TOP 10 ARTICLES 2019

#1
Treating Delirium in the ICU

Delirium in the ICU

1) Common: occurs in 50-75% of ventilated patients

2) Associated with poor outcomes
   - increased mortality
   - longer time on mechanical ventilation
   - longer hospital stay
   - higher risk of long term cognitive impairment
   - higher care cost

Worldwide ABCDEF Survey

(Assessing Pain, Both Spontaneous Awakening and Breathing Trials, Choice of Drugs, Delirium monitoring/management, Early exercise/mobility, and Family Empowerment)

(Critical Care Medicine 2017)

Intensivists: 65% treat delirium with haloperidol

Intensivists: 53% use quetiapine or other atypical antipsychotic for delirium with agitation

FDA Approved Indications

haloperidol: schizophrenia; Tourette’s disorder

ziprasidone: schizophrenia; bipolar I disorder

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Haloperidol and Ziprasidone for Treatment of Delirium in Critical Illness

T.D. Girard, M.C. Exline, S.S. Carson, C.L. Hough, P. Rock, M.N. Gong, I.S. Douglas, A. Malhotra, R.L. Owens, D.J. Feinstein, B. Khan, M.A. Pisani, R.C. Hyzy, G.A. Schmidt, W.D. Schweickert, R.D. Hite, D.L. Bowton, A.L. Masica, J.L. Thompson, R. Chandrasekhar, B.T. Pun, C. Strength, L.M. Boehm, J.C. Jackson, P.P. Pandharipande, N.E. Brummel, C.G. Hughes, M.B. Patel, J.L. Stollings, G.R. Bernard, R.S. Dittus, and E.W. Ely, for the MIND-USA Investigators*

Girard TD et al. New Engl J Med 2018

Randomized, Double-Blind, Placebo-Controlled Trial

- conducted at 16 US medical centers
- enrolled adults in a medical or surgical ICU
  - invasive/noninvasive ventilation
  - vasopressors
  - intra-aortic balloon pump,
- goal to enroll subjects prior to onset of delirium and randomize to study group if delirium occurred
- delirious subjects enrolled with surrogate consent

MANY exclusion criteria:

severe cognitive impairment, high risk for medication side effects because of pregnancy, breast-feeding, a history of torsades de pointes, QT prolongation, a history of neuroleptic malignant syndrome, or allergy to haloperidol or ziprasidone; ongoing treatment with an antipsychotic medication; moribund state; rapidly resolving organ failure; were blind, deaf, or unable to speak or understand English; were incarcerated; and more…..

Subjects randomized to receive:

A. Haloperidol: 2.5 mg → 20 mg/day
B. Ziprasidone: 5 mg → 40 mg/day
C. Placebo

All received “ABCDE” treatment bundle (assess, prevent, and manage pain; both spontaneous awakening and breathing trials; choice of analgesia and sedation; assess, prevent, and manage delirium; and early mobility and exercise).

20,914 patients screened for eligibility

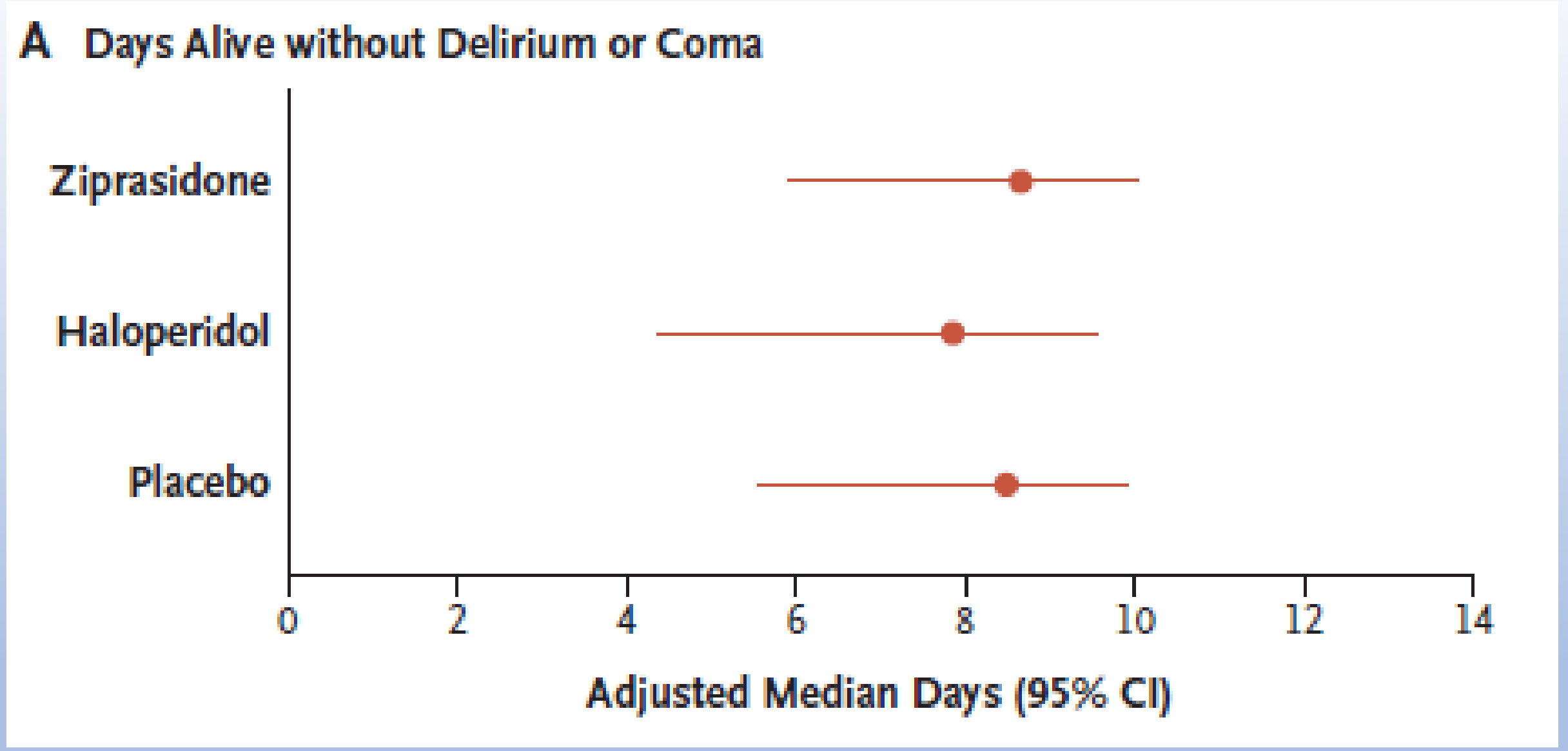
1183 provided written consent and enrolled

571 did not develop delirium

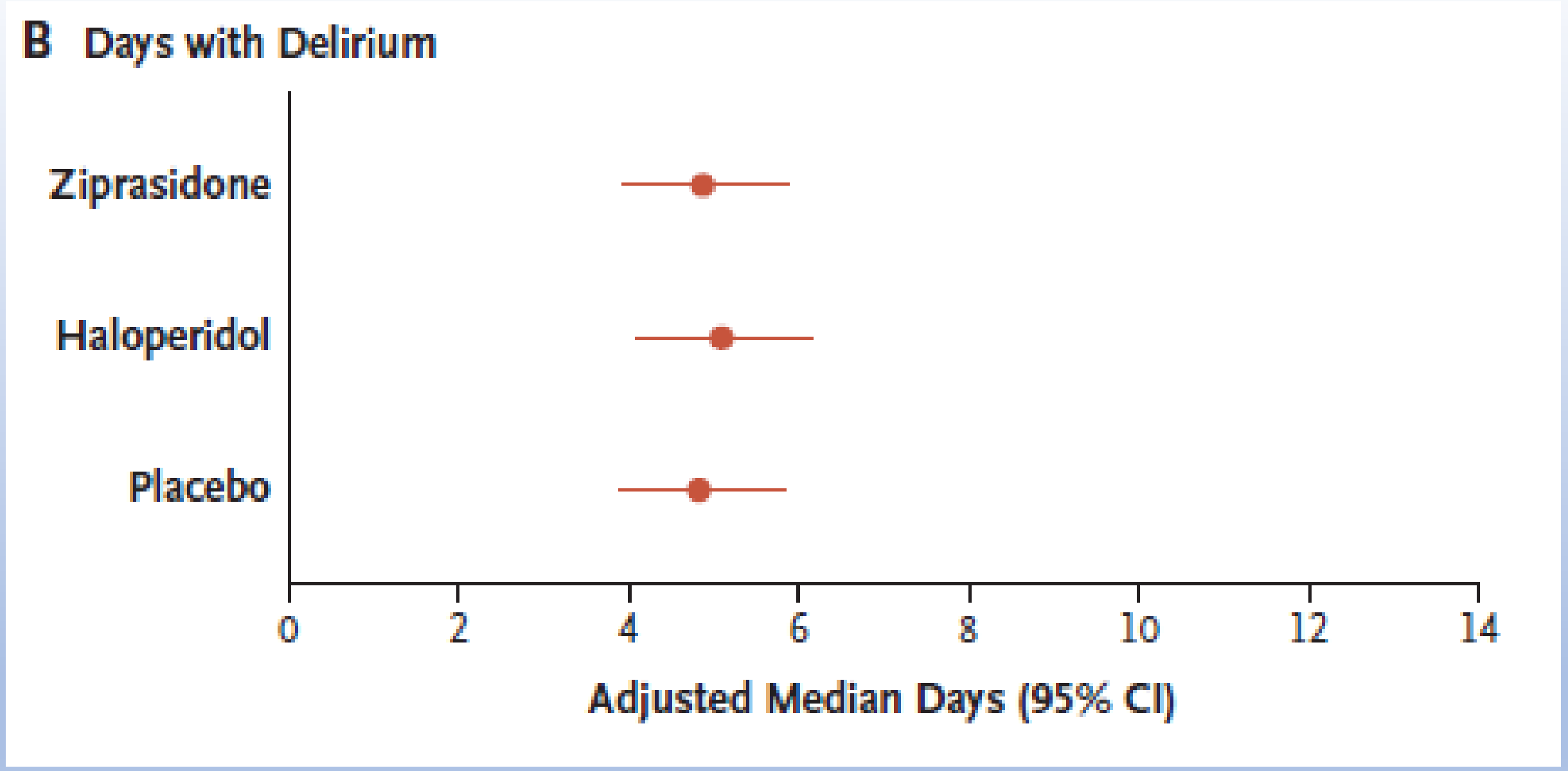
46 excluded for other reasons

566 Underwent randomization

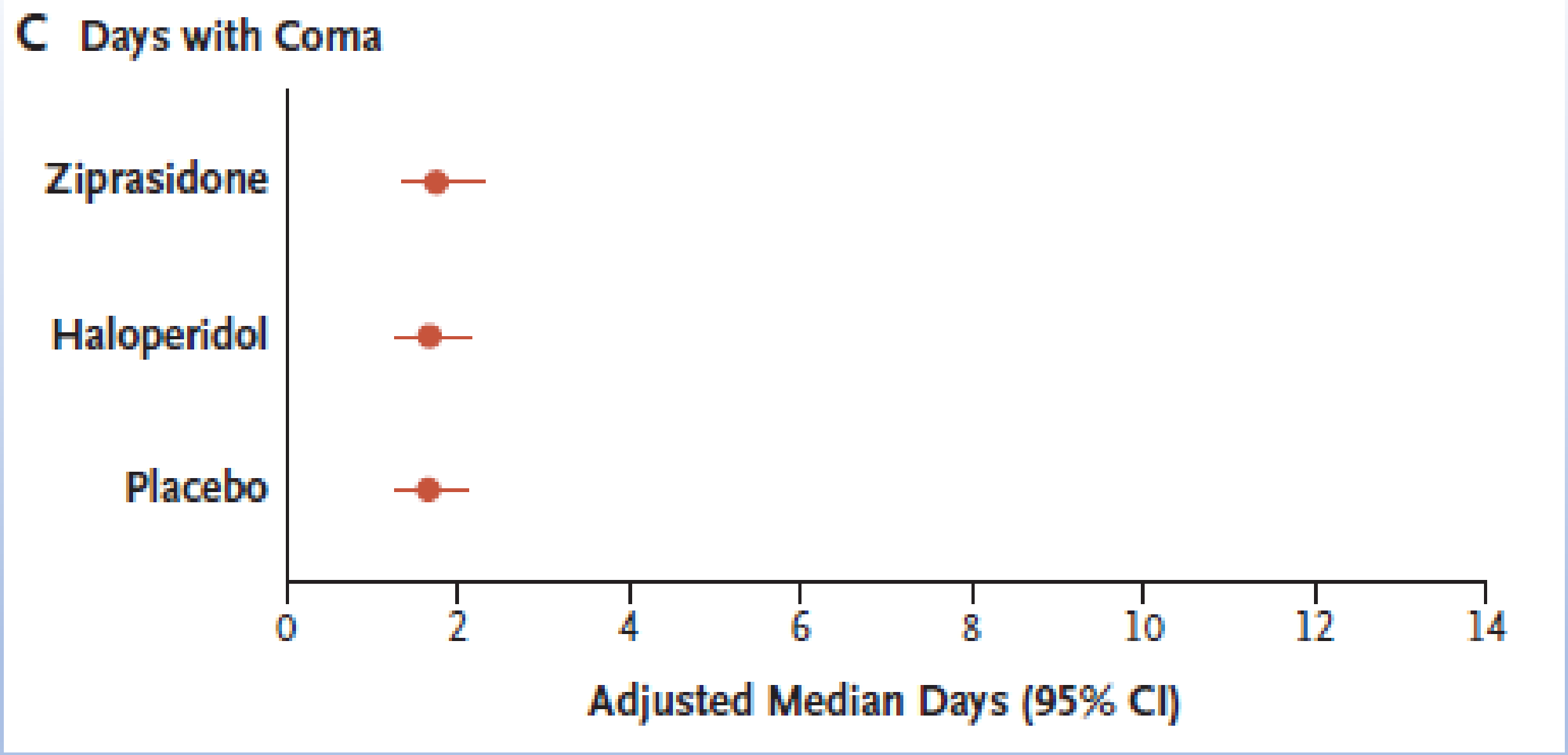
- hypoactive delirium 89%
- hyperactive delirium 11%
- median age 60 years



