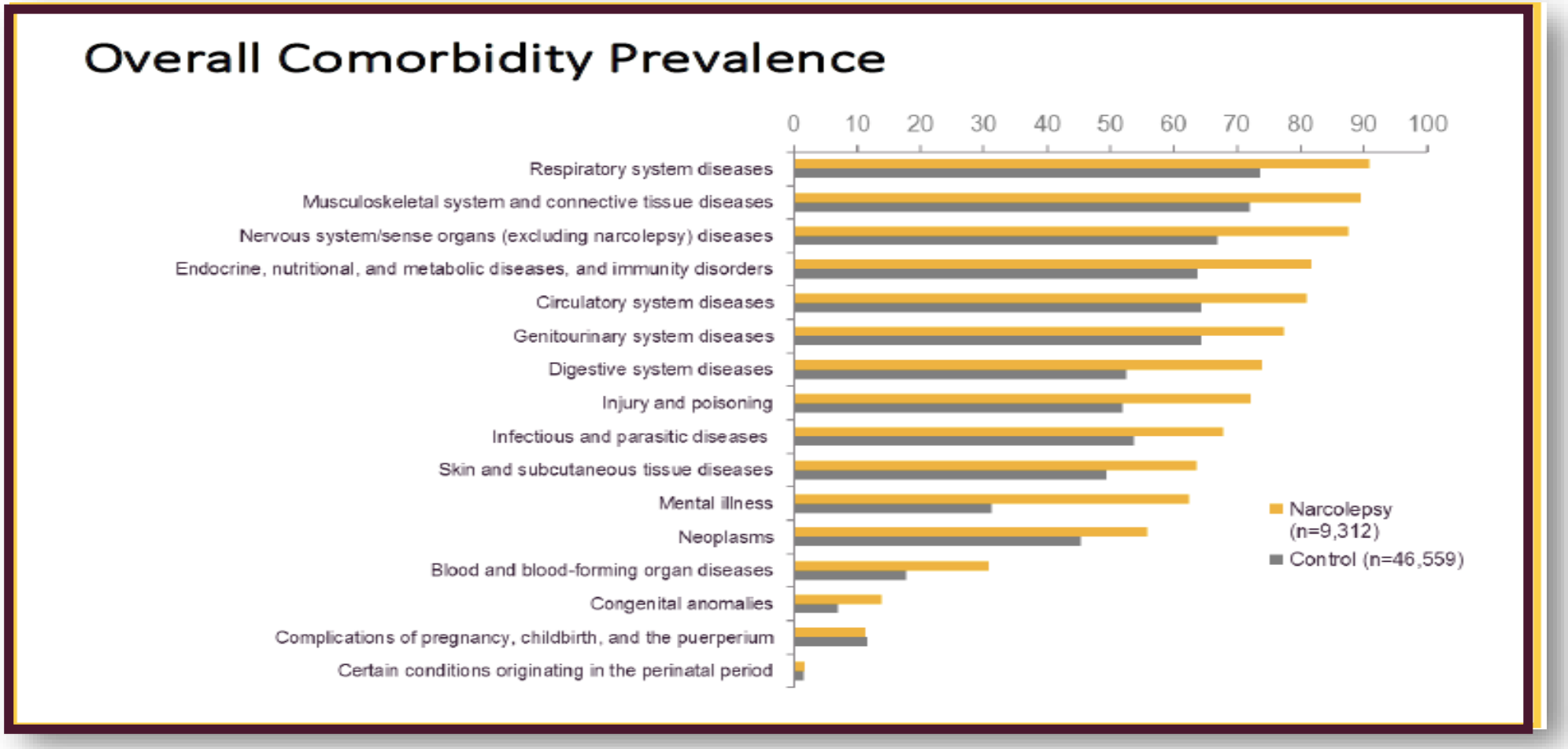
Risk of Cardiovascular Disease and Narcolepsy



Jennum PJ et al Cardiovascular disorders in narcolepsy: Review of associations and determinants, Sleep Medicine Reviews,Volume 58, 2021, 101440,ISSN 1087-0792,

Narcolepsy and Comorbidity: Bond Study

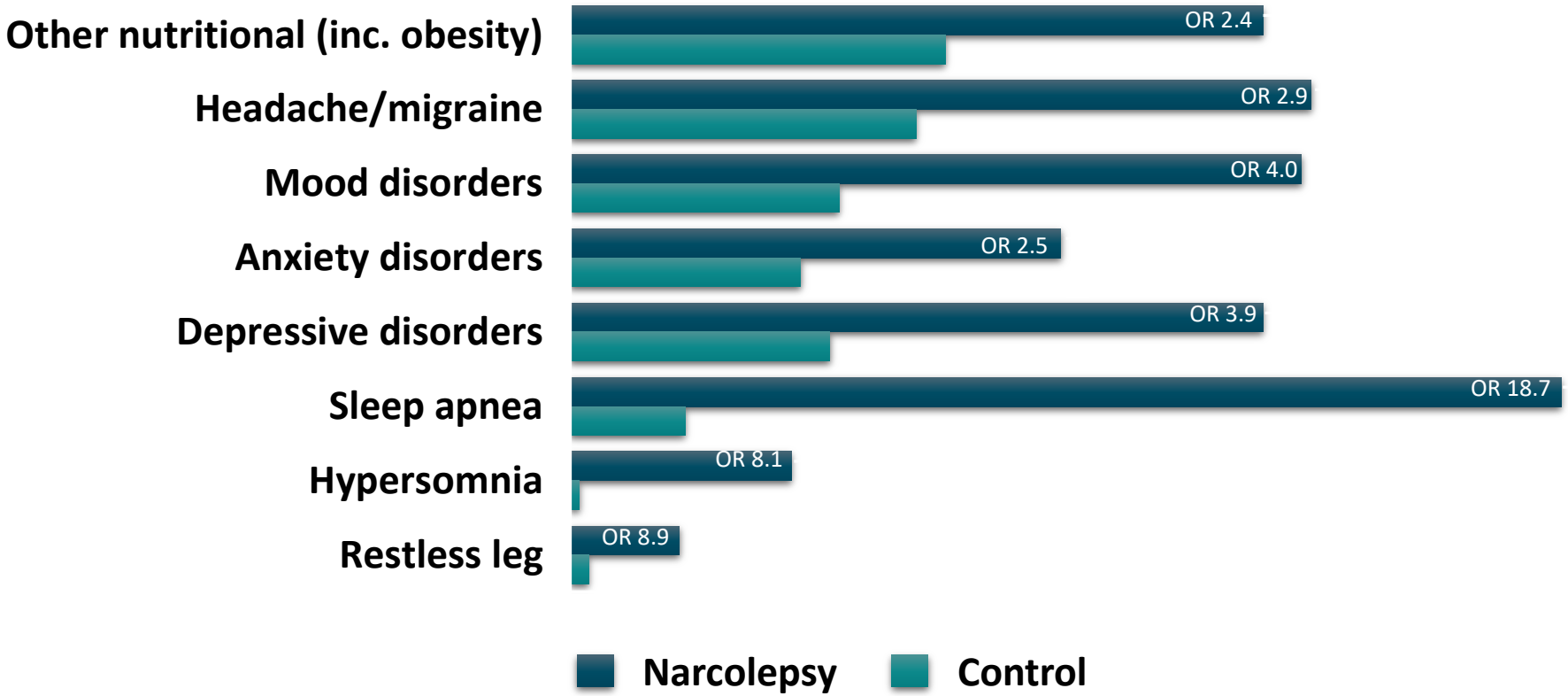
- Retrospective study: 5-year US claims data 2006-2010
- 55,871 adults >18yo, 9,312 with NT1 or NT2 and matched controls



Black J, Reaven NH, Funk SE et al. Sleep Medicine 2017;33:15.

Prevalence of Comorbidity of Narcolepsy (BOND)