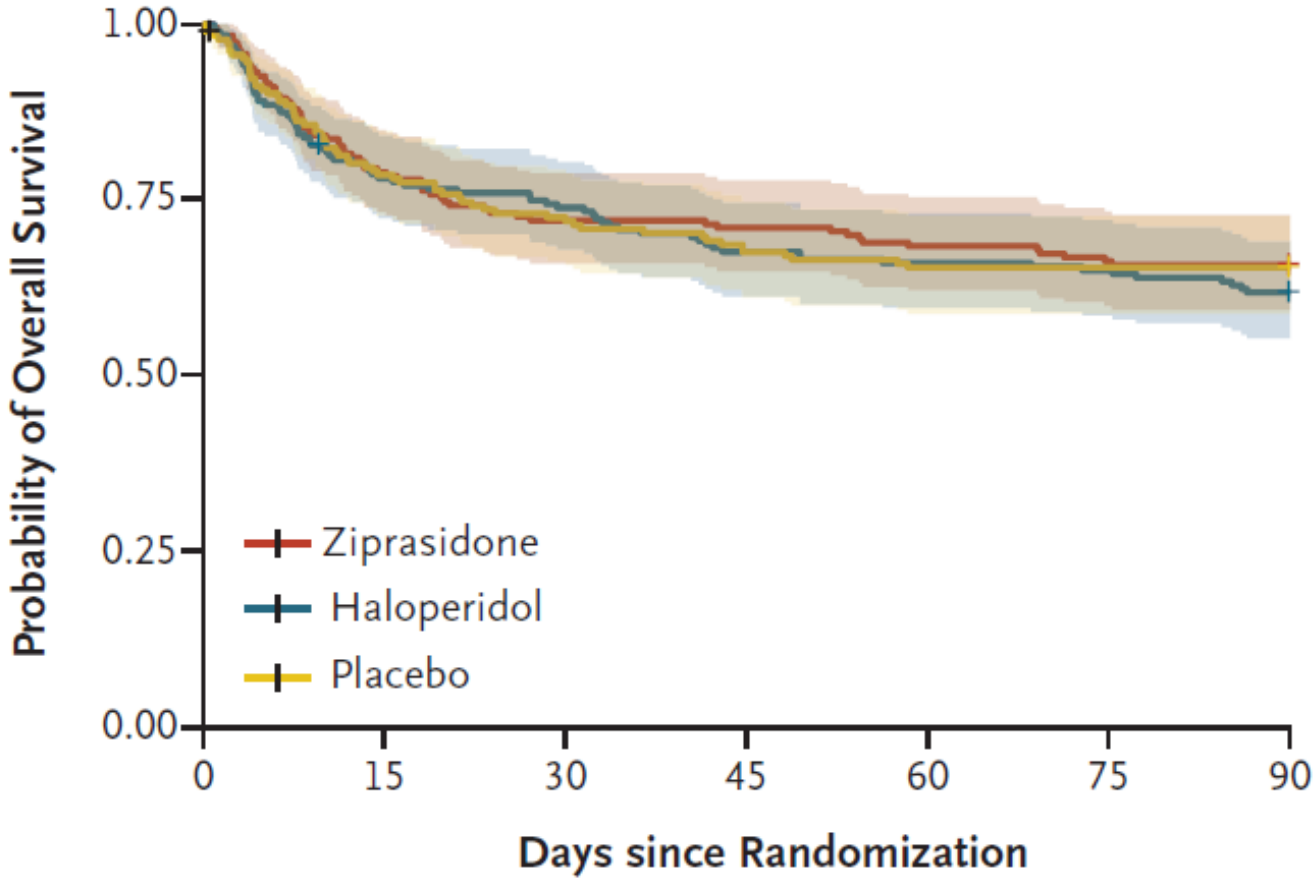
Girard TD et al. New Engl J Med 2018



Girard TD et al. New Engl J Med 2018



Girard TD et al. New Engl J Med 2018



No. at Risk (cumulative no. of deaths)

Ziprasidone	190 (0)	150 (40)	137 (53)	135 (55)	130 (60)	126 (64)	125 (65)
Haloperidol	192 (0)	149 (42)	141 (50)	129 (62)	126 (65)	124 (67)	118 (73)
Placebo	184 (0)	143 (39)	132 (50)	123 (59)	119 (63)	119 (63)	119 (63)

Figure 3. Effects of Haloperidol, Ziprasidone, and Placebo on 90-Day Survival.

Girard TD et al. New Engl J Med 2018

#2
Hepatocellular Carcinoma in Non-Alcoholic Fatty Liver Disease

Established major risk factors for HCC:

- excessive alcohol consumption
- hepatitis B and C
- 20-40% of HCC patients lack these risk factors

NAFLD has become leading cause of chronic liver disease in USA

- 20-30% of cases develop necrosis and fibrosis
- 10-20% of these develop cirrhosis
- risk of HCC due to NAFLD is conflicting in the published studies (variable size and quality of studies)

Gastroenterology 2018;155:1828–1837

Risk of Hepatocellular Cancer in Patients With Non-Alcoholic Fatty Liver Disease

Fasiha Kanwal,[1,2,3] Jennifer R. Kramer,[2,3] Srikar Mapakshi,[2,3] Yamini Natarajan,[1] Maneerat Chayanupatkul,[1] Peter A. Richardson,[2,3] Liang Li,[4] Roxanne Desiderio,[2,3] Aaron P. Thrift,[1,5,6] Steven M. Asch,[7,8] Jinna Chu,[2] and Hashem B. El-Serag[1,2,3]

[1]Section of Gastroenterology and Hepatology, Baylor College of Medicine and Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas; [2]Center for Innovations in Quality, Effectiveness and Safety, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas; [3]Section of Health Services Research, Department of Medicine, Baylor College of Medicine, Houston, Texas; [4]Department of Biostatistics, University of Texas MD Anderson Cancer Center, Houston, Texas; [5]Section of Epidemiology and Population Sciences, Baylor College of Medicine, Houston, Texas; [6]Dan L. Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, Texas; [7]Center for Innovation to Implementation, Palo Alto Veterans Affairs Medical Center, Palo Alto, California; and [8]Division of Primary Care and Population Health, Stanford University, Palo Alto, California

Kanwal F, Kramer JR, Mapakshi S et al. Gastroenterology 2018

Searched the VHA Corporate Data Warehouse (CDW) and Central Cancer Registry (CCR) to identify all patients with at least one visit to a VHA hospital between Jan 1, 2003 and Dec 31, 2011

Operational Definition of NAFLD:

- 2 or more elevated ALT values (alanine aminotransferase concentration ≥ 40 IU/ml for men or 31 IU/ml for women) more than 6 months apart.
- no positive serology for HBV or HCV
- no alcohol-related ICD 9 code
- no positive AUDIT-C score (alcoholism screening test)
- no evidence of rare chronic hepatitides

Operational Control Group Definition:

- had normal ALT test performed between Jan 1, 2004 and Dec 31, 2018
- did not meet definition of NAFLD
- did not have any other liver-related risk factors (HBV, HCV, + AUDIT-C, chronic rare hepatitides)

Identified 296,707 NAFLD patients and an equal number of controls matched for age, sex, index date of initial ALT test and duration of care within VA system

Randomly chose 150 NAFLD patients and 150 Control patients and reviewed EMR in detail to validate diagnosis of NAFLD or lack of NAFLD:

- PPV NAFLD 89%
- NPV NAFLD 98%

For NAFLD and Control groups, authors:

- Identified hepatocellular carcinoma cases in the CCR through histology codes and text searches. Verified by EMR review.
- Identified hepatocellular carcinoma cases in CDW inpatient and outpatient EMR using ICD-9 code.
- discordance between CCR and CDW settled by manual review.

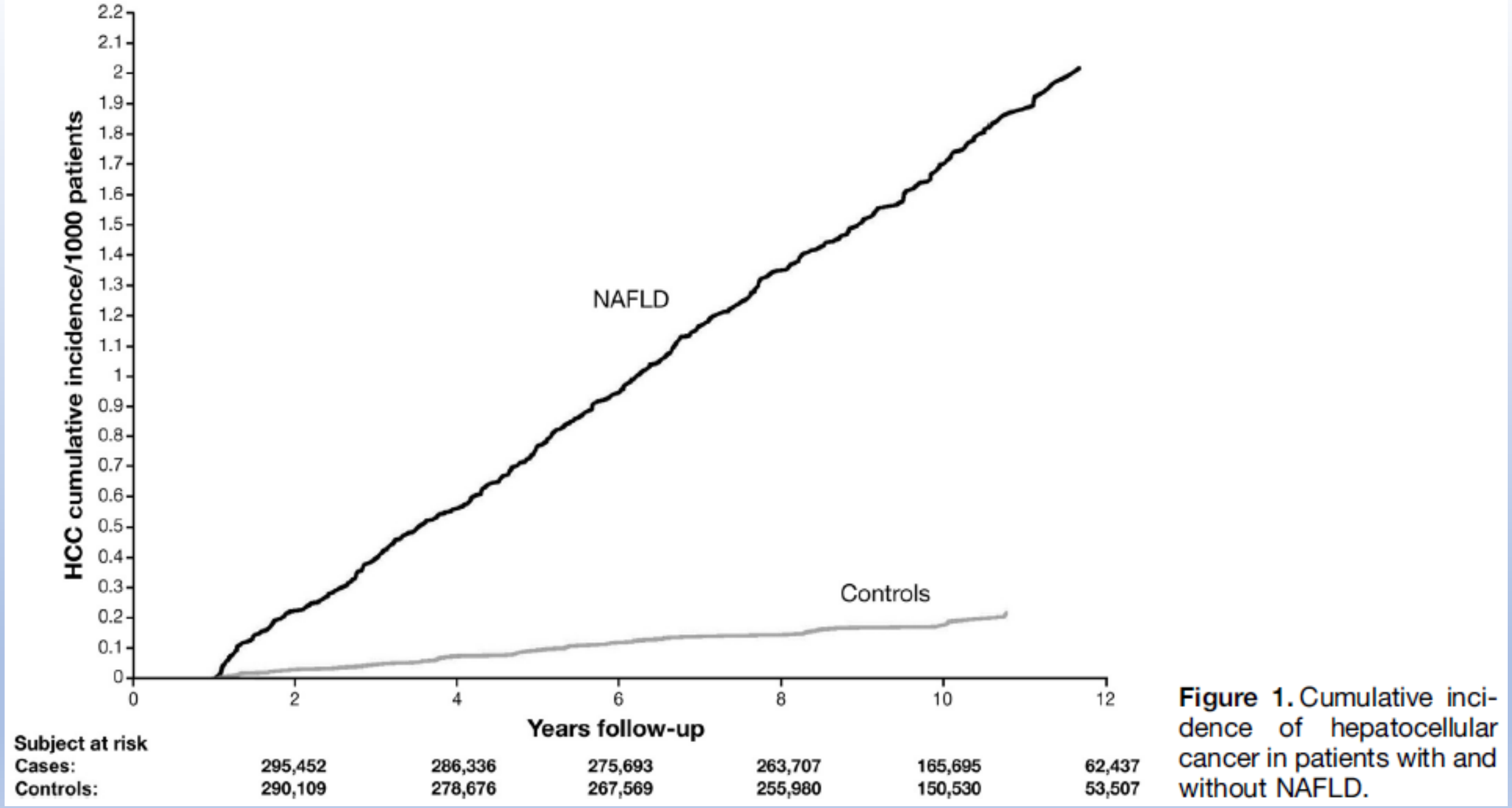


Figure 1. Cumulative incidence of hepatocellular cancer in patients with and without NAFLD.

Kanwal F, Kramer JR, Mapakshi S et al. Gastroenterology 2018

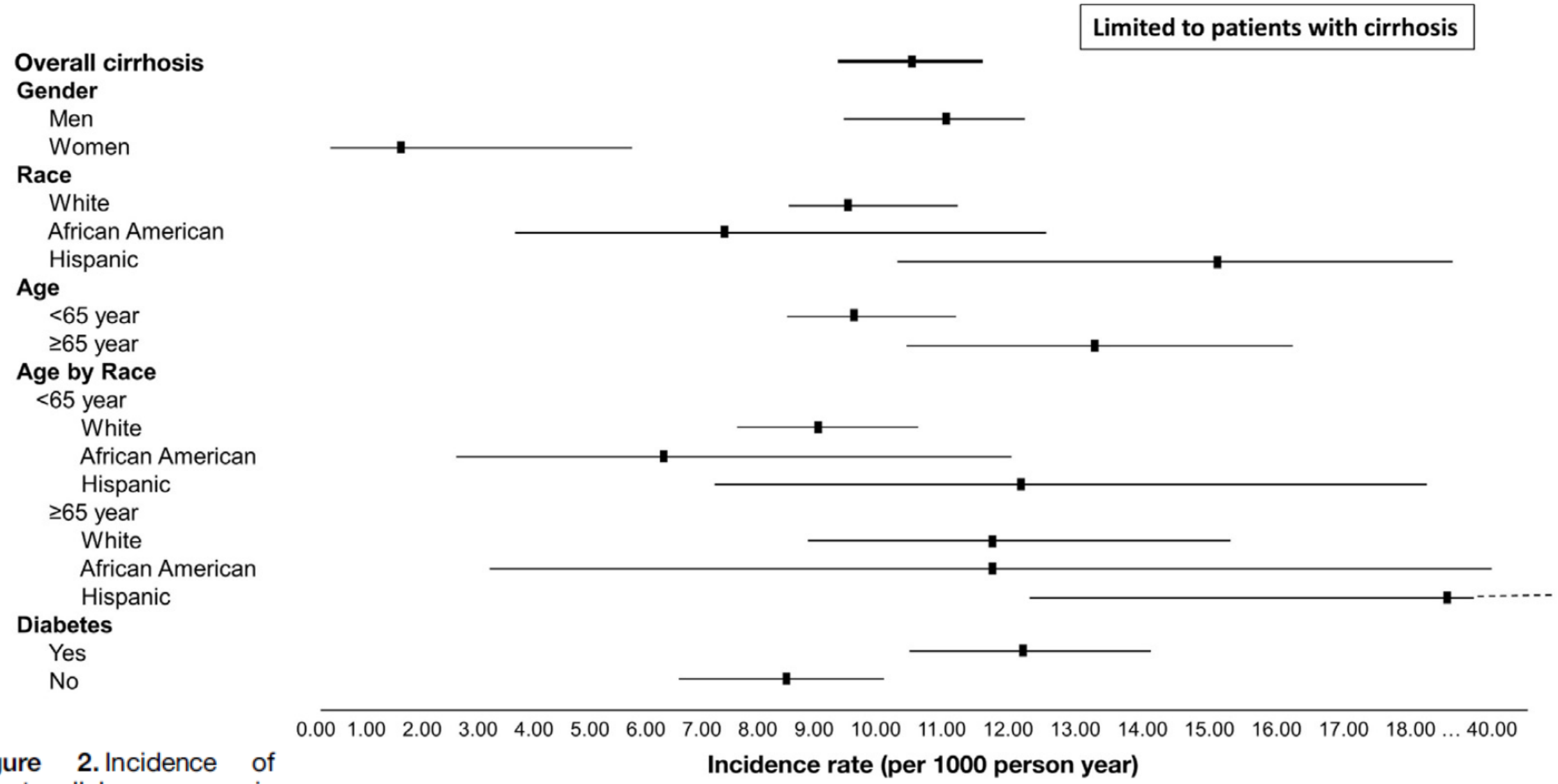


Figure 2. Incidence of hepatocellular cancer in different subgroups of NAFLD patients with cirrhosis.

Kanwal F, Kramer JR, Mapakshi S et al. Gastroenterology 2018

#3
Aspartame and Dementia

ASPARTAME

The effect of aspartame and its metabolites on brain chemistry has been delineated in detail from a biochemical perspective.

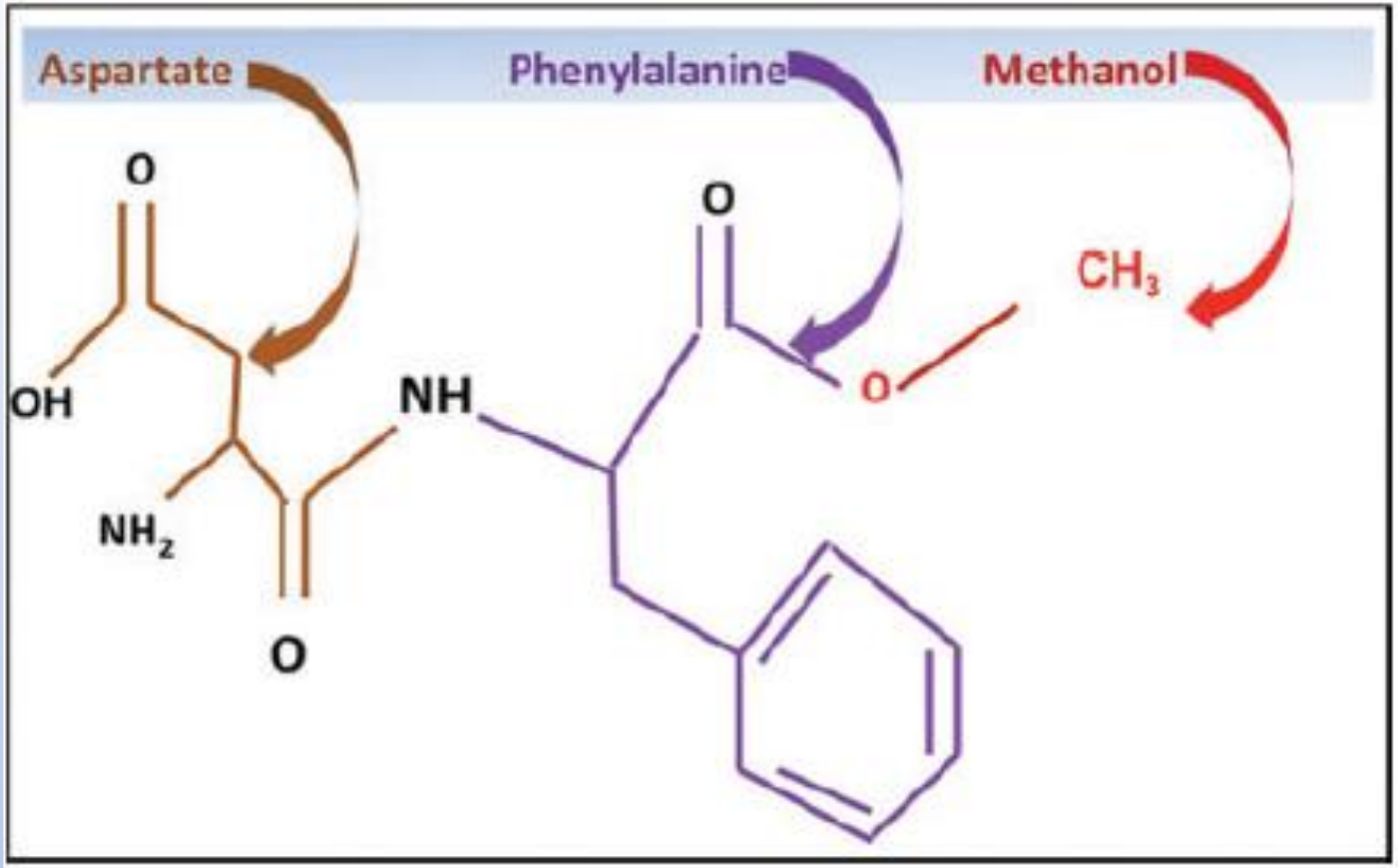


Figure 1 **Structure of aspartame (L-aspartyl-L-phenylalanine methyl ester).**

Choudhary AK & Pretorius E. Revisiting the Safety of Aspartame. *Nutrition Reviews* 2017

Aspartame

- 200-330 x sweeter than sucrose
- lacks metallic or bitter aftertaste
- less expensive than sugar
- added to more than 6000 different commercial food items/vitamins
- added to more than 600 different pharmaceuticals
- European Food Safety Authority: ADI 40 mg/kg of body weight
- The US Food and Drug Administration: ADI 50 mg/kg of body weight
- Rats metabolize aspartame 5-6 x more rapidly than humans, thus safe rat dose must be divided by 5-6 to yield equivalent human dose

ADI: acceptable daily intake

Why would concern be raised regarding aspartame intake and brain function?

Studies of Rats Receiving the Equivalent of Aspartame 40 mg/kg/day

Ashok I & Sheeladevi R. Biochemical responses and mitochondrial mediated activation of apoptosis on long-term effect of aspartame in rat brain. *Redox Biology* 2014:

Increased production of brain free-radicals and decreased anti-apoptotic activity with aspartame dose-equivalent of 40 mg/kg/day

Ahok I et al. Neurobehavioral changes and activation of neurodegenerative apoptosis on long-term consumption of aspartame in the rat brain. *J Nutr Intermed Metabol* 2015:

Increased immobilization; decreased ambulation, rearing, and grooming. Up regulation in apoptotic gene expression along with protein expression in the respective brain region indicating the enhancement of neuronal cell death.

El-Samad AAA. Light and Electron Microscopic Study on the Effect of Aspartame on the Cerebellar Cortex of the Male Albino Rat. *Egypt J Histol* 2010:

Demonstrated various abnormalities in Purkinje cell morphology.

Clinical Sciences

Sugar- and Artificially Sweetened Beverages and the Risks of Incident Stroke and Dementia

A Prospective Cohort Study

Matthew P. Pase, PhD; Jayandra J. Himali, PhD; Alexa S. Beiser, PhD; Hugo J. Aparicio, MD; Claudia L. Satizabal, PhD; Ramachandran S. Vasan, MD; Sudha Seshadri, MD*; Paul F. Jacques, DSc*

Pase MP et al. Stroke 2017
(published more than a year ago, but there was no room for it in last year's presentation)

Framingham Heart Study Offspring Cohort

- cohort initiated in 1971 and enrolled 5124 subjects
- subjects examined every 4 years, most recent 2014
- subjects completed the Harvard semi-quantitative Food Frequency Questionnaire at examination cycles 5 (1991-1995), 6 (1995-1998), and 7 (1998-2001)
- estimated intake of sugary beverages, sugar-sweetened soft drinks, and artificially-sweetened soft drinks
- related beverage intake to 10-year risk of total stroke, ischemic stroke, total dementia, Alzheimer-type dementia beginning with 7th examination cycle (1998-2001)

Three Different Statistical Models

1. adjusted for age, sex, education, total caloric intake

2. model 1 plus adjustment for lifestyle factors (diet, exercise, smoking)

3. model 2 plus adjustment for systolic BP, presence of CVD, AF, LVH, total cholesterol, *diabetes mellitus*, waist-to-hip ratio

Beverage Intake and Risk for Dementia

Statistical Model 1

	Recent Intake				Cumulative Intake			
	All-Cause Dementia		AD Dementia		All-Cause Dementia		AD Dementia	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Total Sugary Beverages								
<1/day (ref)								
1-2/day	1.13 (0.70, 1.82)	0.62	1.21 (0.70, 2.10)	0.50	0.90 (0.56, 1.47)	0.68	0.90 (0.51, 1.59)	0.72
>2/day	1.06 (0.53, 2.13)	0.87	1.62 (0.78, 3.38)	0.20	0.54 (0.22, 1.32)	0.18	0.80 (0.32, 1.99)	0.63
Sugar-Sweetened Soft Drinks								
0/week (ref)								
>0-3/week	0.98 (0.60, 1.61)	0.94	1.03 (0.59, 1.81)	0.91	0.79 (0.48, 1.31)	0.36	0.93 (0.52, 1.67)	0.82
>3/week	0.77 (0.34, 1.74)	0.53	1.04 (0.45, 2.40)	0.93	0.76 (0.35, 1.64)	0.48	0.88 (0.36, 2.11)	0.77
Artificially-Sweetened Soft Drinks								
0/week (ref)								
>0-6/week	1.24 (0.76, 2.03)	0.40	1.25 (0.71, 2.21)	0.44	1.57 (0.90, 2.71)	0.11	1.89 (0.99, 3.62)	0.05
≥1/day	1.58 (0.81, 3.07)	0.18	1.79 (0.85, 3.74)	0.12	**2.28 (1.11, 4.67)**	**0.02**	**2.48 (1.06, 5.84)**	**0.04**

Recent Intake: based upon examination cycle 7 only

Cumulative Intake: based upon average of all three examination cycles

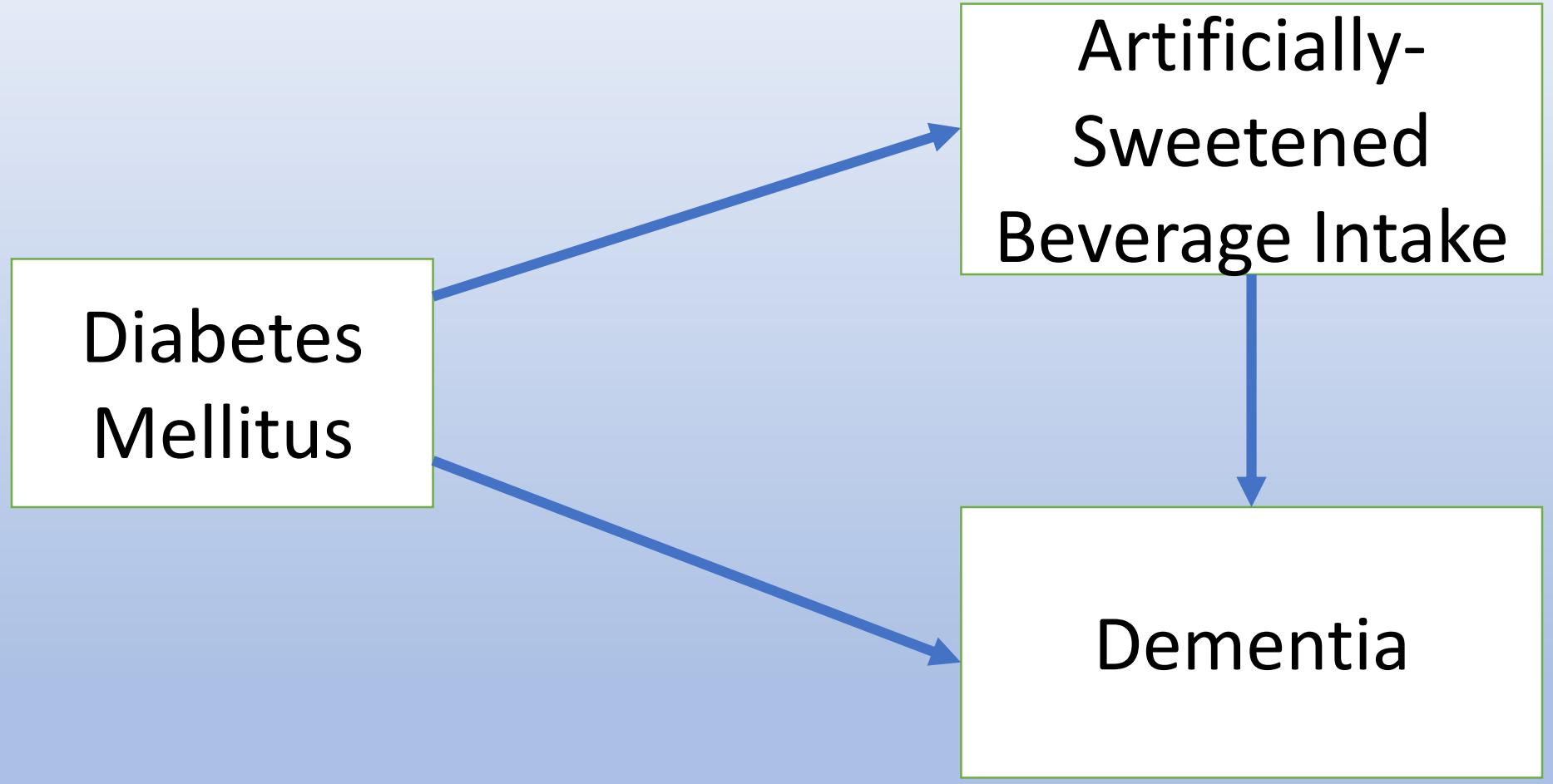
Beverage Intake and Risk for Dementia

Statistical Models 2 and 3

	Model	Recent Intake				Cumulative Intake			
		All-Cause Dementia		AD Dementia		All-Cause Dementia		AD Dementia	
		HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Artificially sweetened soft drinks									
0/wk (ref)	2								
>0–6/wk		1.39 (0.79–2.43)	0.25	1.48 (0.78–2.82)	0.23	1.41 (0.77–2.59)	0.27	1.68 (0.82–3.43)	0.15
≥1/d		2.20 (1.09–4.45)	0.03	2.53 (1.15–5.56)	0.02	2.47 (1.15–5.30)	0.02	2.89 (1.18–7.07)	0.02
0/wk (ref)	3								
>0–6/wk		1.00 (0.60–1.67)	0.99	1.05 (0.59–1.87)	0.87	1.30 (0.74–2.29)	0.36	1.66 (0.86–3.20)	0.13
≥1/d		1.08 (0.54–2.17)	0.83	1.29 (0.59–2.80)	0.53	1.70 (0.80–3.61)	0.17	2.03 (0.83–4.97)	0.12

Statistical Mediation Analysis:

Does the presence of diabetes mellitus mediate the association between artificially-sweetened soft drink intake and dementia?


Artificially-Sweetened Beverage Intake
Diabetes Mellitus
Dementia

Individuals with type 2 diabetes are at ~60% greater risk for the development of dementia compared with those without diabetes.