Targeted Diagnoses

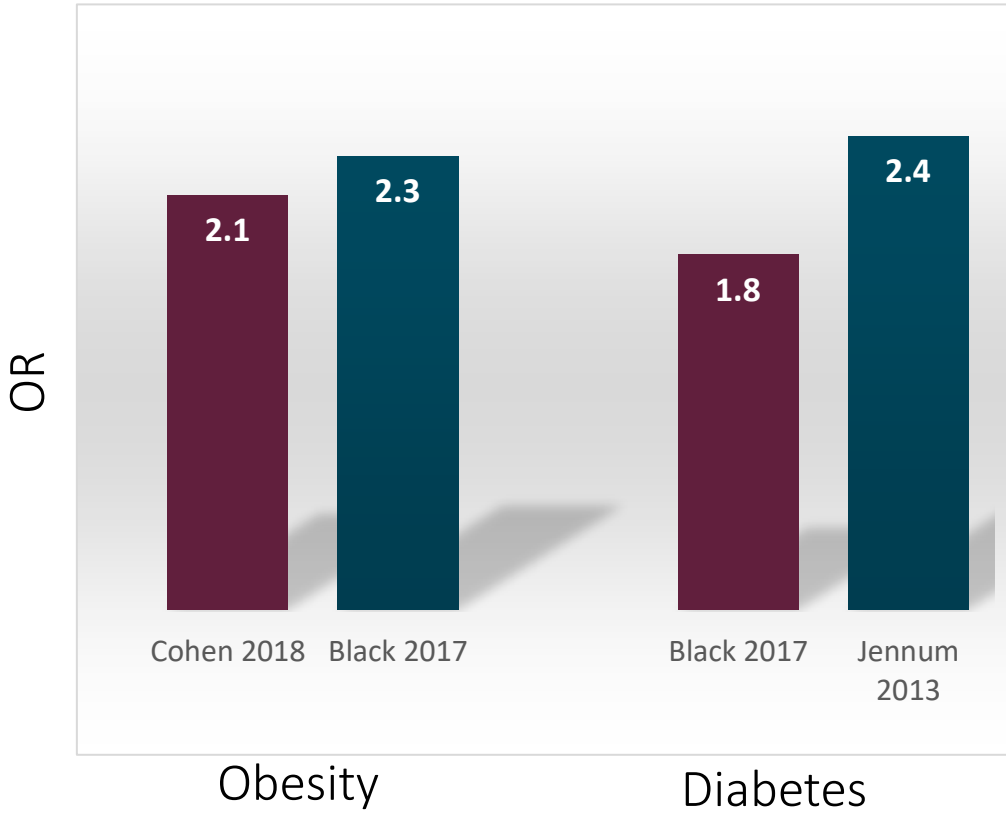


Black J, Reaven NH, Funk SE et al. Sleep Medicine 2017;33:15.

Black J et al. Presented at the 27th Annual Meeting of the Associated Professional Sleep Societies, LLC ; June 1–5, 2013, Baltimore.

Cardiovascular and Cardiometabolic Comorbidities Associated With Narcolepsy

- Obesity is common in adults and children with narcolepsy
- Obesity can predispose to cardiometabolic abnormalities and OSA
- Obesity is most obvious in children and weight increase may occur at time of onset of narcolepsy
  Precocious puberty occurs more commonly
- Narcolepsy patients are at increased risk for insulin resistance and diabetes



Nordstrand SEH et al. Sleep. 2020;43(5):zsz277. Cohen A et al. Sleep Med 2018;43: 14–18. Poli F et al. Sleep. 2013:36:175-81. Jehan S et al. Sleep Med Disord. 2018;2:52-58. Jehan S et al. Sleep Med Disord. 2017;1:00019; Tsuneki H et al, Diabetologia 2008; 51:657-67. Tsuneki H et al, Diabetes 2015;64:459-70. Cohen A et al. Sleep Med. 2018;43:14-18. Jennum P et al. Sleep. 2013;36:835-40. Black J, Reaven NH, Funk SE et al. Sleep Medicine 2017;33:15.

Therapeutic Interventions for Narcolepsy: Alerting Medications

Medication	Mechanism of Action
Caffeine[1]	Adenosine receptor antagonist
Methylphenidate[2]*, amphetamines[3]*	Sympathomimetic; enhance neurotransmission of dopamine, norepinephrine, serotonin
Modafinil[4]*, armodafinil[5]*	Dopamine reuptake inhibitor
Sodium oxybate[6]* Lower-Sodium oxybate[7]*	$GABA_B$ agonist
Solriamfetol[8]*	Dopamine-norepinephrine reuptake inhibitor
Pitolisant[9]*	Histamine H_3 antagonist/inverse agonist
TAK-925/TAK-994[10]†	Hypocretin receptor agonist

1. Aldosari MS et al. Clin Nutr. 2018;37:S208; 2. Ritalin® (methylphenidate) PI 2019; 3. Adderall® (amphetamine and dextroamphetamine) PI 2007; 4. Provigil® (modafinil) PI 2015; 5. Nuvigil® (armodafinil) PI 2018; 6. Xyrem® (sodium oxybate) PI 2018; 7. XywavTM (calcium, magnesium, potassium, and sodium oxybates) PI 2020; 8.SunosiTM (solriamfetol) PI 2019; 9. Wakix ® (pitolisant) PI 2019; 10. Kimura H et al. Sleep. 2019;42(suppl 1):A23.

*FDA approved to treat excessive sleepiness associated with narcolepsy.
†Investigational; not FDA-approved for any indication.

Therapeutic Interventions for Narcolepsy: Cataplexy Medications

Medication	Mechanism of Action
Sodium oxybate[1]* Lower-Sodium oxybate[2]*	$GABA_B$ agonist
Pitolisant[3]*	Histamine H_3 antagonist/inverse agonist
Antidepressants	Monoamine reuptake inhibitors
TAK-925/TAK-994[4]†	Hypocretin receptor agonist

1. Xyrem® (sodium oxybate) PI 2018; 2. XywavTM (calcium, magnesium, potassium, and sodium oxybates) PI 2020; 3. Wakix ® (pitolisant) PI 2019; 4. Kimura H et al. Sleep. 2019;42(suppl 1):A23.

*FDA approved to treat excessive sleepiness associated with narcolepsy.
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Traditional Stimulants

Methylphenidate

- Methylphenidate hydrochloride—Concerta®, Ritalin*, Daytrana®, Metadate CD®*, Methylin®*; IR and ER: 5–60 mg/day
- Dexmethylphenidate—Focalin®: IR and XR: 5–20 mg/day

Amphetamines

- Dextroamphetamine—Dexedrine®*, Dextrostat®*: 5–60 mg
- Methamphetamine—Desoxyn®; 10–60 mg/day
- Lisdexamfetamine—Vyvanse®
- Mixed amphetamine salts—Adderall®; IR* and XR; 5–40 mg

*FDA Indicated for narcolepsy

IR = immediate release; ER and XR = extended release.

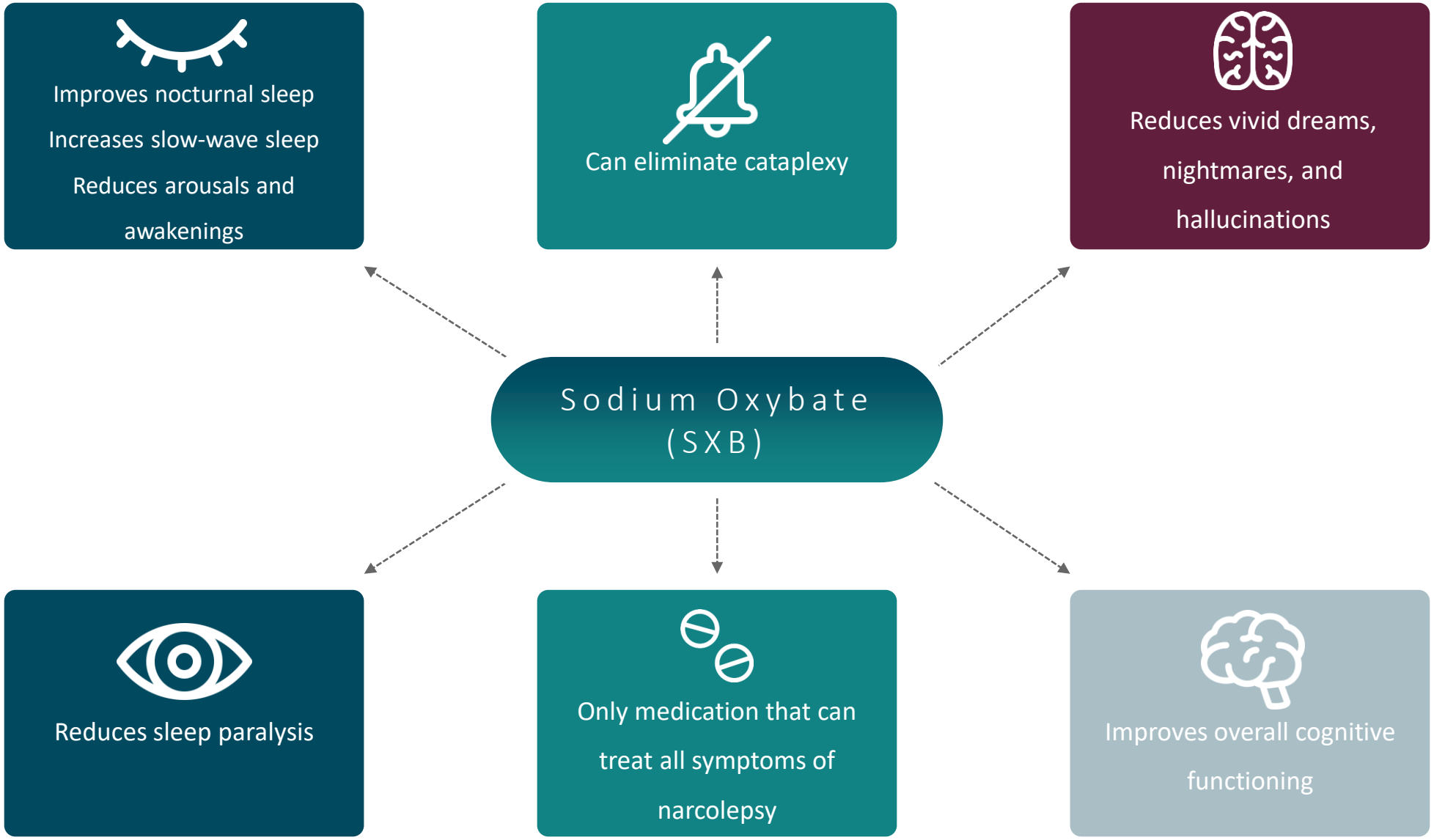
Predominantly dopaminergic

Retrospective analysis (n=1,529) of the use of antihypertensive medications
Patients taking modafinil required new or increased use of antihypertensive medications (2.4%) vs patients taking placebo (0.7%)

Increased monitoring of BP may be appropriate

Decreases ethinylestradiol therefore an alternative non-hormonal contraceptive method advised

Potential for serious allergic reactions


Improves nocturnal sleep
Increases slow-wave sleep
Reduces arousals and awakenings
Can eliminate cataplexy
Reduces vivid dreams, nightmares, and hallucinations
Sodium Oxybate (SXB)
Reduces sleep paralysis
Only medication that can treat all symptoms of narcolepsy
Improves overall cognitive functioning

Sodium Oxybate (SXB)

First-line drug for treatment of narcolepsy

Split dosing according to clinical situation

- 2 doses per night
- Varying initial and subsequent dose amounts depending on clinical situation

At 6–9 g/night, sodium oxybate contributes 1100–1640 mg to daily sodium intake

Sleep, Sodium, and CVD

Sodium Oxybate Impact on Cardiometabolic Risk

Consequences of excessive sodium intake

- Fluid retention
- Heart failure
- Hypertension
- Stroke
- Cardiomyopathy
- Renal disease

AASM practice parameters: sodium oxybate is a standard of care for the treatment of cataplexy, EDS, and disrupted nighttime sleep in patients with narcolepsy1

FDA approved for the treatment of cataplexy and EDS in patients ≥7 years with narcolepsy2

At 6–9 g/night, sodium oxybate treatment contributes 1,100–1,640 mg to daily sodium intake2

The American Heart Association recommends total daily sodium intake of <1,500 mg/day as ideal and 2,300 mg/day as the upper limit3

The National Academy of Sciences established a threshold of 2,300 mg/day above which reductions in sodium intake are expected to reduce chronic disease risk4

1. Morgenthaler TI, Kapur VK, Brown T et al [published correction appears in *Sleep*. 2008 Feb 1;31] *Sleep*. 2007;30(12):1705-1711.; 2. Xyrem® (sodium oxybate) PI 2018; 3. https://www.heart.org/en/healthy-living/healthy-eating/eat-smart/sodium/effects-of-excess-sodium-infographic; 4. National Academies of Sciences, Engineering, and Medicine. 2019. Dietary Reference Intakes for Sodium and Potassium. Washington, DC: The National Academies Press. https://doi.org/10.17226/25353.

Low Sodium Oxybate [LXB]

- Calcium, magnesium, potassium, and sodium oxybates
- Previously known as JZP-258
- A novel oxybate formulation with the same active moiety as SXB but a unique composition of cations, resulting in 92% less sodium
  - **a reduction of 1013–1509 mg at a dose range of 6–9 g/night**
- Lower-sodium oxybate (LXB) approved 7/21/20; available Q4 2020.
  Approved for same indication as SXB with additional approval for Idiopathic Hypersomnia 8/2021

Solriamfetol – FDA Approved 3/21/2019

Dopamine norepinephrine reuptake inhibitor (DNRI)—Schedule IV

Half-life 7 hours, Tmax 2 hours

Contraindicated with MAOIs (monoamine oxidase inhibitors)

Renal excretion (95%): reduced dose in renal disease

Can cause increased BP and HR, no effect on QTc

Avoid use in unstable cardiovascular disease

No effect on cataplexy

No effect on oral contraceptives

Solriamfetol (Sunosi™) PI 2019 (http://pp.jazzpharma.com/pi/sunosi.en.USPI.pdf). Accessed 5/29/2020.

Thorpy MJ et al. Ann Neurol. 2019;85:359-370.

Pitolisant - FDA-Approved 8/14/19, Became Available 11/4/19

Dosing

Recommended dosage range: 17.8–35.6 mg once daily

Adjustments in patients with hepatic or renal impairment or poor metabolizers of CYP2D6

Contraindications

Patients with severe hepatic impairment

Warnings & Precautions

Increases QTc interval; avoid use in patients who:

Are taking other drugs that prolong QTc interval

Have risk factors for prolonged QTc interval

Pregnancy & Lactation

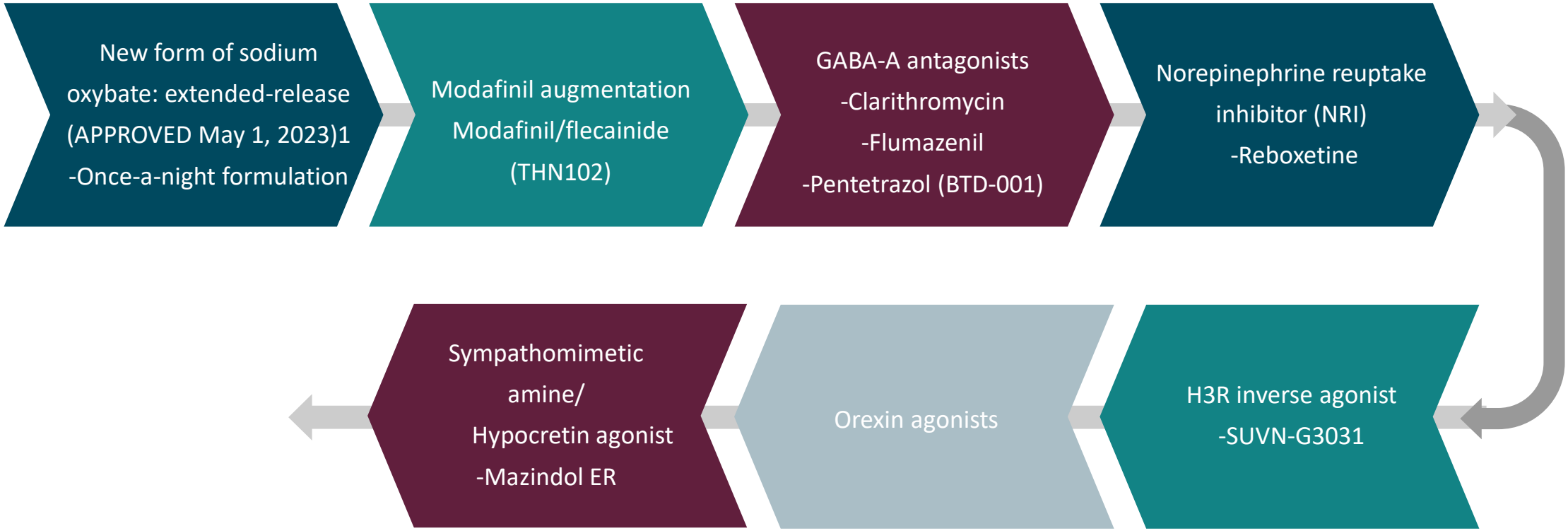
Unknown (present in rat milk)

Alternative non-hormonal contraceptive method during and for at least 21 days after discontinuation of treatment

- FDA approved for treatment of EDS in adults with narcolepsy
- Not controlled, not scheduled

Romigi A et al. Drug Des Devel Ther. 2018;12:2665-2675. Pitolisant (Wakix®) PI 2019 (www.accessdata.fda.gov/drugsatfda_docs/label/2019/0211150s000lbl.pdf). FDA drug approvals (www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2019). NCT03433131 (https://clinicaltrials.gov/ct2/show/NCT03433131?term=NCT03433131&draw= 2&rank=1). Accessed 5/29/2020.

Agents Under Investigation



1. FDA Product label https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/214755Orig1s000lbl.pdf

Summary

Sleep homeostasis is fundamental for health and survival.

Sleep disturbance increases cardiovascular, CNS* risk.

Excessive sleepiness increases cardiovascular risk.

Narcolepsy patients have co-morbidities including cardiovascular risks.

Orexin physiological effects have increasing importance in understanding state stability, autonomic regulation.

Medication alternatives allow consideration of patient targeted therapy.

Recognition and management of co-morbidities is part of care.

Future treatments will target hypocretin systems.