Chatterjee S, Peters SA, Woodward M, Mejia Arango S, Batty GD, Beckett N, et al. Type 2 diabetes as a risk factor for dementia in women compared with men: a pooled analysis of 2.3 million people comprising more than 100,000 cases of dementia. *Diabetes Care*. 2016;39:300–307. doi: 10.2337/dc15-1588.

My conclusion: This study does not demonstrate that the dementia associated with artificial soft-drink sweeteners cannot be explained adequately by factors such as diabetes. However, there is good basic science suggesting aspartame can damage brain tissue at usual doses, so I have switched to…..


NO SUGAR
NO CALORIES
Diet Coke
with
Splenda
Brand Sweetener
0
CALORIES
PER CAN
12 FL OZ
(355 mL)
Diet Coke with SPLENDA® BRAND SWEETENER

#4/5
E-Cigarettes

DOES THE USE OF E-CIGARETTES IMPROVE THE RATE OF SMOKING CESSATION AMONG ESTABLISHED CIGARETTE SMOKERS?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy

Peter Hajek, Ph.D., Anna Phillips-Waller, B.Sc., Dunja Przulj, Ph.D., Francesca Pesola, Ph.D., Katie Myers Smith, D.Psych., Natalie Bisal, M.Sc., Jinshuo Li, M.Phil., Steve Parrott, M.Sc., Peter Sasieni, Ph.D., Lynne Dawkins, Ph.D., Louise Ross, Maciej Goniewicz, Ph.D., Pharm.D., Qi Wu, M.Sc., and Hayden J. McRobbie, Ph.D.

Hajek P et al. New Engl J Med 2019

1. National Health Service (NHS) stop-smoking services are available free across the United Kingdom.

2. Invited adult smokers who
    a. had no strong preference for nicotine replacement vs. e-cigarettes
    b. not currently using either product.

3. Randomization and product use occurred on subject-chosen “quit date”

4. Weekly one-on-one sessions with local clinicians

INTERVENTIONS

Nicotine Replacement: choice of one or more of patch, gum, lozenge, nasal spray, inhalator, mouth spray, mouthstrip, and microtabs

a. free to switch type(s) at will

b. NHS paid for first 3 months

E-Cigarette: device plus 30-ml bottle e-liquid

a. NHS paid for device and initial bottle

PRIMARY OUTCOME

One-year sustained abstinence, calculated as a self-report of smoking no more than five cigarettes from two weeks after the quit date, validated by expired carbon monoxide level

884 subjects included in Primary Analysis

Table 2. Abstinence Rates at Different Time Points and Smoking Reduction at 52 Weeks.*

Outcome	E-Cigarettes (N = 438)	Nicotine Replacement (N = 446)	Primary Analysis: Relative Risk (95% CI)†	Sensitivity Analysis: Adjusted Relative Risk (95% CI)
Primary outcome: abstinence at 52 wk — no. (%)	79 (18.0)	44 (9.9)	1.83 (1.30–2.58)	1.75 (1.24–2.46)‡
Secondary outcomes				
Abstinence between wk 26 and wk 52 — no. (%)	93 (21.2)	53 (11.9)	1.79 (1.32–2.44)	1.82 (1.34–2.47)§
Abstinence at 4 wk after target quit date — no. (%)	192 (43.8)	134 (30.0)	1.45 (1.22–1.74)	1.43 (1.20–1.71)¶
Abstinence at 26 wk after target quit date — no. (%)	155 (35.4)	112 (25.1)	1.40 (1.14–1.72)	1.36 (1.15–1.67)‡
Carbon monoxide–validated reduction in smoking of ≥50% in participants without abstinence between wk 26 and wk 52 — no./total no. (%)	44/345 (12.8)	29/393 (7.4)	1.75 (1.12–2.72)	1.73 (1.11–2.69)‖

Hajek P et al. New Engl J Med 2019

Table 4. Urges to Smoke in Participants with Abstinence at 1 Week or 4 Weeks after Quit Date.*

Variable	1 Wk after Quit Date		Mean Difference (95% CI)	4 Wk after Quit Date		Mean Difference (95% CI)
	E-Cigarettes (N=158)	Nicotine Replacement (N=131)		E-Cigarettes (N=186)	Nicotine Replacement (N=132)	
Score for frequency of urge	2.5±1.1	2.8±0.9	−0.4 (−0.6 to −0.1)	1.9±0.9	2.2±0.8	−0.3 (−0.5 to −0.1)
Score for strength of urge	2.7±1.1	3.2±1.0	−0.5 (−0.7 to −0.2)	2.1±1.1	2.4±1.0	−0.3 (−0.6 to −0.1)
Composite urge score	2.6±1.0	3.0±0.9	−0.4 (−0.6 to −0.2)	2.0±1.0	2.3±0.9	−0.3 (−0.5 to −0.1)

Hajek P et al. New Engl J Med 2019

ADDICTION

SSA SOCIETY FOR THE STUDY OF ADDICTION

ADDICTION DEBATE

doi:10.1111/add.13394

A framework for evaluating the public health impact of e-cigarettes and other vaporized nicotine products

David T. Levy[1], K. Michael Cummings[2], Andrea C. Villanti[3,4], Ray Niaura[1,3,4], David B. Abrams[1,3,4], Geoffrey T. Fong[5,6,7] & Ron Borland[8]

Department of Oncology, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC USA,[1] Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC USA,[2] The Schroeder Institute for Tobacco Research and Policy Studies at Truth Initiative, Washington, DC USA,[3] Department of Health, Behavior and Society, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD USA,[4] Department of Psychology, University of Waterloo, Waterloo, Ontario Canada,[5] School of Public Health and Health Systems, University of Waterloo, Waterloo, Ontario Canada,[6] Ontario Institute for Cancer Research, Toronto, Ontario Canada[7] and Nigel Gray Distinguished Fellow in Cancer Prevention, The Cancer Council Victoria, Melbourne, Victoria Australia[8]

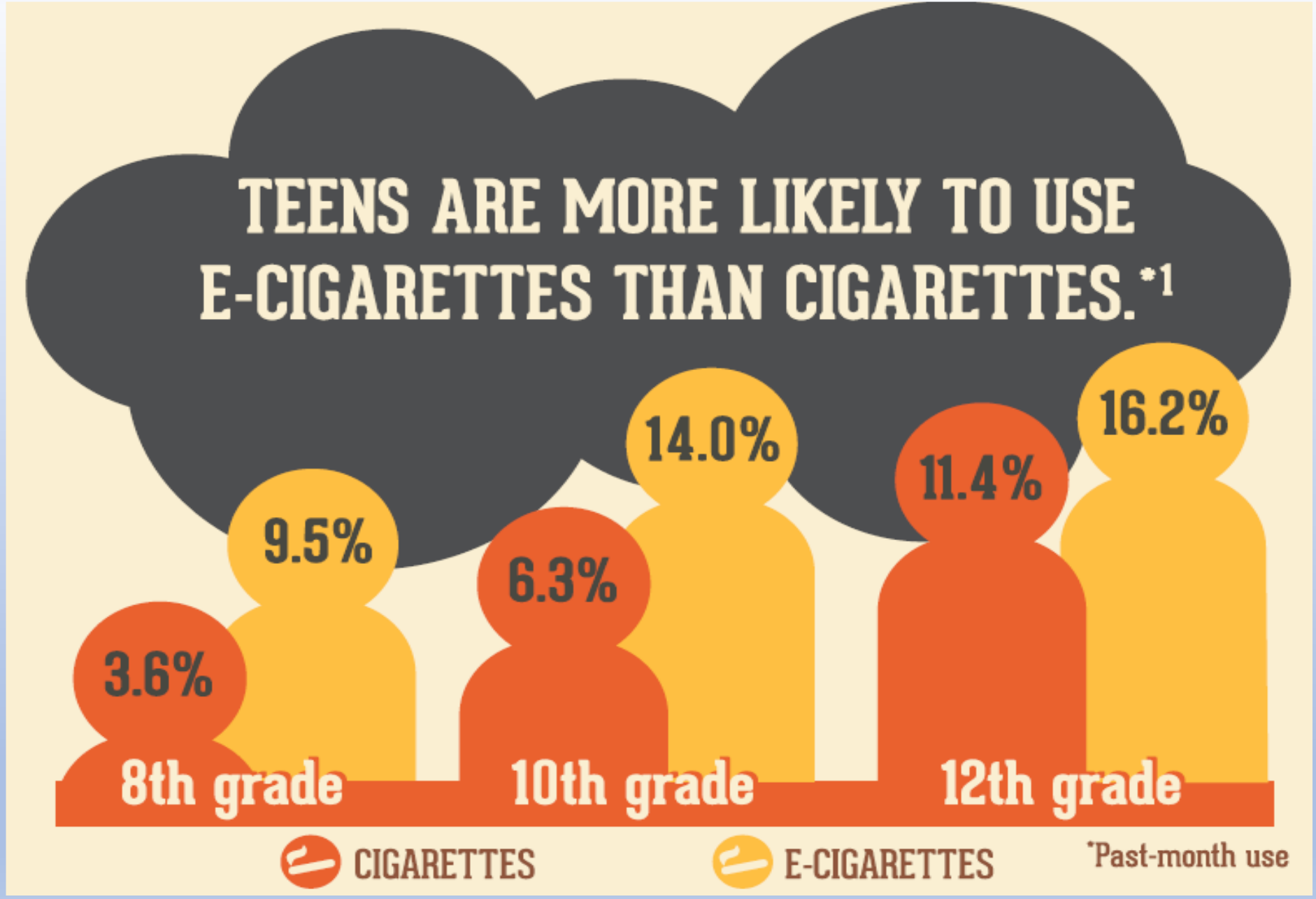
Levy DT et al. Addiction 2016

“From a public health perspective, VNP (vaporized nicotine products) policies should aim to discourage experimental and regular use of VNPs by never smokers who would not have smoked otherwise while encouraging innovations in VNP products that promote smoking cessation.”

Levy DT et al. Addiction 2016

“A never smoker may transition from trying VNP to exclusive VNP use, exclusive cigarette use, dual use or quit using cigarettes and VNPs. The population health impact depends critically upon whether the never smoker who tries VNPs would have smoked cigarettes in the absence of VNPs.”

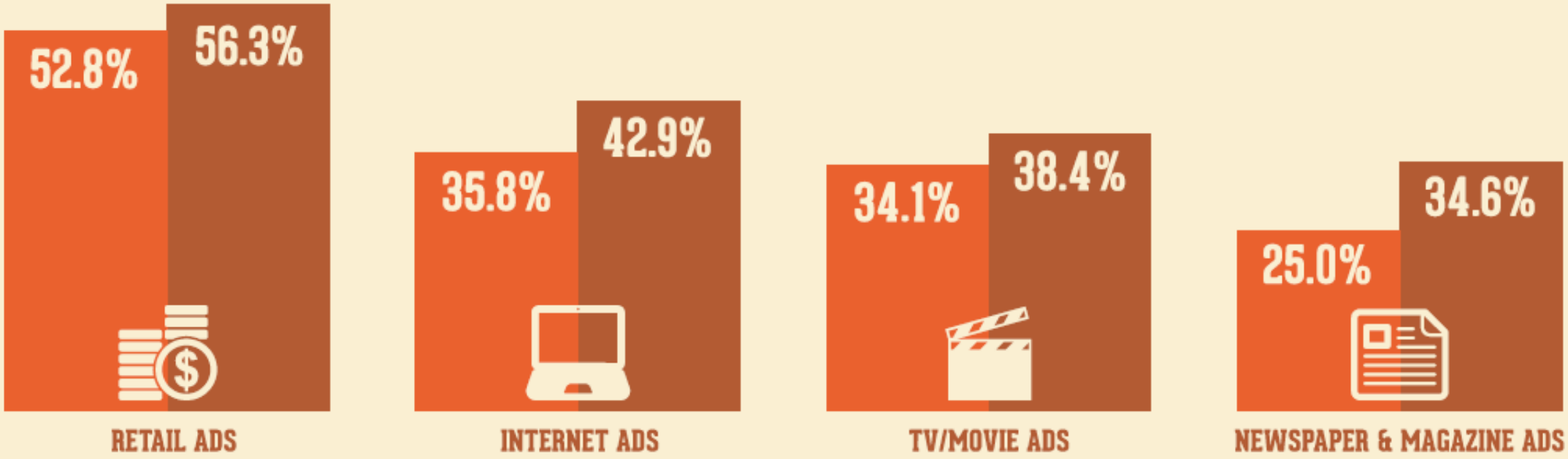
Levy DT et al. Addiction 2016



National Institute on Drug Abuse

National Institute on Drug Abuse

HIGH TEEN EXPOSURE TO E-CIG ADVERTISING[1]