*CNS Central Nervous System

CASE Presentation: Narcolepsy Type 1

- 39-year-old female
- Onset of EDS age 15 years. Diagnosed age 24.
- History of excessive sleepiness ESS 19, frequent cataplexy, DNS, sleep paralysis, sleep/wake transition hallucinations, RBD.
- BMI 34
- BP 139/89
- Mild OSA
- Mild depression/anxiety
- Borderline metabolic syndrome

ESS Epworth Sleepiness Score 0-24
DNS disturbed nocturnal sleep
RBD REM behavior disorder
OSA obstructive sleep apnea

Narcolepsy Type 1 Current Medications

Sodium oxybate 4.5grams hs and 3.75 grams 4 hours later

Rescue IR amphetamine 10mg at noon prn

Solriamfetol 150mg q AM

Venlafaxine 75mg q AM

Oral steroidal contraceptive

Pitolisant 17.8mg q AM

Practical Strategies to Address the Impact of Increased Sodium Consumption on CVD Risk

Deborah J. Clegg, PhD, RD

Vice President for Research

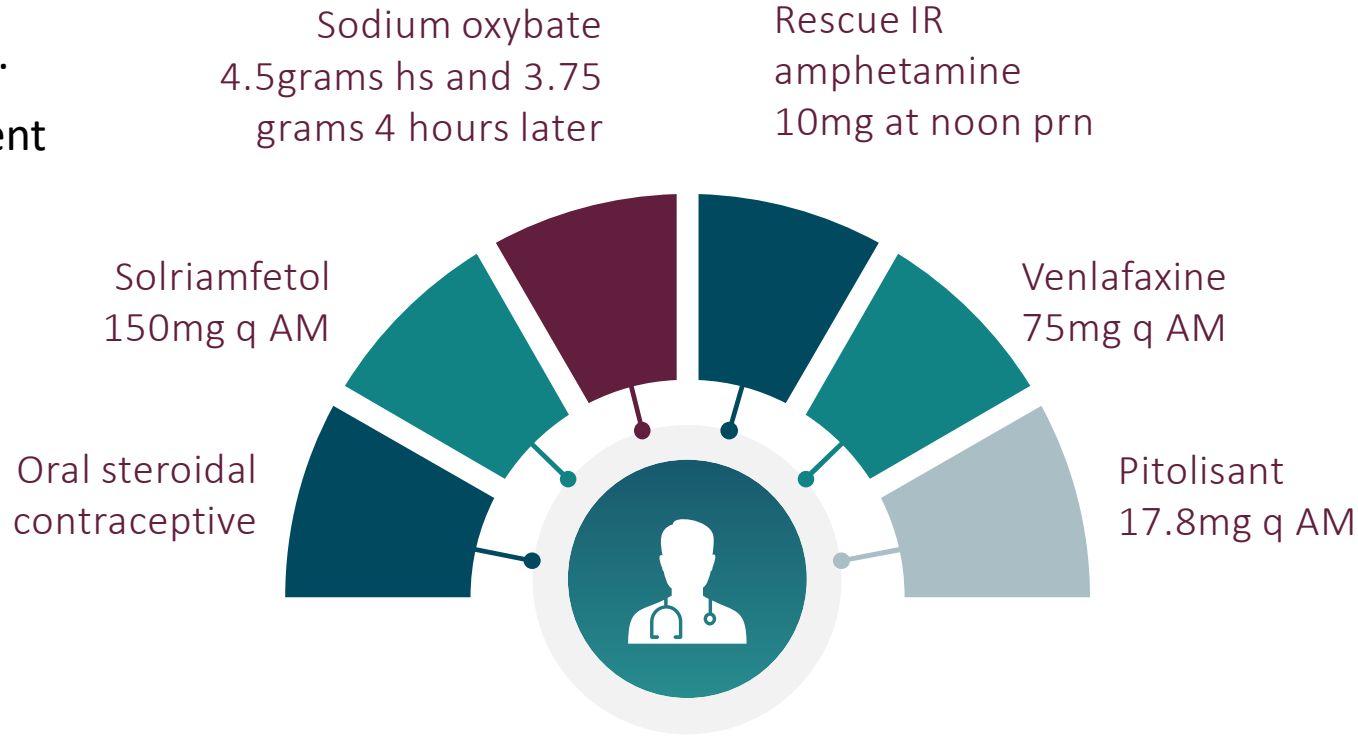
Professor, Internal Medicine

Texas Tech University Health Sciences Center

El Paso, TX

CASE Continuation: Narcolepsy Type 1

- 39 years female
- Onset of EDS age 15 years. Diagnosed age 24.
- History of excessive sleepiness ESS 19, frequent cataplexy, DNS, sleep paralysis, sleep/wake transition hallucinations, RBD.
- BMI 34
- BP 139/89
- Mild OSA
- Mild depression/anxiety
- Borderline metabolic syndrome



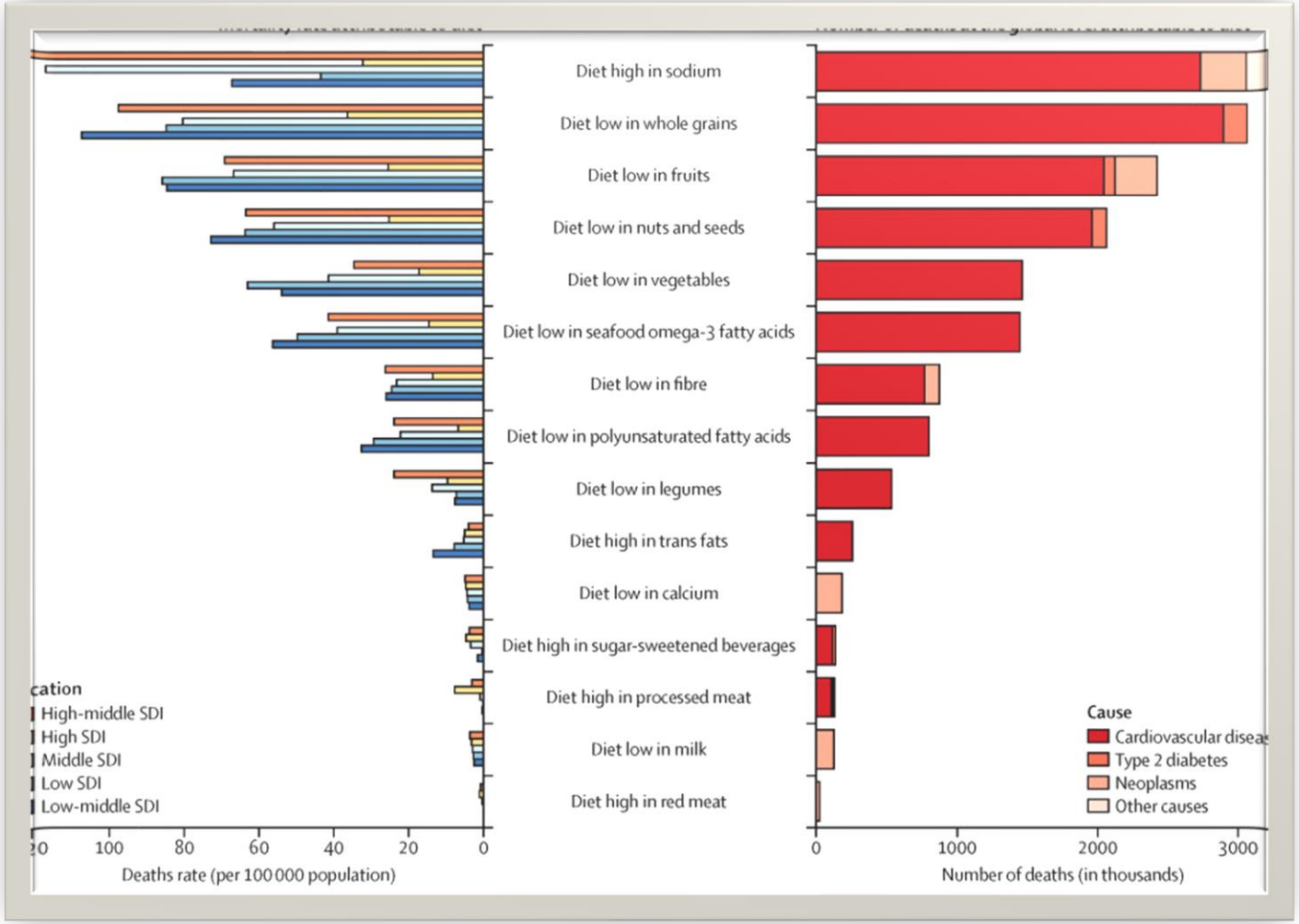
ESS Epworth Sleepiness Score 0-24
DNS disturbed nocturnal sleep
RBD REM behavior disorder
OSA obstructive sleep apnea

Her diet consists of processed foods for lunch and dinner due to time constraints

AGENDA

1. Challenge of addressing overall eating behaviors
2. Suggestions/advice as to how to reduce dietary intake of salt
3. Reducing the impact of commonly-used medications with high sodium content
4. Importance of considering total sodium intake when weighing treatment options
5. The impact of non-dietary sources of sodium: overview of medications used for narcolepsy and their sodium content

Mortality Associated with High Salt Intake



Sodium and Salt in the Diet

Sodium is a mineral our body needs to help control blood pressure and other functions in our body.

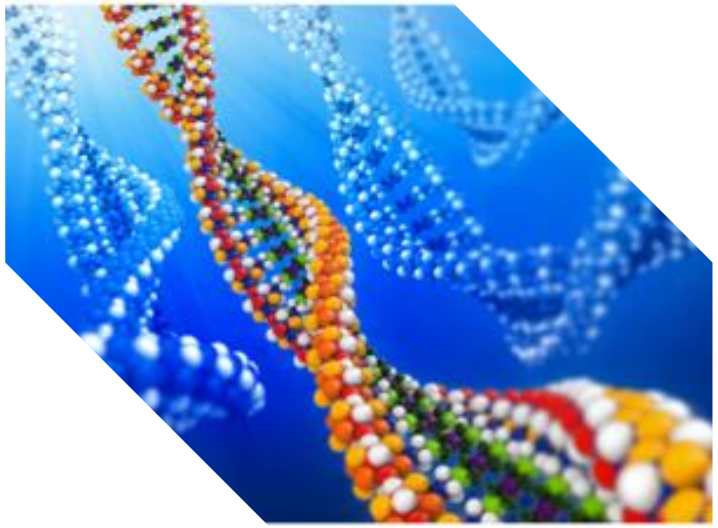
When we talk about salt, we are referring to the substance you add to dishes, which is a source of sodium.