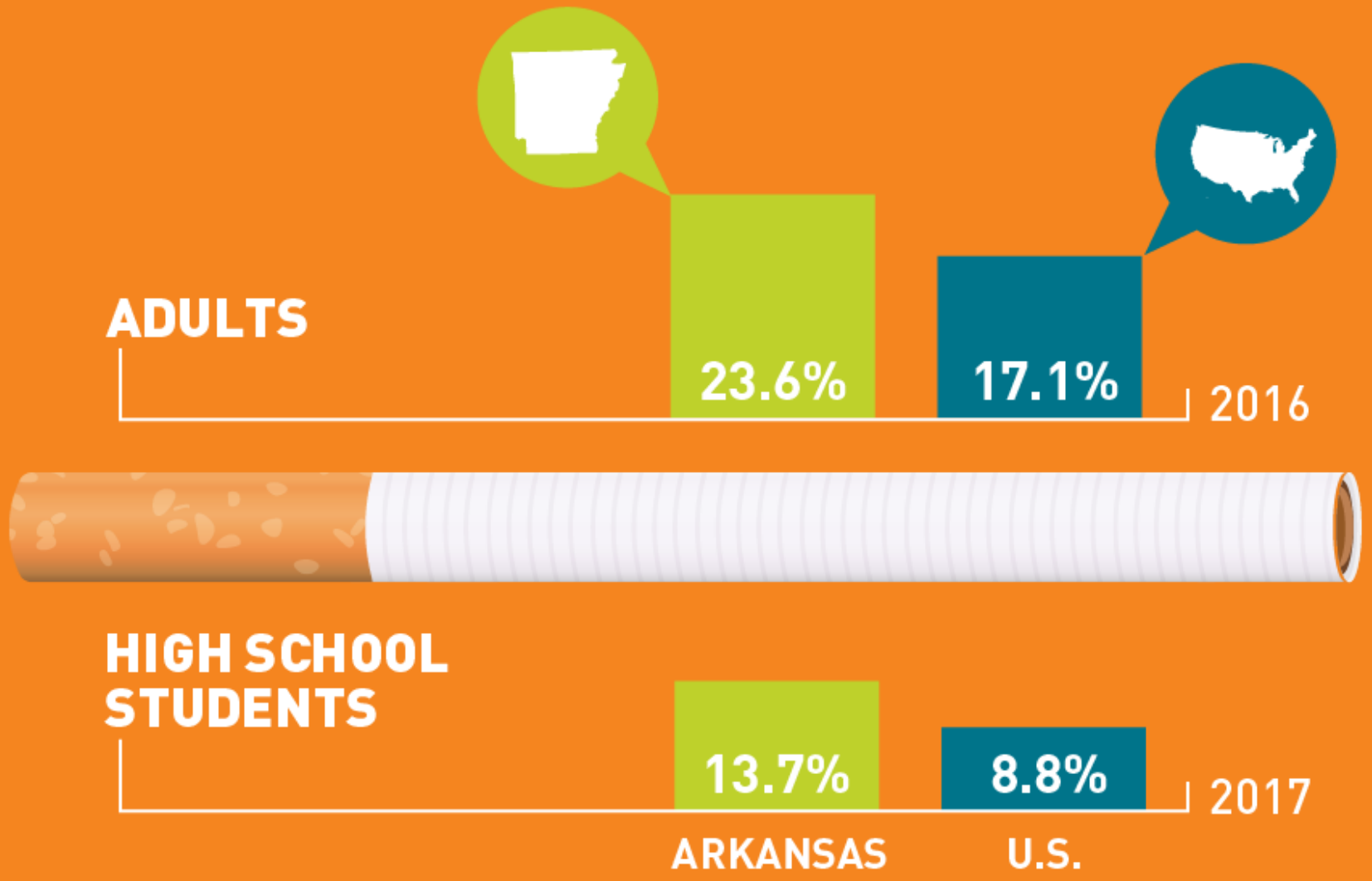


Nat'l Inst. on Drug Abuse

ARKANSAS

CIGARETTE USE

among adults and high school students



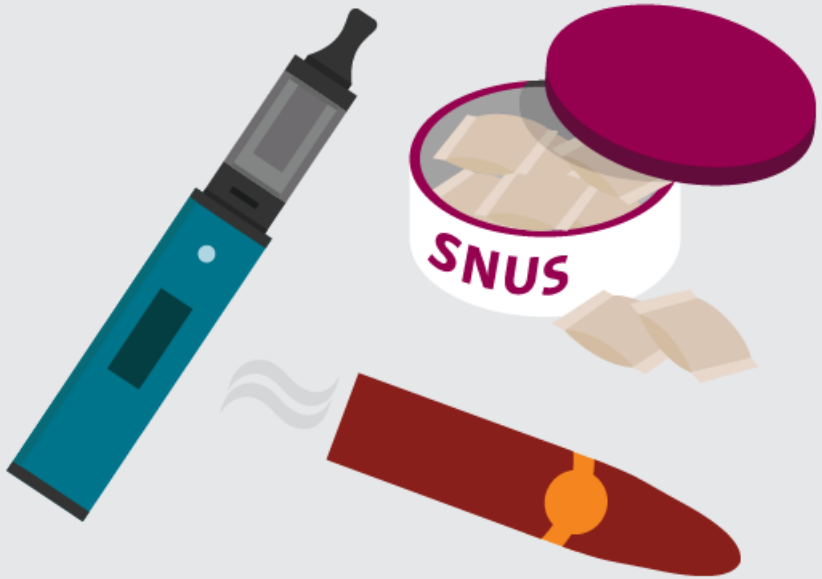
Truth Initiative
900 G Street, NW
Fourth Floor
Washington, DC
20001

ARKANSAS

OTHER TOBACCO PRODUCT USE

among adults and high school students

ADULTS (2015)



HIGH SCHOOL STUDENTS (2017)

Truth Initiative
900 G Street, NW
Fourth Floor
Washington, DC 20001

“A growing number of prospective studies indicate that ENDS (electronic nicotine delivery systems) use among never cigarette smokers/cigarette-naïve participants is associated with subsequent cigarette initiation up to 16 months later, even after controlling for various socio-demographic, intrapersonal, and contextual factors (Barrington-Trimis et al., 2016; Leventhal et al., 2015; Primack, Soneji, Stoolmiller, Fine, & Sargent, 2015; Wills et al., 2016; Wills, Sargent, Gibbons, Pagano, & Schweitzer, 2016).”

Loukas A et al. Addictive Behaviors 2018

Contents lists available at ScienceDirect

Addictive Behaviors

journal homepage: www.elsevier.com/locate/addictbeh

Exclusive e-cigarette use predicts cigarette initiation among college students

Alexandra Loukas[a,*], C. Nathan Marti[a], Maria Cooper[b], Keryn E. Pasch[a], Cheryl L. Perry[b]

[a] University of Texas at Austin, 2109 San Jacinto Blvd, Austin, TX 78712-1415, USA
[b] UTHealth School of Public Health in Austin, 1616 Guadalupe Street Suite 6.300, Austin, TX 78701, USA

HIGHLIGHTS

- 11% of college students initiated cigarette use over the 1.5 year study period.
- More ENDS users than non-users initiated cigarette use during the study period.
- Exclusive ENDS use predicted subsequent cigarette initiation.

Loukas A et al. Addictive Behaviors 2018

Project M-PACT

(Marketing and Promotion across Colleges in Texas)

Repetitive rapid-response survey of a cohort of 2558 “never-used cigarettes at baseline” students attending 24 colleges in Texas

Wave 1 survey: Nov. 2014 – Feb. 2015
Wave 2 survey: 6 months later after wave 1; retention rate 90%
Wave 3 survey: 12 months after wave 1; retention rate 89%
Wave 4 survey: 18 months after wave 1; retention rate 92%

Cigarette Use Susceptibility

Question 1: “If one of your friends were to offer you these products, would you smoke/use it?”

Question 2: “Do you think you will use any of the following in the next 12 months?”

Susceptible Response: “probably not,” “probably yes,” or “definitely yes”

Not Susceptible Response : “definitely not”

Period	Number of cigarette initiators in period	Number of students at risk for initiation[a]	Hazard	Hazard standard error	Survival
1 (wave 1–2)	119	2558	0.05	0.004	0.95
2 (wave 2–3)	85	2347	0.04	0.004	0.92
3 (wave 3–4)	78	2151	0.04	0.004	0.89

[a] The number of students at risk after period 1is the number from the prior period minus those who initiated cigarettes in the prior period *and* those missing data at each period (n = 92 and 111 in period 2 and 3, respectively).

Loukas A et al. Addictive Behaviors 2018

Baseline Predictors of Subsequent Cigarette Use

	Adj. Odds Ratio
• cigarette susceptibility	3.02
• family of origin tobacco use	1.35
• friend's cigarette use	1.44
• ever other tobacco use	2.85
• ever e-cigarette use	1.36

How can we better isolate the effect of starting ENDS use in predicting risk of initiating cigarette smoking?

Compare the effect of using ENDS on future cigarette use for “never user of tobacco product” students:

<u>Never tobacco user/ yes ENDS use</u>

Never tobacco user/ no ENDS use **OR = 2.26**

(Odds Ratio = 2.26; CI = 1.35 – 3.76)

#6 Hypertension and Dementia

Observational Studies: hypertension is a risk factor for dementia and mild cognitive impairment (MCI)

Pathologic Studies: Alzheimer's dementia exhibits vascular damage in combination with β-amyloid and tau neuropathology

Literature: no long-term study of treating hypertension with expert assessment of cognitive outcomes are available

CNS Small Vessel Disease

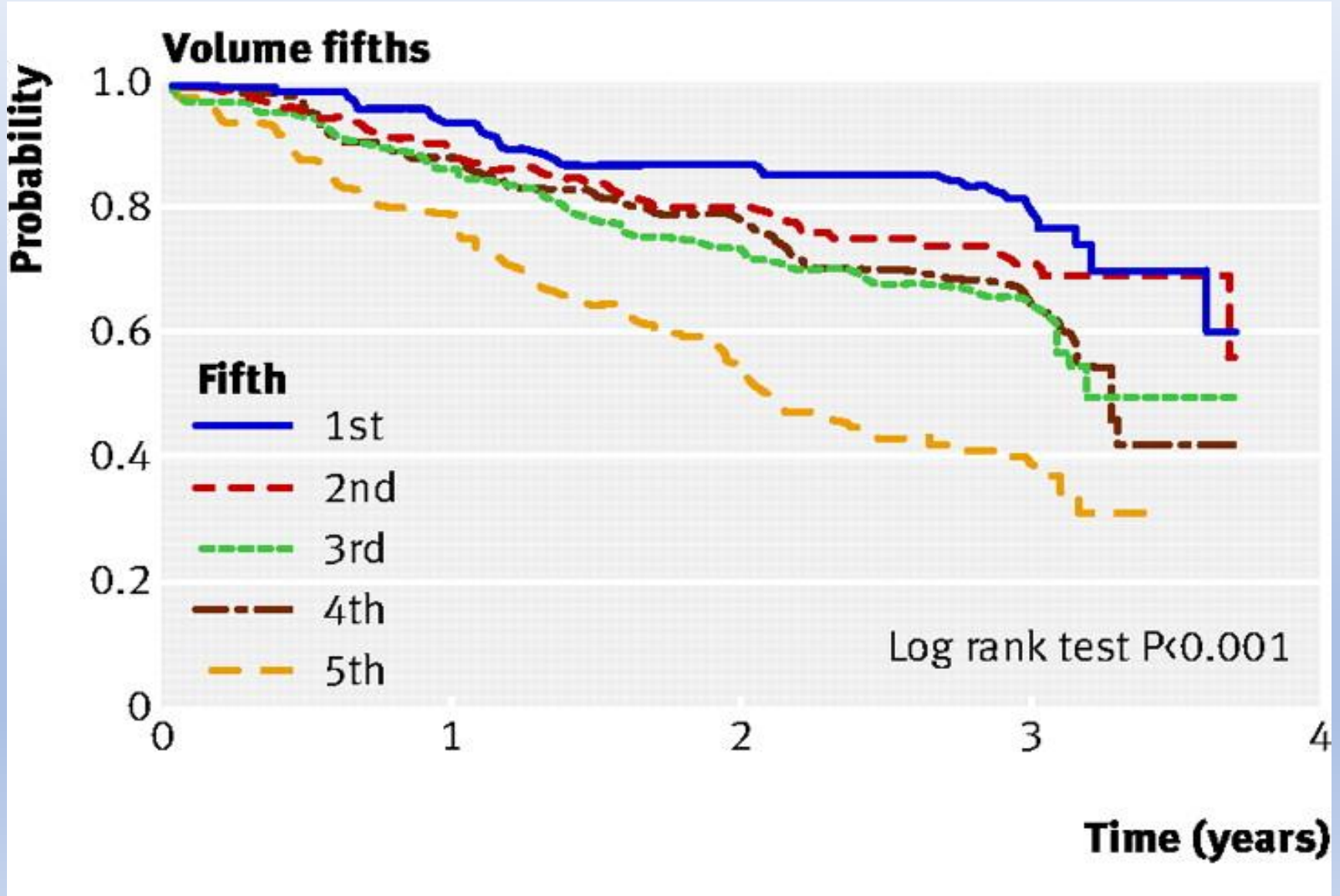
(white matter hyperintensities; lacunar infarctions; hypertension-related microangiopathy)

Contributes to 45% of dementia cases

Leading risk factor is hypertension

- relative risk for hypertension: 1.5 – 4.9

Transition from independence in instrumental activities daily living to disability or death according to baseline severity grades in age related changes in white matter. Inzitari D et al. BMJ 2009



SPRINT MIND Study

Research

JAMA | Original Investigation

Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia

A Randomized Clinical Trial

The SPRINT MIND Investigators for the SPRINT Research Group

SPRINT MIND investigators. JAMA 2019

Multicenter randomized clinical trial (sub-study of the SPRINT Trial)

Hypertensive older adults @ increased cardiovascular risk

Compared 2 BP targets: 140 systolic vs. 120 systolic

Inclusion Criteria:

- age greater than 50 years
- BP systolic 130-180
- known cardiovascular disease *or* EGFR < 60 *or* Framingham Risk Score of ≥15% *or* age > 75 years

Exclusion Criteria:

- nursing home resident
- dementia diagnosis *or* receiving drug used for dementia therapy
- diabetes mellitus
- history of stroke

INTERVENTION

Randomized to:

1. systolic BP goal of < 140 mm Hg
2. systolic BP goal of < 120 mm Hg

Specific anti-hypertensive drugs up to local MD

Study “encouraged”

a. thiazide as a first-line agent
b. loop diuretics for participants with chronic kidney disease
c. β-blockers for participants with coronary artery disease

Systolic Blood Pressure Intervention Trial (SPRINT)