By including salt in your diet, you are giving your body sodium to help it work properly.

Our bodies need only very small amounts of sodium.

One teaspoon of salt is equal to about 2,300 milligrams of sodium.

Current Dietary Intake of Sodium and K+



Mismatch between the modern diet introduced over the last 10,000 years, and the nutritional requirements encoded into the human genome, which developed over the several million years from the Stone age[1]

K+ intake of prehistoric man was estimated to be 15,000 mg/day[2]

Diet has shifted from:

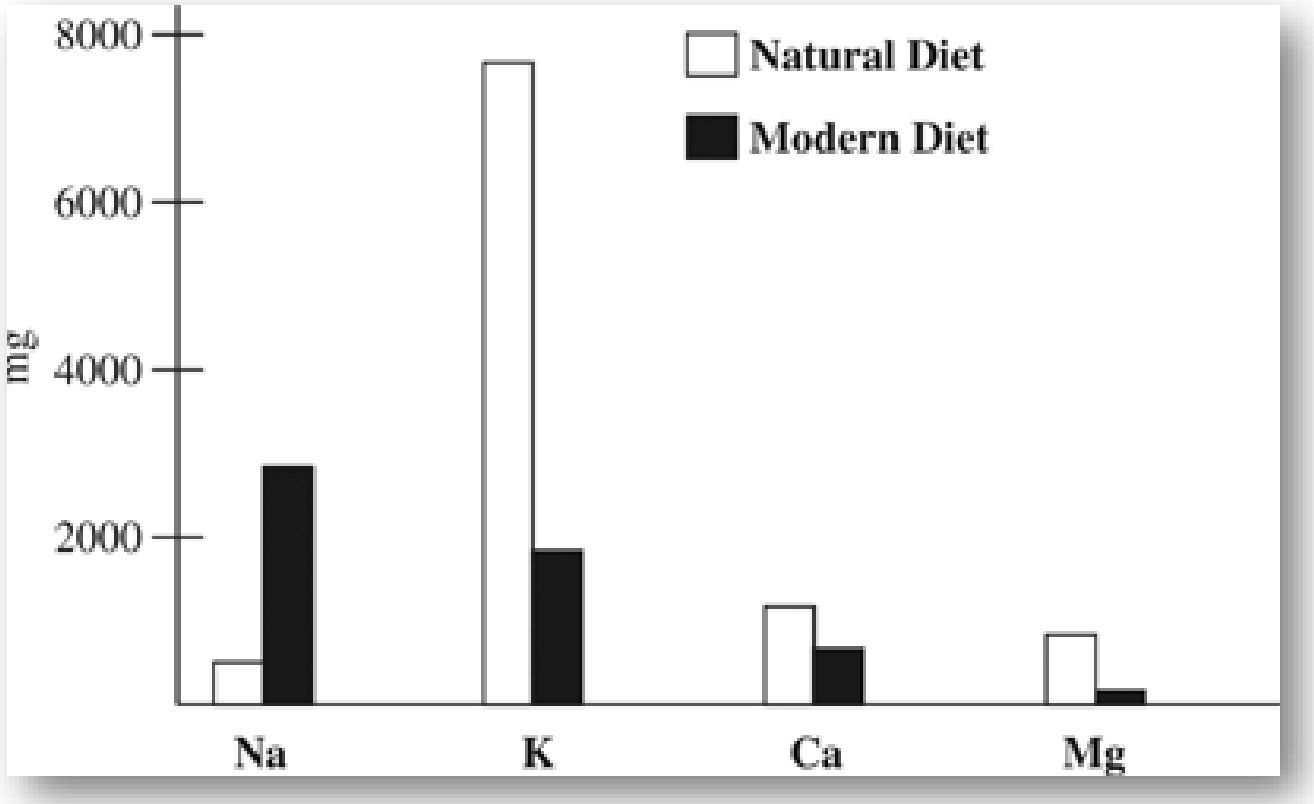
HIGH K^+ ➡ LOW Na

to

LOW K^+ ➡ HIGH Na

1. Milne G. Archaeology International 2015;18:84–96; 2. Palmer BF, Clegg DJ. Mayo Clin Proc 2016;91:496–508

Dietary ‘Evolution’



Potassium and Sodium: Yin – Yang

Low K+ intake reduces sodium excretion:

-K+ deficiency effects WNK (With-No-Lysine) kinase pathway

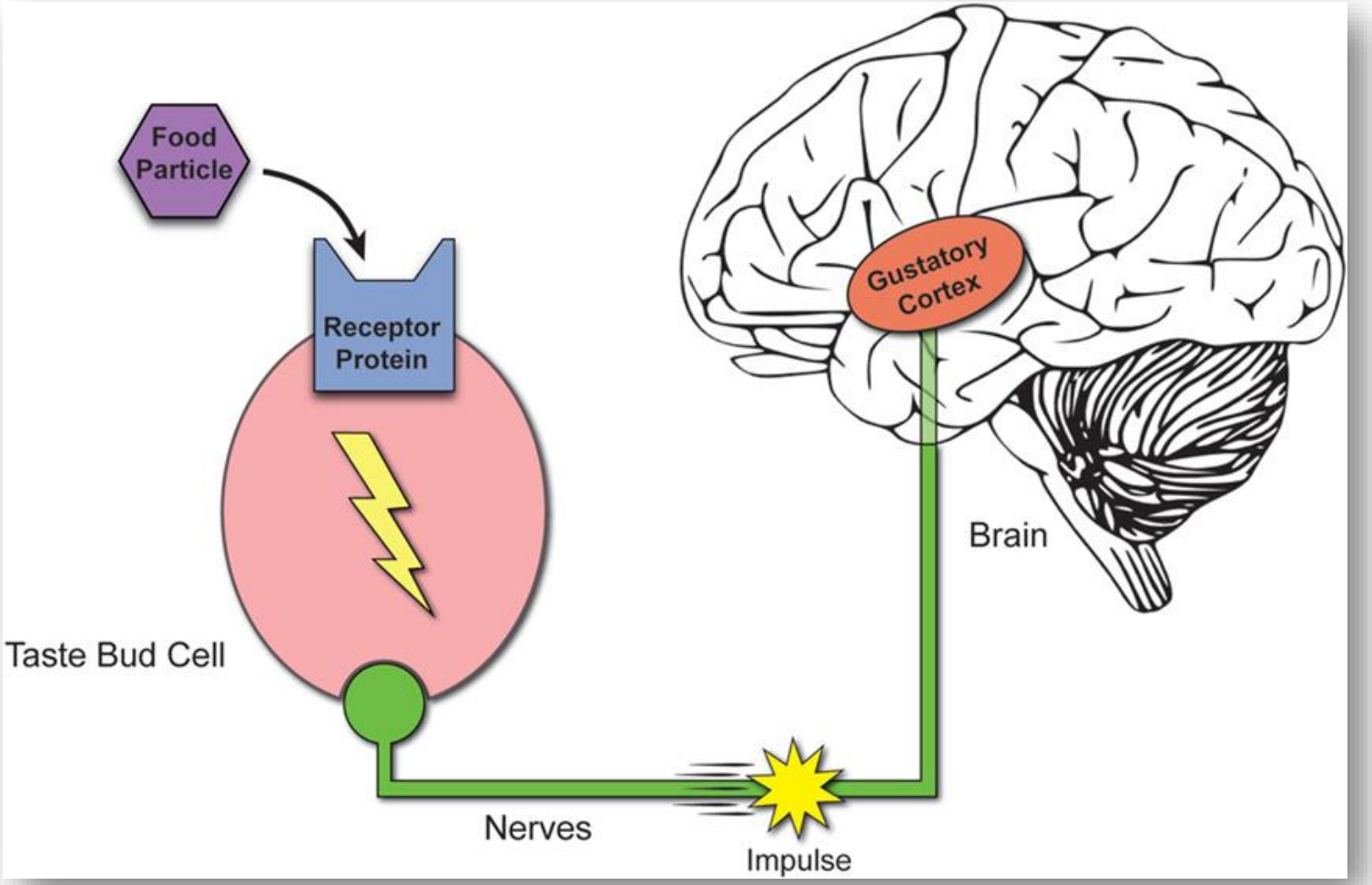
-activates the thiazide-sensitive NaCl cotransporter