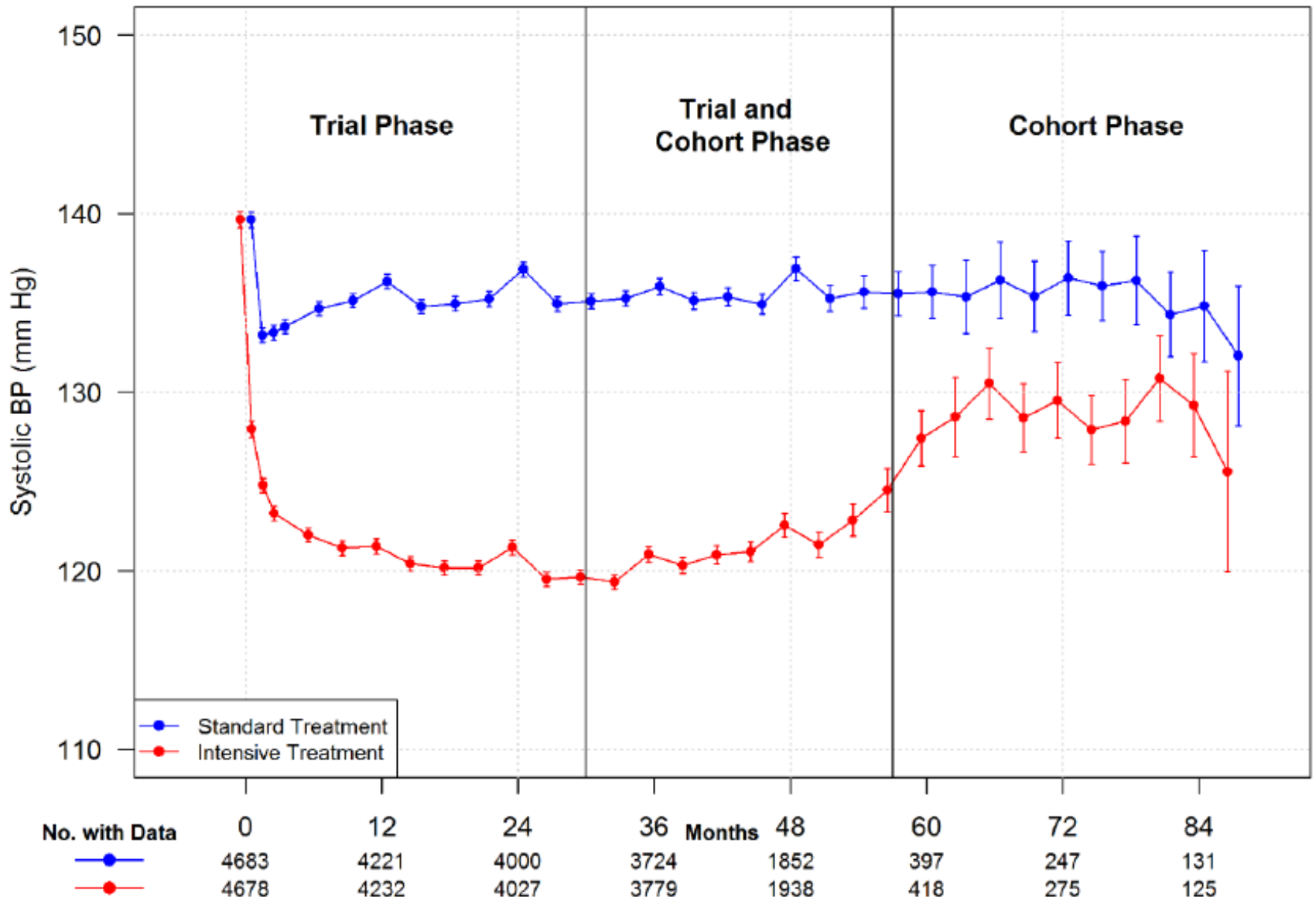
Primary End Point: cardiovascular events

Secondary End Point: renal function

Secondary End Point: probable dementia, MCI

- 9361 subjects randomized between November 2010 and March 2013
- cognitive assessments planned at baseline, 2 years, and 4 years after entry (end March 2017)
- study stopped early (August 20, 2015) because the primary endpoint had been reached
- BP goals returned to PCP after August 20, 2015 but follow up for BP and cognitive function was continued

eFigure 3. Systolic Blood Pressure in the Two Treatment Groups Over the Course of Follow-up



SPRINT MIND investigators. JAMA 2019

OUTCOMES

Table 2. Incidence of Probable Dementia and Mild Cognitive Impairment by Treatment Group

Outcomes	Treatment Group				Hazard Ratio (95% CI)[a]	*P* Value
	Intensive		Standard			
	No. With Outcome/Person-Years	Cases per 1000 Person-Years	No. With Outcome/Person-Years	Cases per 1000 Person-Years		
Probable dementia	149/20 569	7.2	176/20 378	8.6	0.83 (0.67-1.04)	.10
Mild cognitive impairment[b]	287/19 690	14.6	353/19 281	18.3	0.81 (0.69-0.95)	.007
Composite of mild cognitive impairment or probable dementia	402/19 873	20.2	469/19 488	24.1	0.85 (0.74-0.97)	.01

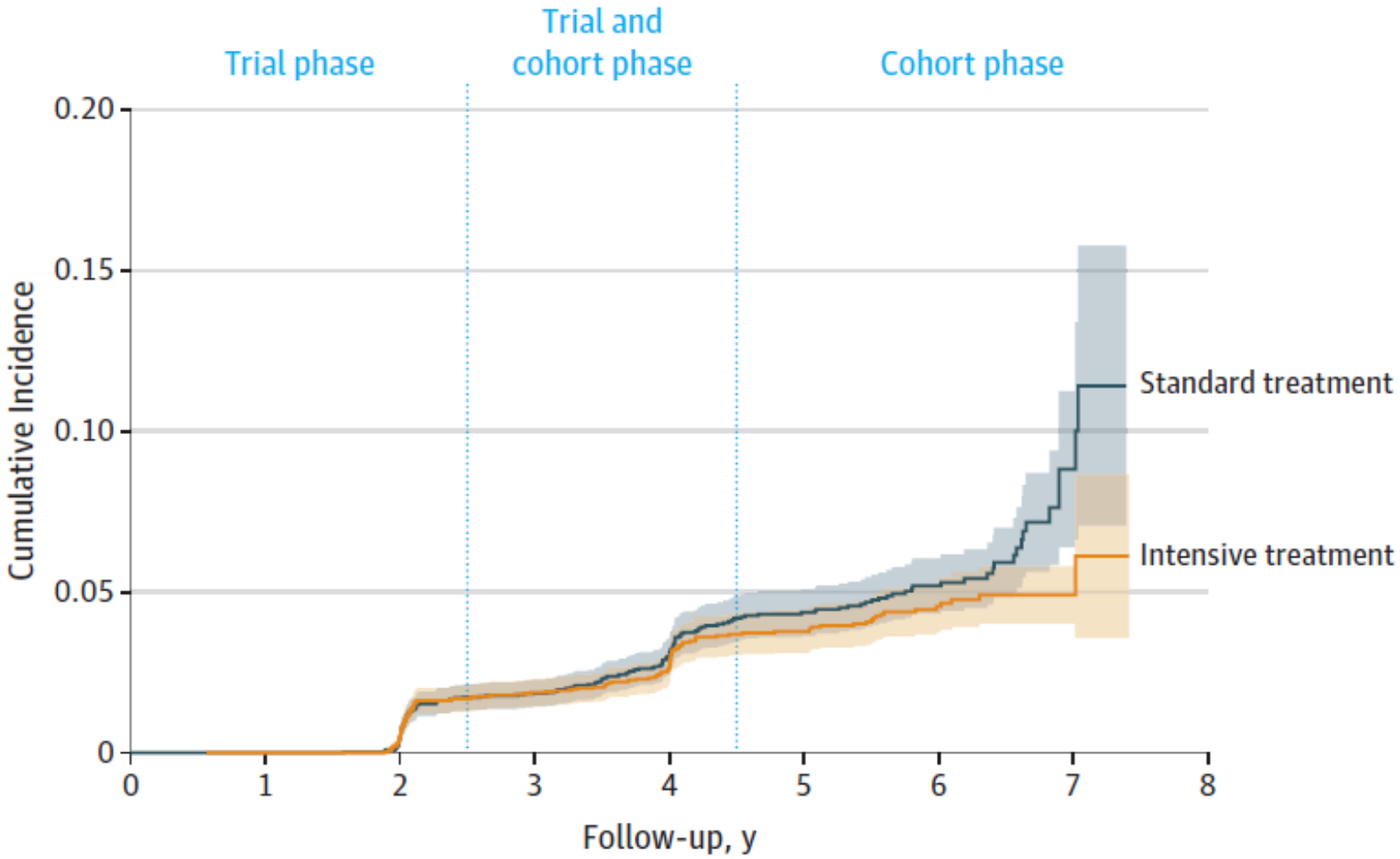
[a] Intensive treatment group vs standard treatment group based on Cox proportional hazards regression.

[b] Participants adjudicated as having probable dementia at the first follow-up visit (year 2) do not contribute to the analyses of mild cognitive impairment.

median follow-up of 5.1 years

SPRINT MIND investigators. JAMA 2019

Figure 2. Probable Dementia by Treatment Group



No. at risk									
Standard treatment	4285	4282	4168	3886	2829	2107	989	87	0
Intensive treatment	4278	4277	4171	3917	2893	2189	1027	93	0

shaded areas represent 95% confidence intervals

7#
Nutritional Support of the Medical Inpatient

Does individualized nutritional support of general medical inpatients who are at nutritional risk improve outcome?

Individualised nutritional support in medical inpatients at nutritional risk: a randomised clinical trial

Philipp Schuetz, Rebecca Fehr, Valerie Baechli, Martina Geiser, Manuela Deiss, Filomena Gomes, Alexander Kutz, Pascal Tribolet, Thomas Bregenzer, Nina Braun, Claus Hoess, Vojtech Pavlicek, Sarah Schmid, Stefan Bilz, Sarah Sigrist, Michael Brändle, Carmen Benz, Christoph Henzen, Silvia Mattmann, Robert Thomann, Claudia Brand, Jonas Rutishauser, Drahomir Aujesky, Nicolas Rodondi, Jacques Donzé, Zeno Stanga, Beat Mueller**

Schuetz P, Fehr R, Baechli V et al. Lancet 2019

Eight Swiss secondary and tertiary care hospitals

Evaluated all general medicine admissions for nutritional status and nutritional requirements

Randomized subjects to individualized nutritional support program or usual hospital food based upon patient preference/appetite

Nutritional Risk Screening (NRS 2002)

Impaired nutritional status	
Absent Score 0	Normal nutritional status
Mild Score 1	Wt loss $>5\%$ in 3 months Or Food intake below 50–75% of normal requirement in preceding week
Moderate Score 2	Wt loss $>5\%$ in 2 months Or BMI 18.5 – 20.5 + impaired general condition Or Food intake 25–50% of normal requirement in preceding week
Severe Score 3	Wt loss $>5\%$ in 1 month ($\approx$ $>15\%$ in 3 months (17)) Or BMI <18.5 + impaired general condition (17) Or Food intake 0–25% of normal requirement in preceding week in preceding week.

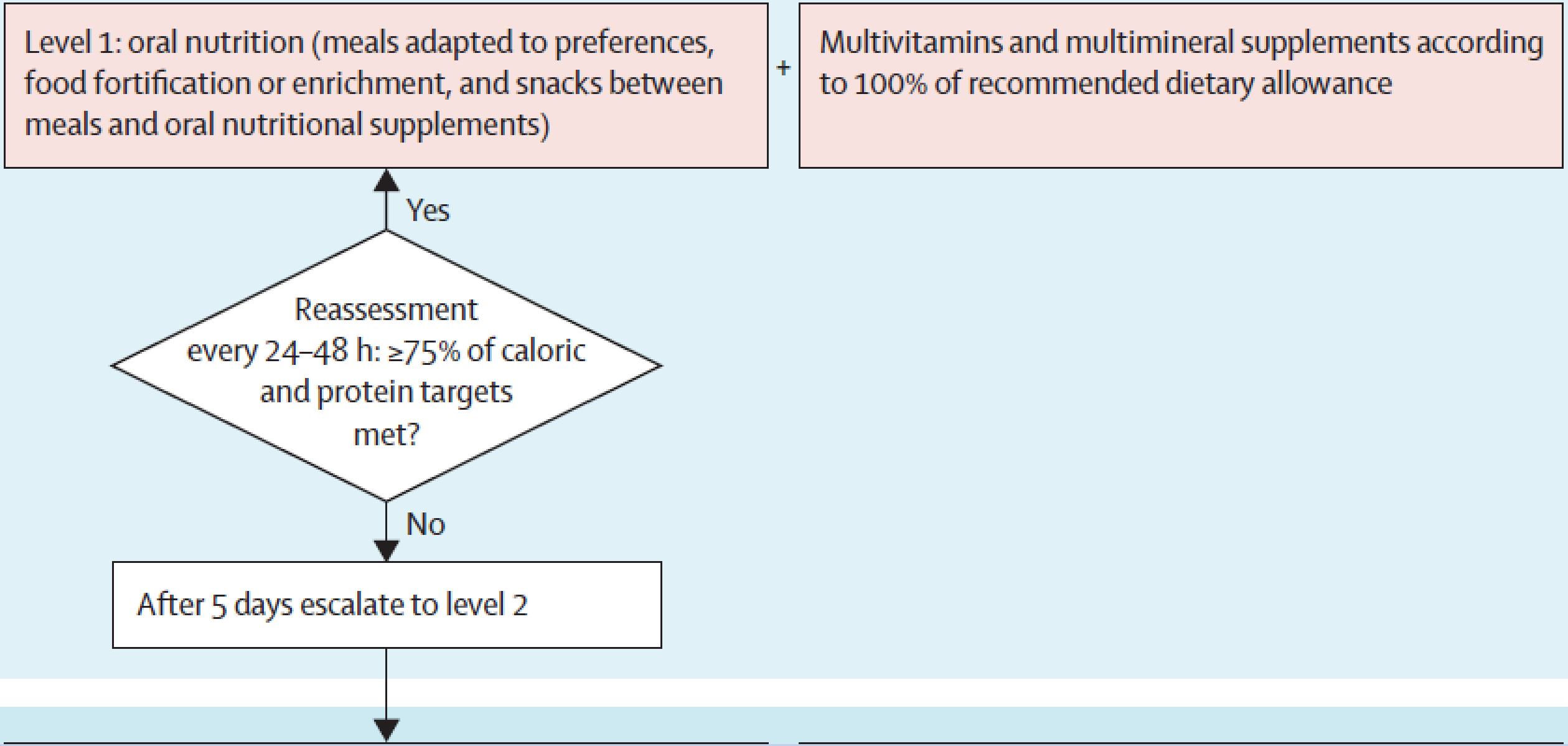
Nutritional Risk Screening (NRS 2002)

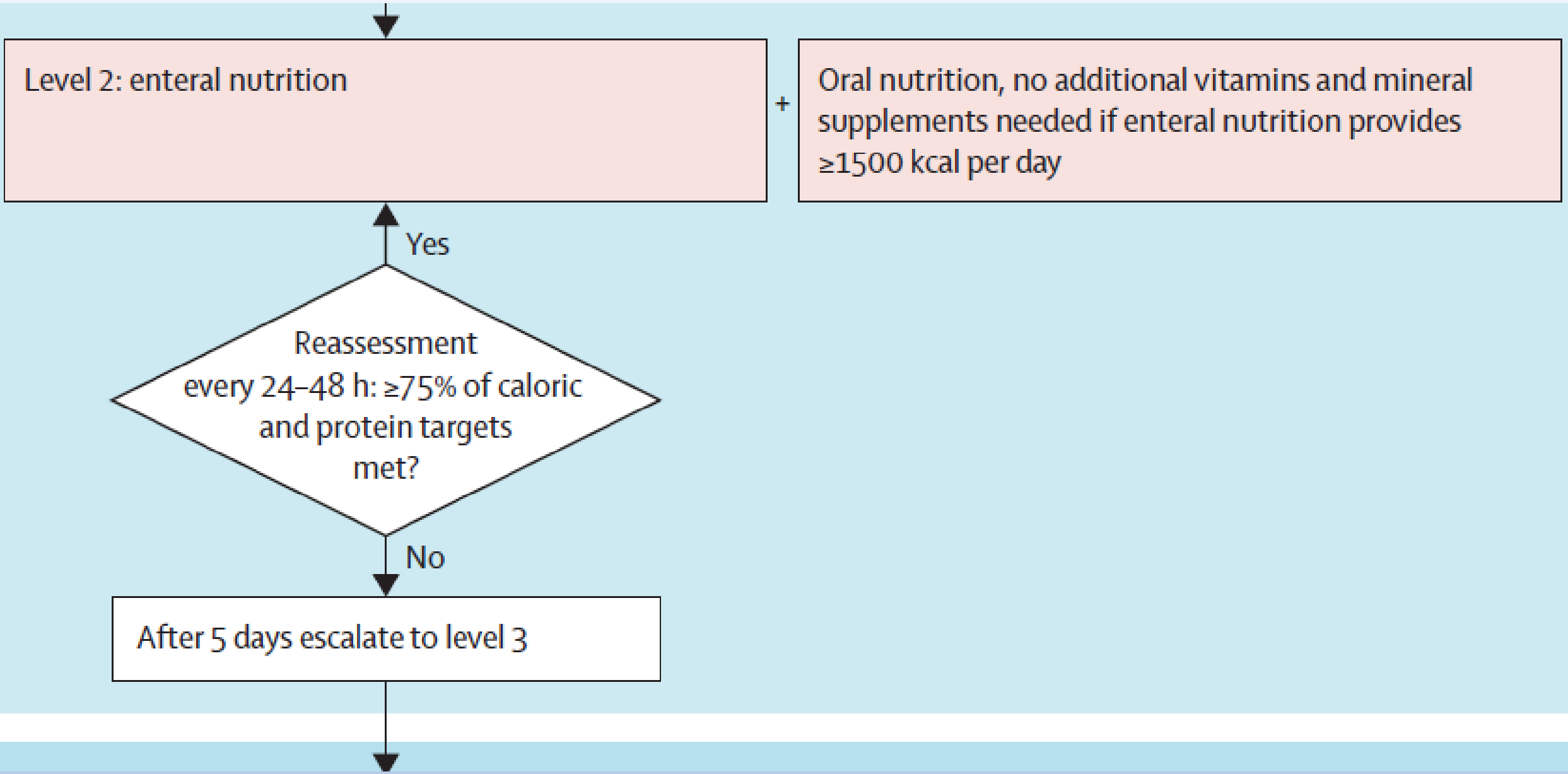
Severity of disease (≈stress metabolism)	
Absent Score 0	Normal nutritional requirements
Mild Score 1	Hip fracture Chronic patients, in particular with acute complications: cirrhosis COPD (12) *Chronic hemodialysis, diabetes, oncology*
Moderate Score 2	Major abdominal surgery (13–15). Stroke (16) *Severe pneumonia, hematologic malignancy*
Severe Score 3	Head injury (18, 19) Bone marrow transplantation (20) *Intensive care patients (APACHE 10*

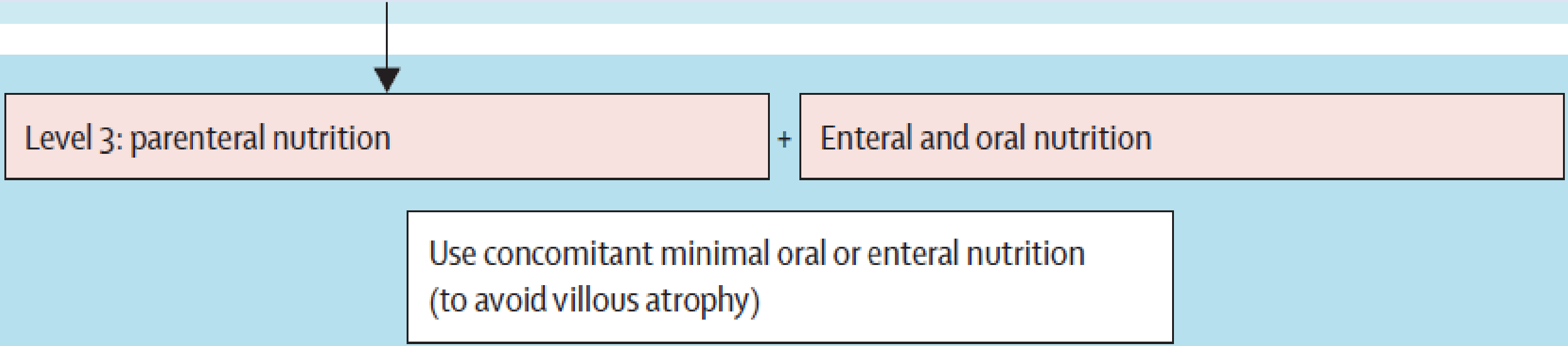
Individual nutrition targets

Caloric requirements	Protein requirements	Micronutrient requirements	Specific targets
Harris-Benedict equation with adjusted bodyweight or indirect calorimetry	1·2–1·5 g/kg bodyweight per day (0·8 g/kg of bodyweight per day in patients with renal failure with no dialysis)	Multivitamin use; other micronutrients according to specific laboratory results	Disease-specific adaptations (eg, medium-chain triglycerides, low potassium in patients with renal failure)

Strategy to reach the nutrition targets




Level 2: enteral nutrition
+
Oral nutrition, no additional vitamins and mineral supplements needed if enteral nutrition provides ≥1500 kcal per day
Yes
Reassessment every 24–48 h: ≥75% of caloric and protein targets met?
No
After 5 days escalate to level 3


Level 3: parenteral nutrition
+
Enteral and oral nutrition
Use concomitant minimal oral or enteral nutrition
(to avoid villous atrophy)

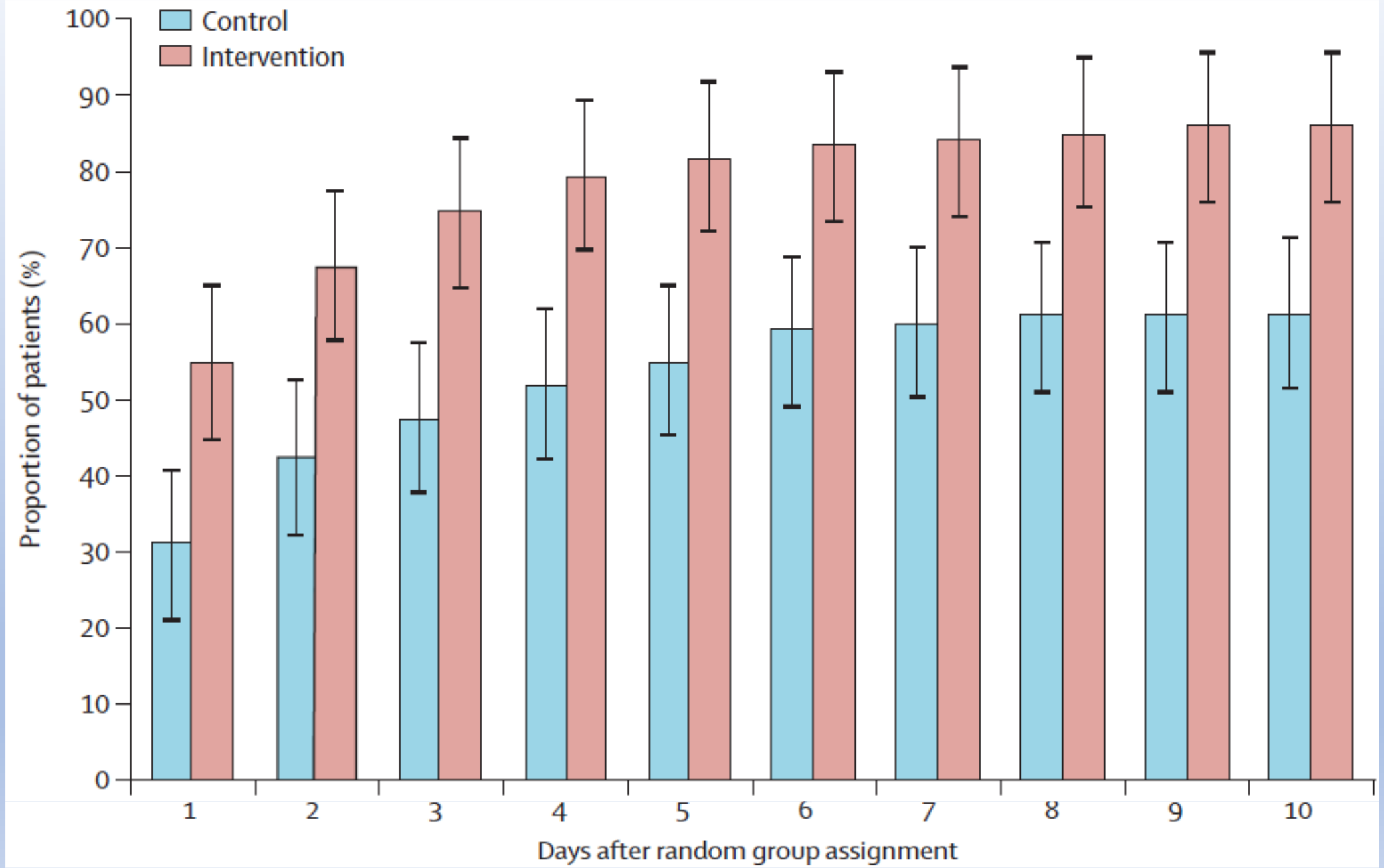
Inclusion Criteria: Age ≥ 18 years
Nutrition Risk Score ≥ 3
Expected LOS > 4 days

Exclusion Criteria: surgical patients; unable to ingest oral nutrition; terminal condition; already receiving nutritional therapy on admission; hospitalized because of anorexia nervosa; acute pancreatitis; acute liver failure; cystic fibrosis; stem cell transplantation; malnutrition after gastric bypass operations

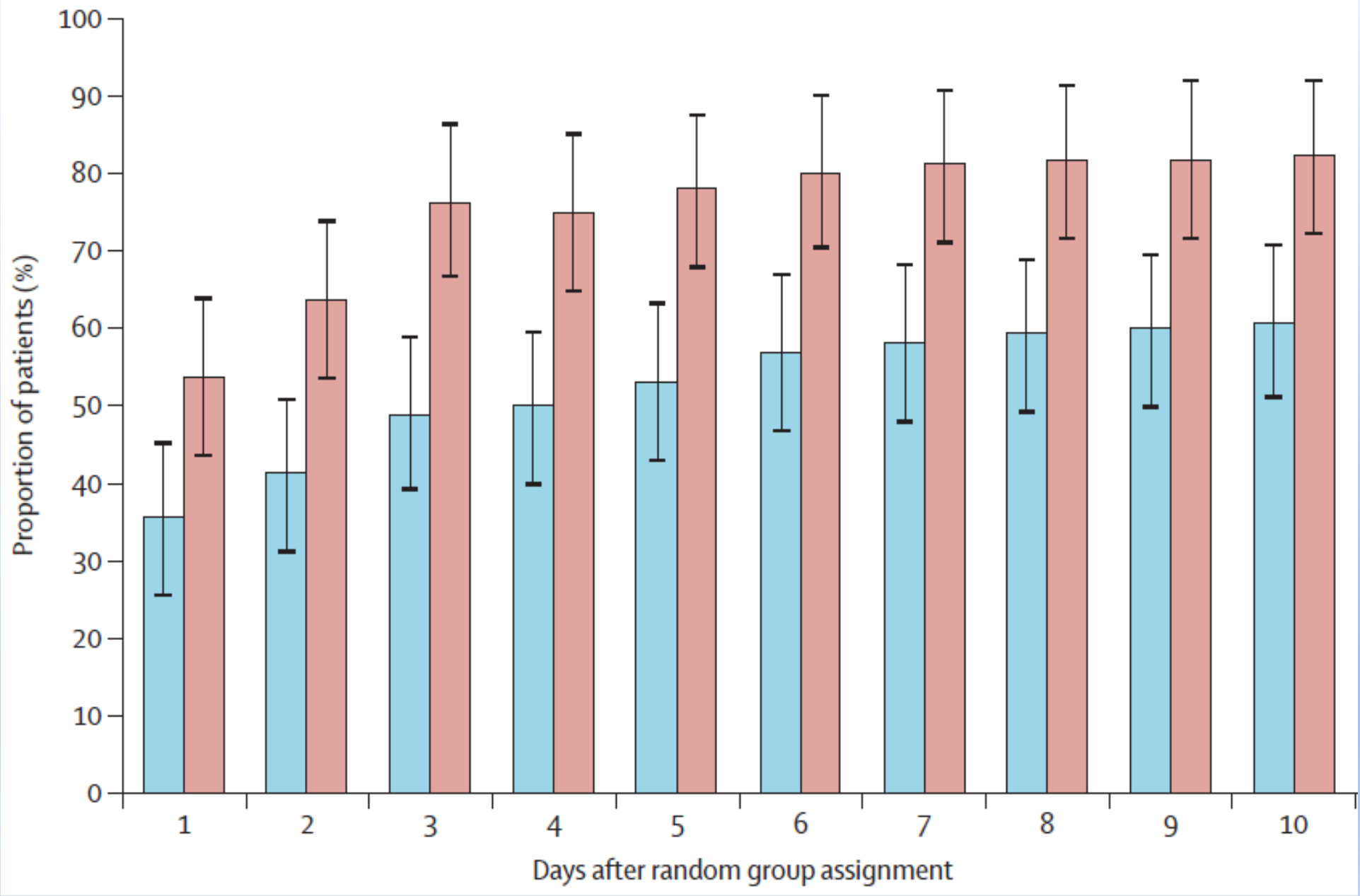
Composite Primary Endpoint

<u>Adverse clinical outcome within 30 days</u>
comprising all-cause mortality; admission to ICU; non-elective re-admission; major complications as a new occurrence including nosocomial infection, respiratory failure, a major cardiovascular event, acute renal failure, gastro-intestinal failure (ie, hemorrhage, intestinal perforation, acute pancreatitis); decline in functional status of ≥ 10%

Percent achieving caloric requirements



Percent achieving protein requirements



OUTCOMES

	Intervention group (n=1015)	Control group (n=1013)	Odds ratio or coefficient (95% CI)	p value
Outcomes				
Primary outcome				
Adverse outcome within 30 days	232 (23%)	272 (27%)	0·79 (0·64 to 0·97)	0·023
Single components of primary outcome				
All-cause mortality	73 (7%)	100 (10%)	0·65 (0·47 to 0·91)	0·011
Decline in functional status of ≥10%*	35 (4%) of 942	55 (6%) of 913	0·62 (0·40 to 0·96)	0·034
Additional secondary outcomes				
Mean length of stay (days)	9·5 (7·0)	9·6 (6·1)	–0·21 (–0·76 to 0·35)	0·46
Mean Barthel score (points)*	88 (26)	85 (30)	3·26 (0·93 to 5·60)	0·006
Mean EQ-5D VAS (points)†	59 (26)	56 (29)	3·06 (0·53 to 5·59)	<0·0001
Mean EQ-5D index (points)	0·75 (0·32)	0·73 (0·34)	0·13 (0·09 to 0·17)	0·018

#8
CANCER THERAPY

CLOSING IN ON
THE SILVER BULLET

The Cancer Silver Bullet

100% Lethal to cancer cells

100% Harmless to patient cells

Step 1: identify a gene that is absolutely required for cancer cell survival but not for patient cell survival

Step 2: destroy or turn off the gene

What Makes a Cell Malignant?