High K+ intake increases sodium excretion

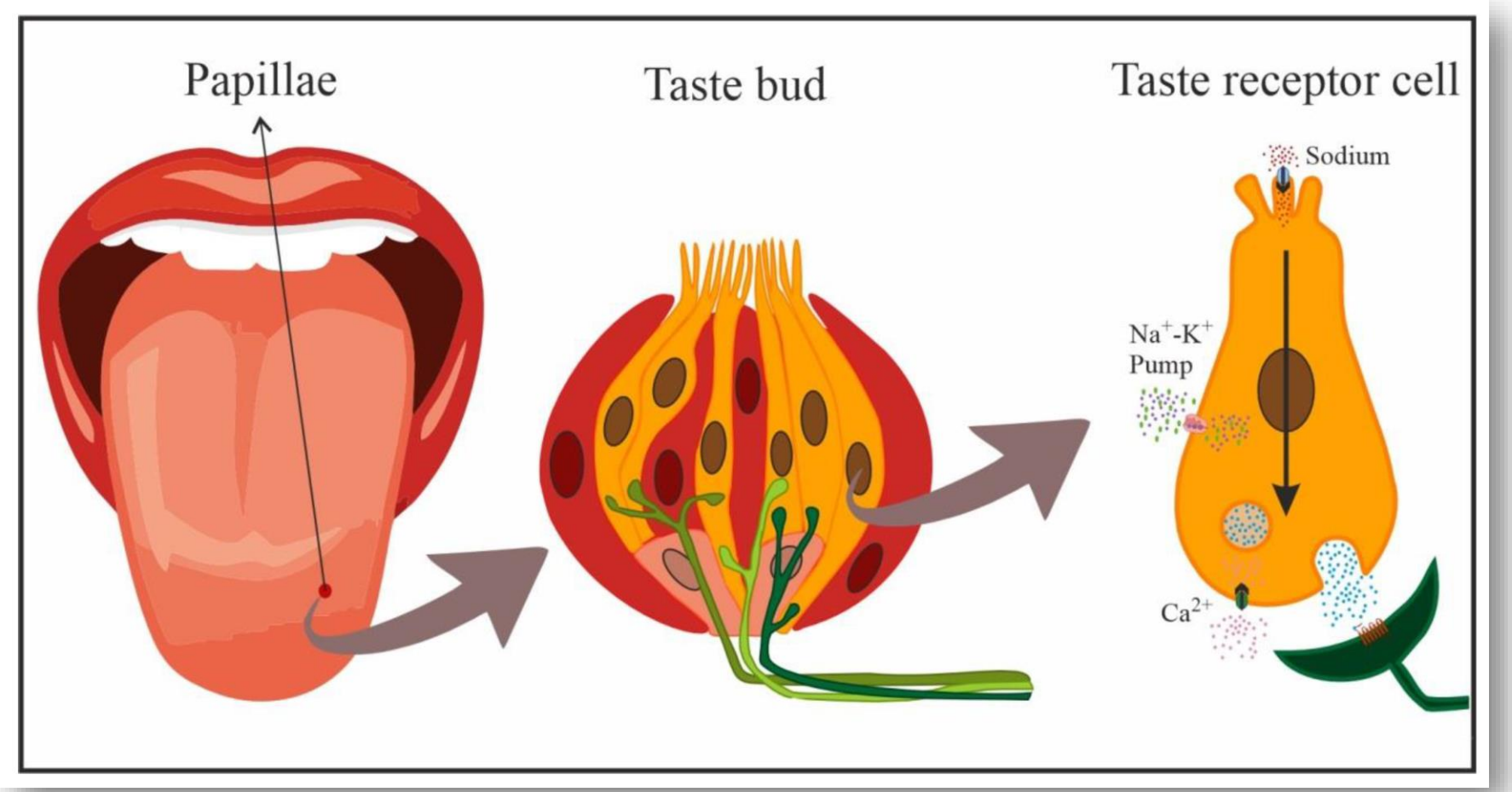
Potassium "sensing" via basolateral K+ channels in the distal convoluted tubule plays a key role in these pathways

Terker AS, et al. Cell Metab. 2015;21:39; Palygin O, et al. JCI Insight. 2017;2(18):e92331.

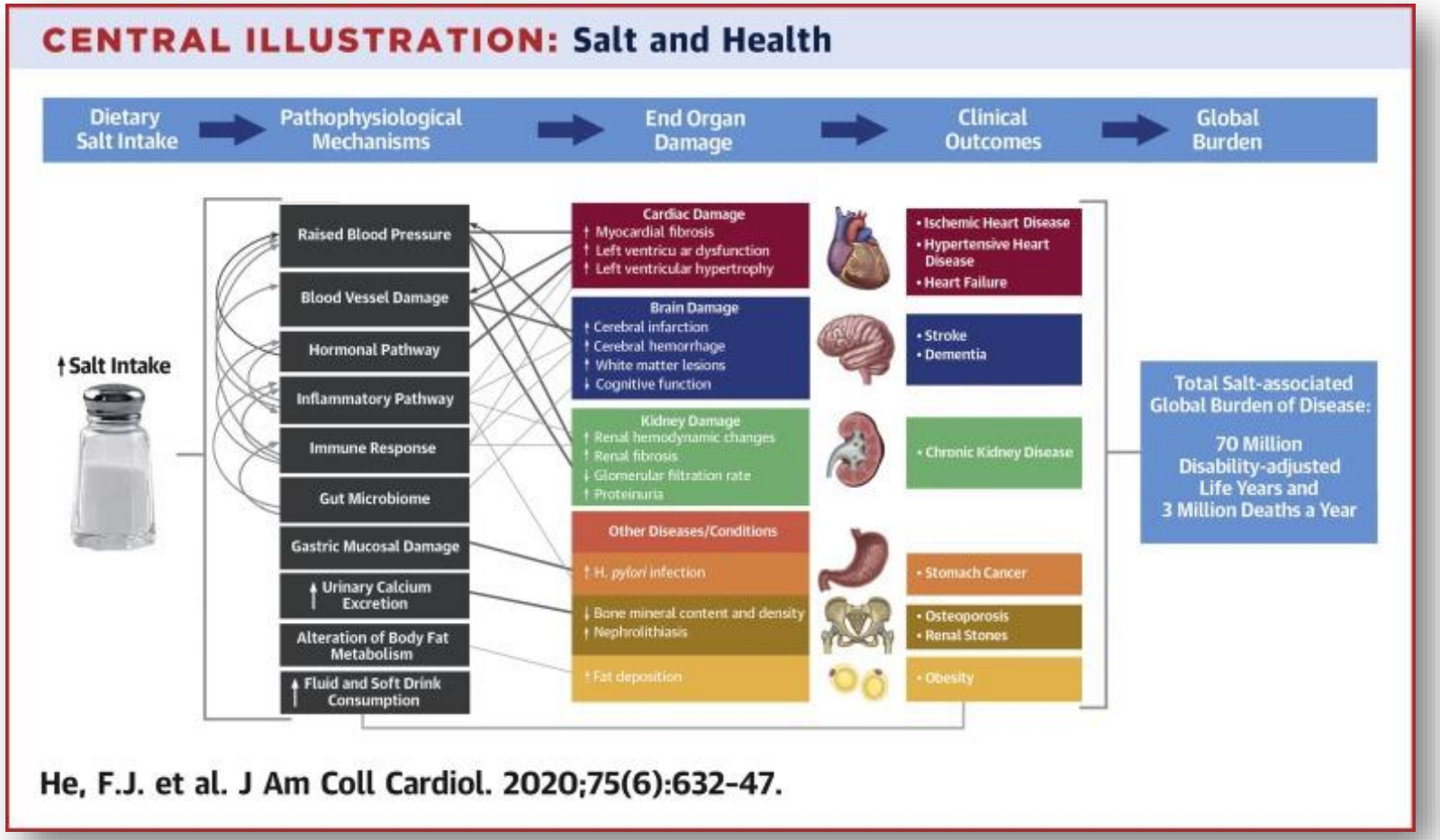
Sodium ‘Pleasure’ is a ‘Learned Response



Sodium is ‘Sensed’ on the Tongue



Sodium Intake Recommendations



Food Labels List Sodium Content

Critical to Know HOW to Read Food Labels

The serving size represents the typical amount eaten by an adult.

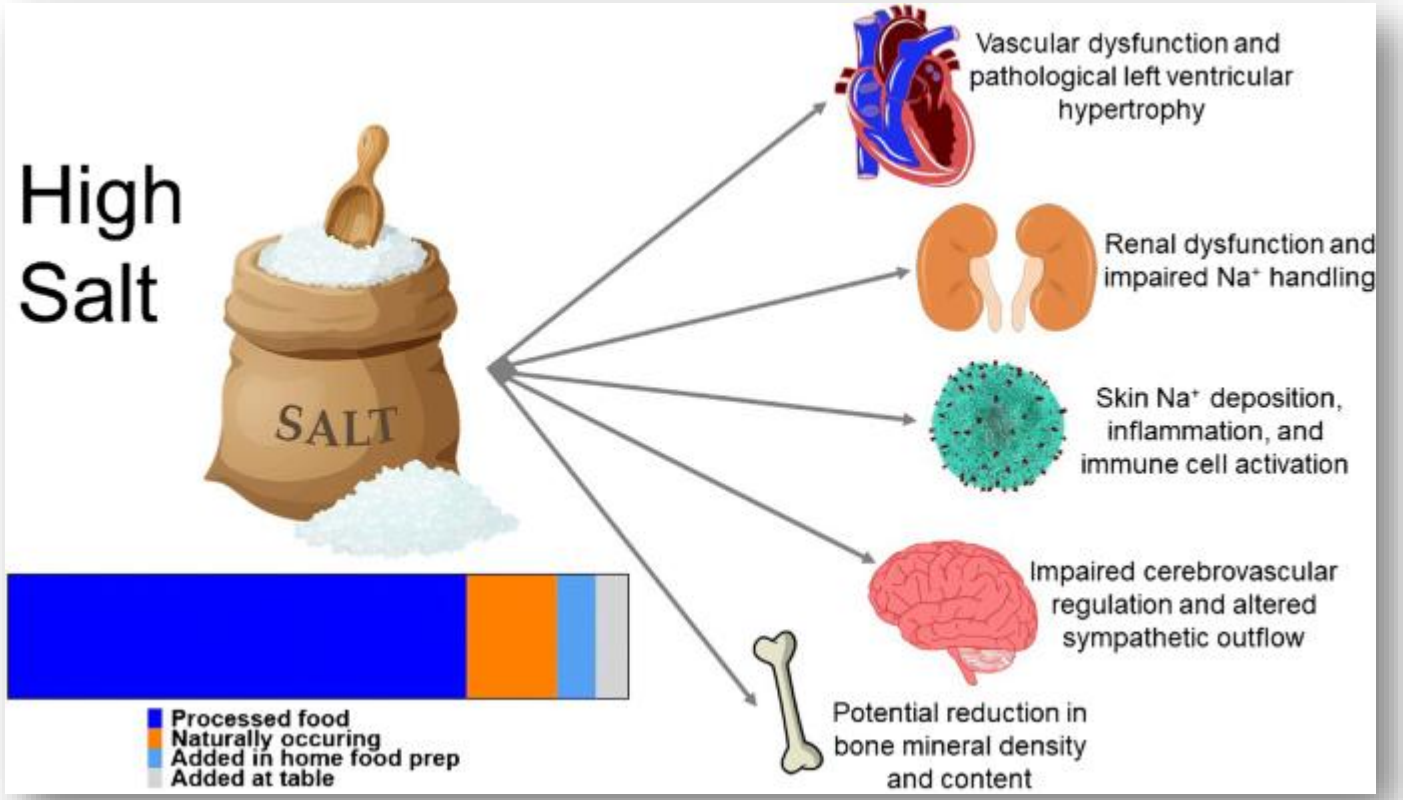
The sodium content is listed on the food label **per serving size**. Ignore the % daily value and focus on the amount of mg sodium per serving. Remember, if you eat more than one serving, you will get more sodium than the amount listed.

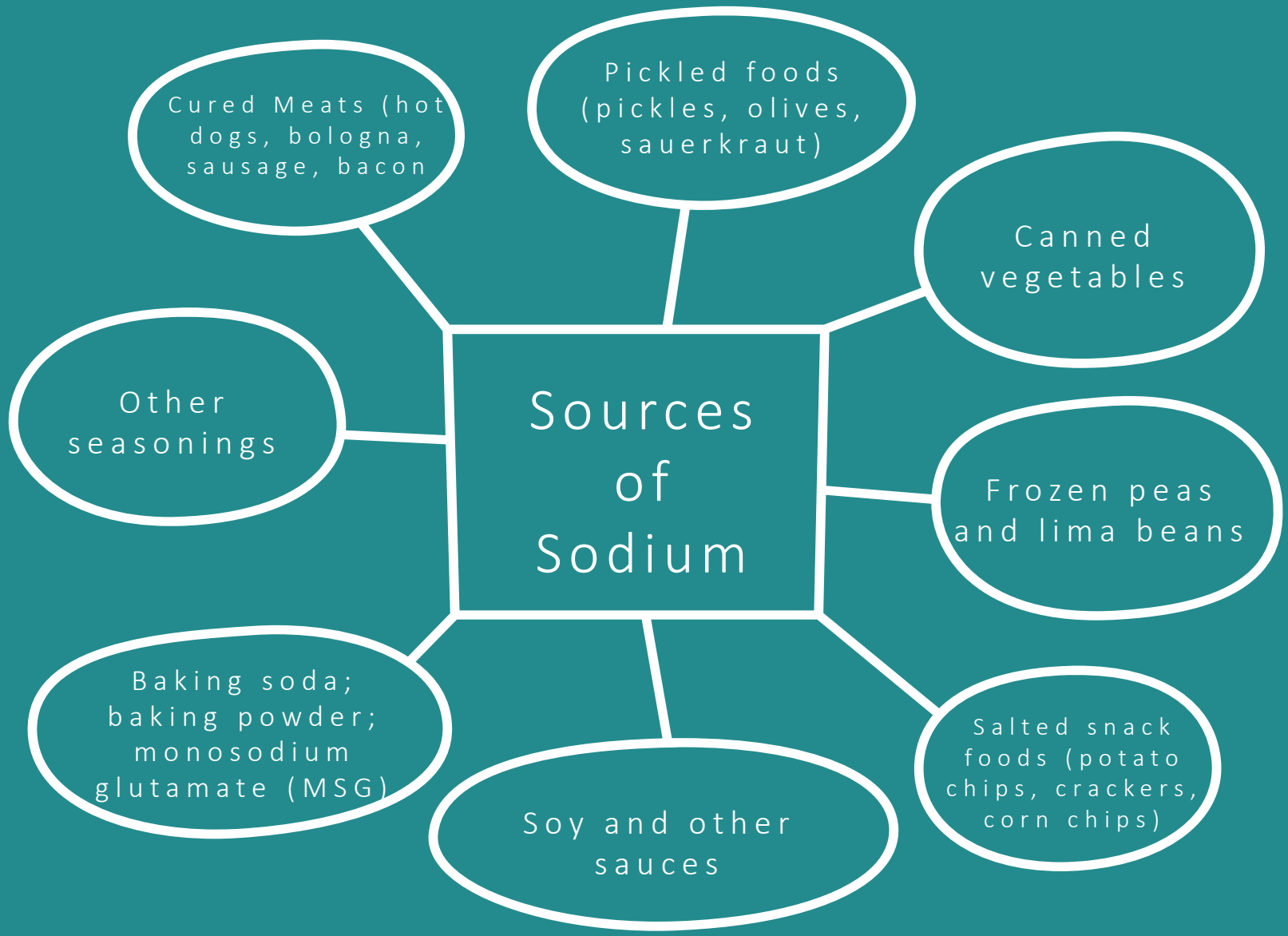
"Low sodium" = 140 mg or less per serving

"No sodium" = less than 5 mg per serving

Nutrition Facts			
Serving Size	1 cup (228 g)		
Servings per container:	2		
Amount Per Serving			
Calories			90
Fat Calories			30
			% Daily Value*
Total Fat	3g		5%
Saturated Fat	0g		0%
Trans Fat	0g		
Cholesterol	0mg		0%
Sodium	300mg		13%
Total Carbohydrate	13g		4%
Dietary Fiber	3g		12%
Sugars	3g		
Protein	3g		
Vitamin A	80%	Vitamin C	60%
Calcium	4%	Iron	4%
*Percent Daily Values (DV) are based on a 2,000 calorie diet. Your daily values may be higher or lower, depending on your calorie needs.			

Sources of Sodium in Our Diets




Sources of Sodium
Cured Meats (hot dogs, bologna, sausage, bacon
Pickled foods (pickles, olives, sauerkraut)
Canned vegetables
Other seasonings
Frozen peas and lima beans
Baking soda; baking powder; monosodium glutamate (MSG)
Soy and other sauces
Salted snack foods (potato chips, crackers, corn chips)

Processing of Foods Adds Sodium

Processing Adds Sodium

1 oz. hard cheese
176 mg sodium

1 oz. processed cheese
407 mg sodium

Hypertension CANADA

Why is Sodium Added to Foods?

To Enhance Flavor

- Adds a salty taste
- Boosts flavor balance and can enhance the sweetness of sugary items
- Masks bitterness
- Makes some types of processed food more palatable

To Preserve Freshness

- Increases shelf life
- Helps prevent growth of bacteria and other disease-causing agents

To Improve Texture & Appearance

- Makes the product seem thicker or fuller
- Enhances color and hue
- Helps retain moisture in processed meat products
- Stabilizes texture, allowing bread to risk and cheese to stick together
- Prevents unwanted chemical changes to other ingredients in many baked items

Sodium Additives in Processed Food

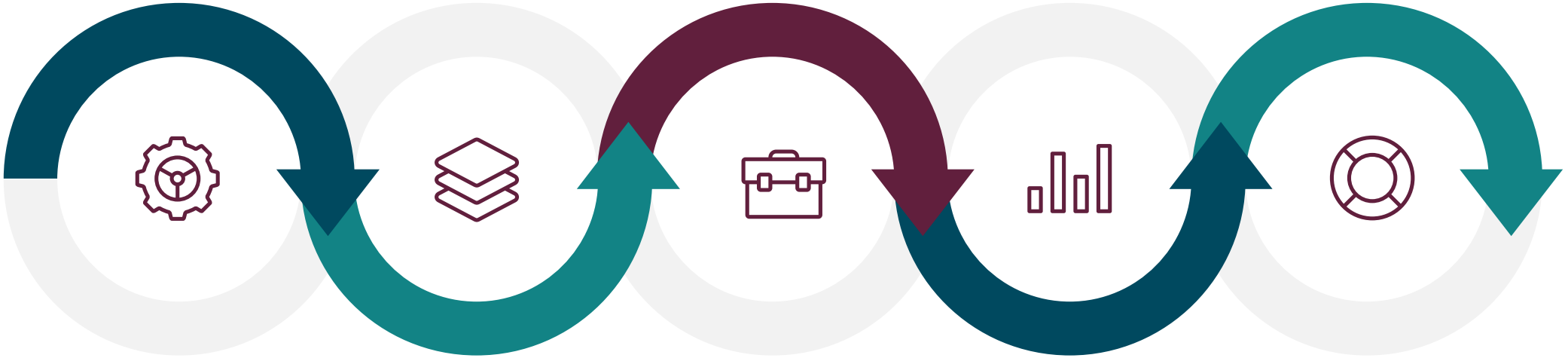
Bread, chips (snacks), processed meats, unprocessed meats, wine, processed juices.

Stabilizers, preservation, altering texture, improvement of flavor.

Dietary Recommendations for a Low Sodium Diet

A sodium restricted diet should be treated as you would treat any prescription medication.

A low sodium diet is a 2000mg diet and is the most commonly ordered. This is approximately ½ of the recommended daily intake.

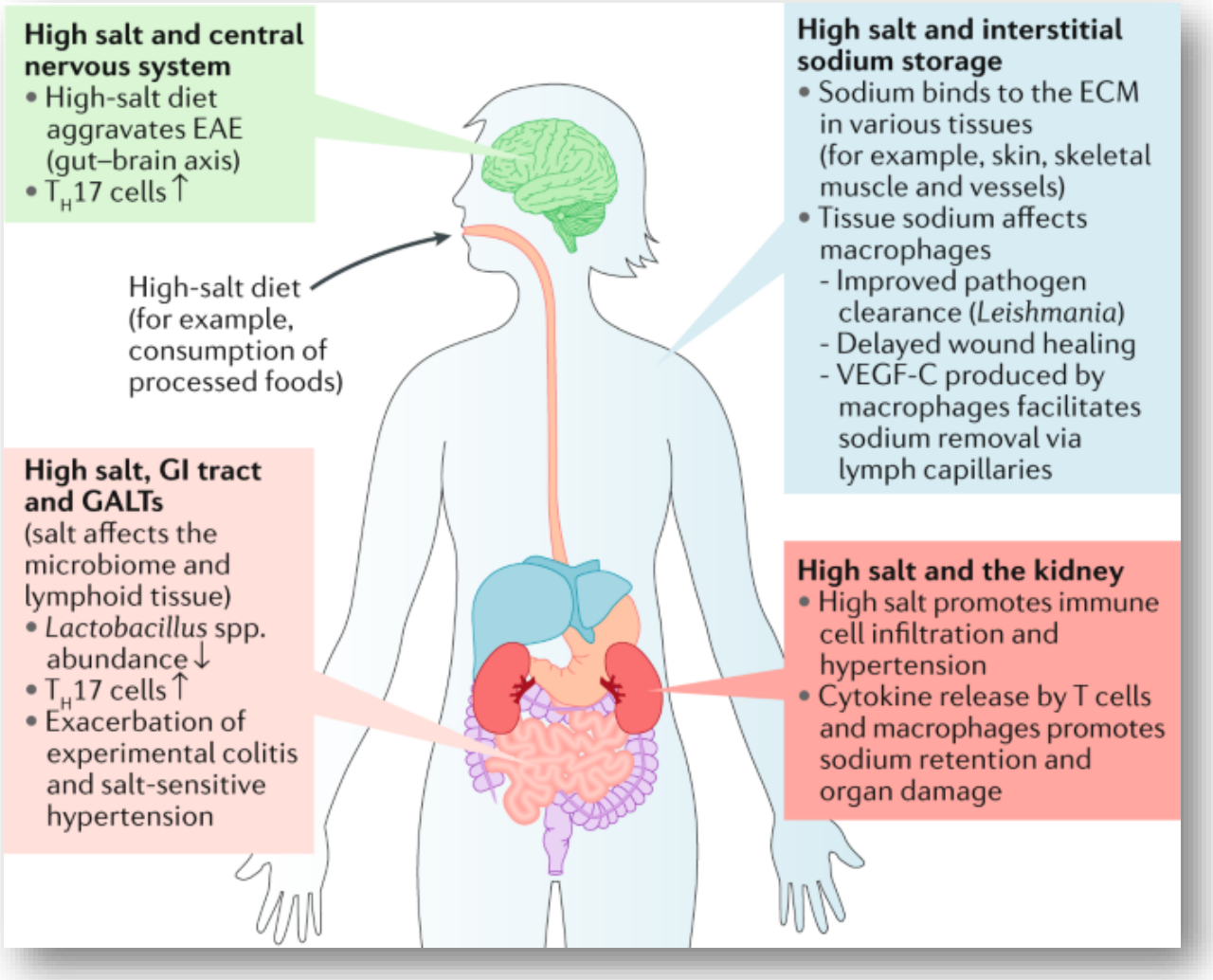


Maintaining a sodium restricted diet.

The amount of sodium will be prescribed in milligrams.

One teaspoon of salt contains approximately 2000mg of sodium.

Health Benefits of a Low Sodium Diet



Suggestions/Advice for Reducing Dietary Sodium

Acids can make dishes go from dull and boring to exciting and more flavorful.

Before you reach for the salt, try adding an acid.

Like salt, acid can increase flavor. It can also bring out more flavors than salt.

Other acids include juice of citrus fruits like lemons, limes and oranges.

Different types of acids that can be used in cooking include vinegars, tomatoes and wine.

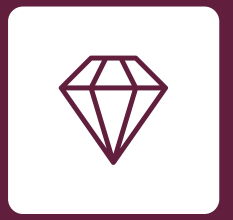
If using acid to increase flavor in a dish, add a splash of vinegar, wine or some tomatoes at the beginning of cooking, and add a splash of citrus juice at the end of cooking.

Suggestions/Advice for Reducing Dietary Sodium

Skipping the breadbasket.

- Breads add a lot of sodium to our diet because we eat a lot of it.
- Breads don't taste salty, so we may not know how much sodium we are eating.

Avoiding menu items that have a lot of cheese or include processed meats, such as bacon, ham and salami.



Avoiding foods that are pickled or smoked.

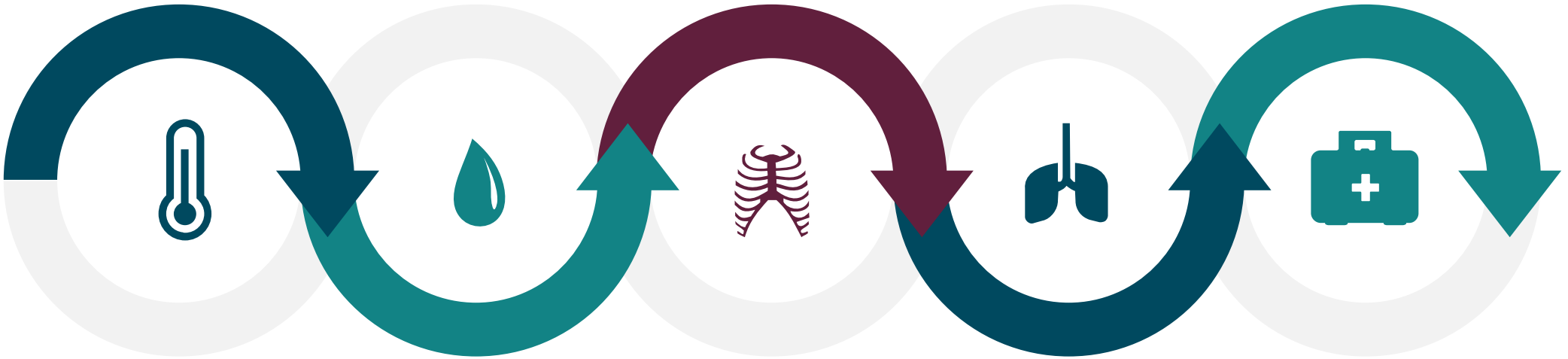
- Smoked foods are often high in sodium because of the marinades (acidic sauce), rubs (blend of spices) and brines (water with salt) that are used before the meat or fish is smoked.

What About ‘Other’ Forms of Sodium?

Does Himalayan salt raise sodium levels?

Some people believe that pink Himalayan salt is lower in sodium than regular table salt. However, both types consist of approximately 98 percent sodium chloride. As pink salt often has larger crystals than table salt, it technically contains less sodium per teaspoon.

Dietary Salt and Sleep



Potential Barriers to Nutritional Therapy

- Patients and physicians often are not well-versed about food sources and content of sodium
- Diverse cultural and ethnic diets and lifestyles
- Low reimbursement rates and billing implementation may limit referral to nutritional therapy
- Communication challenges
- Patient time limitations and access to care
- Patient compliance and adherence to dietary adjustments