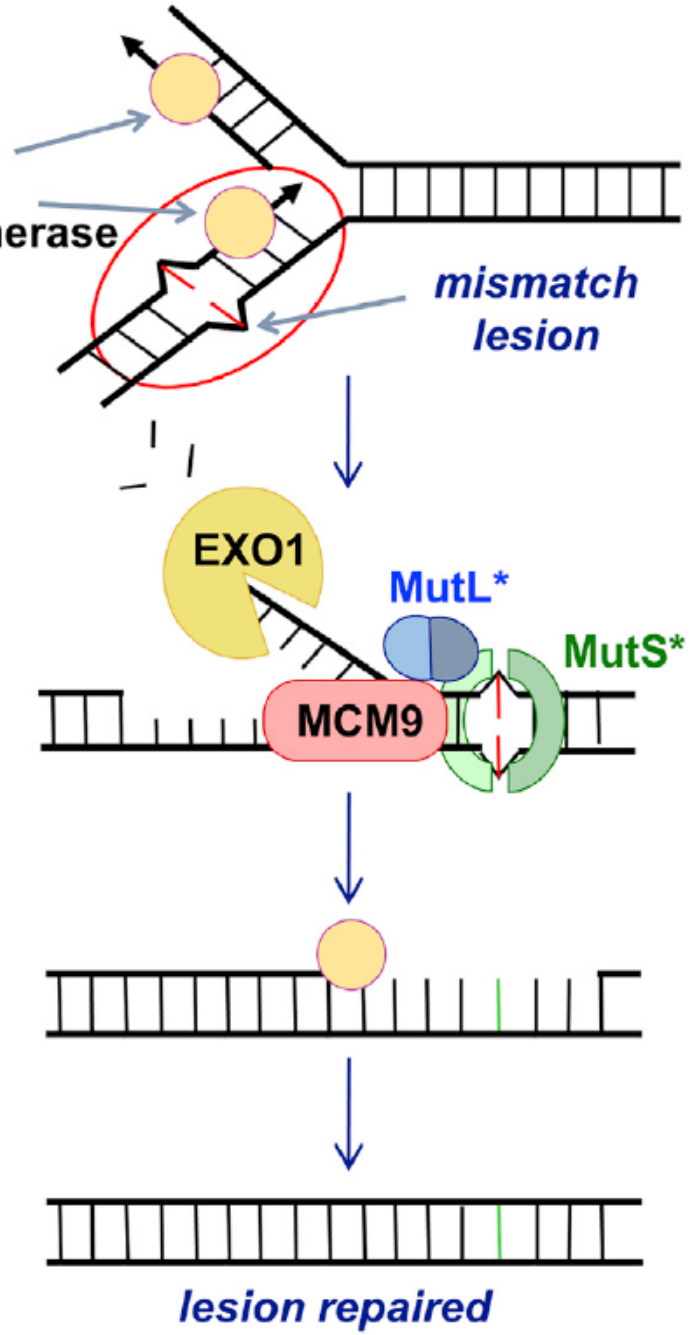
- genetic/epigenetic mutations
- suppression of apoptosis
- enhancement of cell growth/division

Accumulation of Mutations → Malignancy

Accumulation of Mutations → Oncogenic Addiction

- loss of redundant metabolic pathways required for cell survival
- remaining pathway dependent upon one or two genes (addiction)
- increased number of mutations ?→ Increased oncogene addiction

Proposed Role of MCM9 Helicase Activity in MMR



MMR = Mismatch Repair

Multiple gene products (proteins) required for repair

Over time, failure of mismatch repair leads to sequences of repeating bases in the DNA called ***microsatellites.***

Microsatellite instability (**MSI**) is the condition of genetic hypermutability (predisposition to mutation) that results from impaired DNA mismatch repair (MMR). The presence of MSI represents phenotypic evidence that MMR is not functioning normally.

Many cancers (e.g. Lynch Syndrome) are characterized by high levels of MSI indicative of defects in MMR.

Hypermutation caused by defective MMR plays a role in the malignant behavior of a cell.

There are multiple mechanisms of MMR and as a developing cancer cell loses these due to mutations, it may become highly dependent upon a residual functioning MMR gene.

Oncogene Addiction: In general, many cancers are critically dependent upon certain genes for survival while the surrounding normal tissue is not.

LETTER

https://doi.org/10.1038/s41586-019-1102-x

WRN helicase is a synthetic lethal target in microsatellite unstable cancers

Chan EM, Iorio F, Picco G et al. Nature 2019

ARTICLE

https://doi.org/10.1038/s41586-019-1103-9

Prioritization of cancer therapeutic targets using CRISPR–Cas9 screens

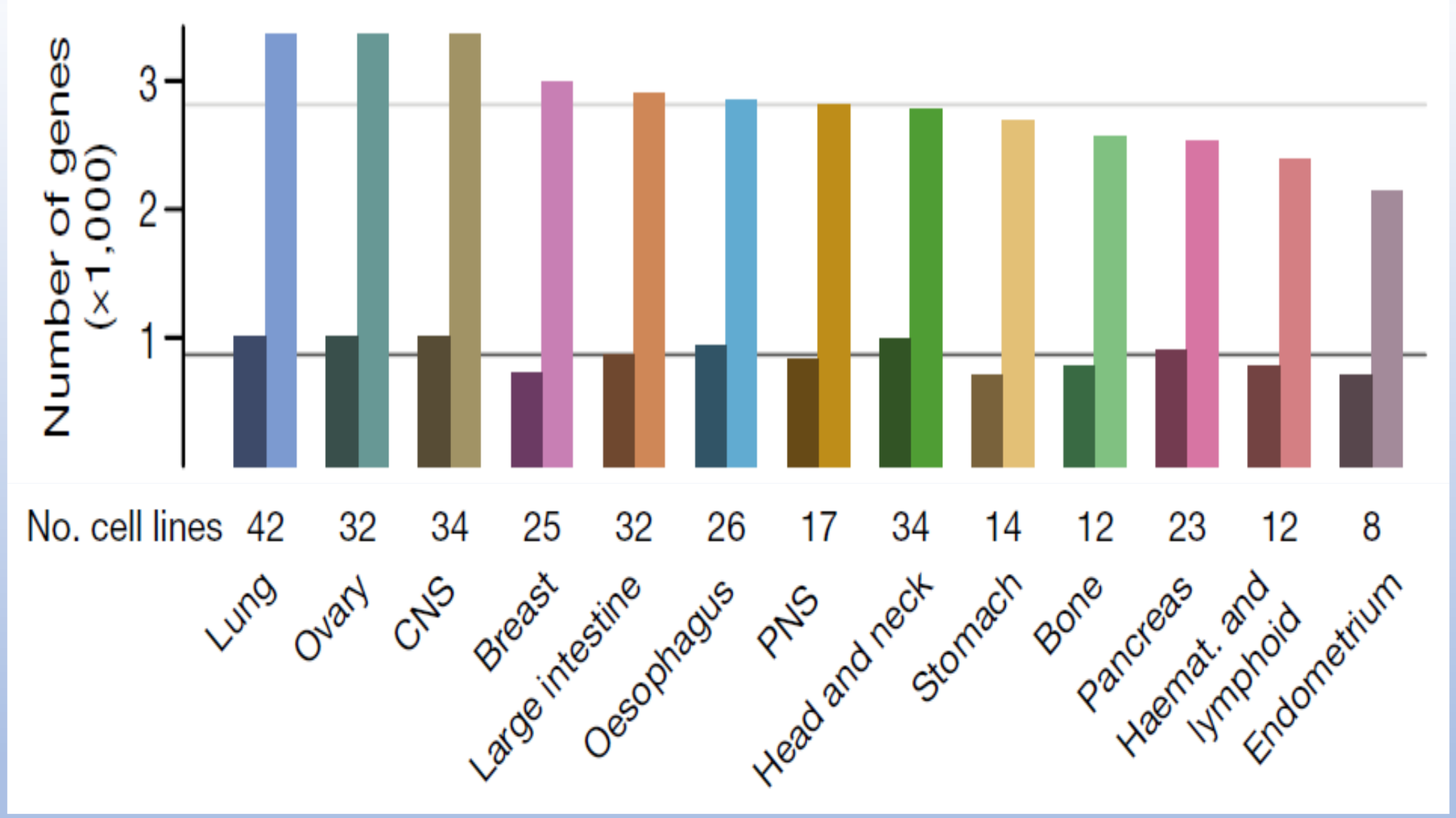
Fiona M. Behan[1,2,12], Francesco Iorio[1,2,3,12], Gabriele Picco[1,12], Emanuel Gonçalves[1], Charlotte M. Beaver[1], Giorgia Migliardi[4,5], Rita Santos[6], Yanhua Rao[7], Francesco Sassi[4], Marika Pinnelli[4,5], Rizwan Ansari[1], Sarah Harper[1], David Adam Jackson[1], Rebecca McRae[1], Rachel Pooley[1], Piers Wilkinson[1], Dieudonne van der Meer[1], David Dow[2,6], Carolyn Buser-Doepner[2,7], Andrea Bertotti[4,5], Livio Trusolino[4,5], Euan A. Stronach[2,6], Julio Saez-Rodriguez[2,3,8,9,10], Kosuke Yusa[1,2,11,13]* & Mathew J. Garnett[1,2,13]*

Behan FM, Shibue T, McFarland JM et al. Nature 2019

Chan EM, Iorio F, Picco G et al. Nature 2019
Behan FM, Shibue T, McFarland JM et al. Nature 2019

Looking for oncogenic addiction target genes

- targeted 18,009 genes in 339 cancer cell lines
- turned off each gene individually and observed for effect on cell growth/survival
- result: high sensitivity, specificity and precision in classifying essential and non-essential genes in cancer cell lines



Dark Bar: genes essential for cancer and adjacent normal tissue
Light Bar: genes essential for cancer only

WRN Helicase

- diverse roles in DNA repair, replication, transcription and telomere maintenance

- Cancer cell WRN-dependency (oncogenic addiction) correlated with the number of microsatellite deletions within a MSI cell line (**biomarker**)

- Knockout of WRN gene in identified cancer cell lines
  a) impaired cell growth
  b) caused DNA breaks/chromosome fragmentation

In Microsatellite Instability cancers (very common) the frequency of the Microsatellite Instability (easily measured) correlates with the degree to which mismatch repair is impaired and the likelihood of there being oncogenic addiction to the WRN Helicase gene product.

Silver Bullet Target

CONCLUSION

Using the currently available genetic/biochemical toolbox researchers can:

- test hundreds of cancer cell lines *for*
- thousands of essential cancer genes *and also*
- determine which of these genes are not essential for normal tissue (The Silver Bullet Target)

Next Step: refine the individual bullets for these targets (develop drugs which specifically turn off the Silver Bullet Target genes)

9
ECSTASY
&
PTSD

Post-Traumatic Stress Disorder

- 8% lifetime incidence in US population
- 35% of PTSD patients have debilitating symptoms not responsive to treatment
- 27-40% therapy dropout rate, often due to worsening of symptoms, hospitalization
- after the most effective therapies (cognitive processing therapy; prolonged exposure therapy) 60–72% of veterans still meet PTSD diagnostic criteria

New Idea: *drug administration during therapy to decrease dropout, failure, avoidance*

Two randomized, controlled pilot studies suggested safety and efficacy of MDMA (Ecstasy)

"Trauma theorists have asserted that emotional engagement is necessary for processing traumatic experiences and, under the influence of MDMA, people are able to remain emotionally connected while working with difficult traumatic material."

Ot'alora G M. Psychopharmacology 2018

3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomised, double-blind, dose-response, phase 2 clinical trial

Michael C Mithoefer, Ann T Mithoefer, Allison A Feduccia, Lisa Jerome, Mark Wagner, Joy Wymer, Julie Holland, Scott Hamilton, Berra Yazar-Klosinski, Amy Emerson, Rick Doblin

Mithoefer MC at al. Lancet Psychiatry 2018

3,4-Methylenedioxymethamphetamine-assisted psychotherapy for treatment of chronic posttraumatic stress disorder: A randomized phase 2 controlled trial

Marcela Ot'alora G[1], Jim Grigsby[2], Bruce Poulter[1],

Ot'alora G M et al. Journal of Psychopharamocology 2018

Mithoefer

- veterans, firefighters, police officers with chronic PTSD
- failed Cognitive Behavioral Therapy, Eye Movement Desensitization Reprocessing, Prolonged Exposure, Group and Individual Psychotherapy

Ot'alora

- mixed group: childhood abuse; combat; assaults, etc.
- failed Cognitive Behavioral Therapy, Eye Movement Desensitization Reprocessing, Prolonged Exposure, Group Psychotherapy

All psychiatric drugs were tapered and stopped prior to trial

PRIMARY OUTCOME: change in CAPS-IV score

CAPS-IV Categories of Questions

- Re-experiencing symptoms
- Avoidance symptoms
- Negative alterations in cognition and mood
- Alterations in arousal and reactivity

Secondary Endpoints:

- Beck Depression Inventory
- Pittsburgh Sleep Quality Index
- Global Assessment of Functioning
- Dissociative Experiences Scale II
- Post-Traumatic Growth Inventory

Experimental Intervention

Active Control: 30-40 mg MDMA
Intervention: 75-125 mg MDMA

2 or 3 eight-hour psychotherapy sessions after receiving study drug

Frequent telephone follow-up and 90-minute therapy sessions without drug between drug sessions

Ot'alora

	40 mg MDMA (*n*=6)	100 mg MDMA (*n*=9)	125 mg MDMA (*n*=12)[a]
Primary efficacy variable, PP set			
CAPS-IV total score, mean (SD)			
Baseline	84.6 (9.0)	94.4 (20.2)	91.6 (19.7)
Post 2 blinded sessions	80.6 (18.8)	70.0 (28.2)	54.6 (31.9)
Change[b]	−4.0 (11.9)	−24.4 (24.2)	−37.0 (20.9)
p Value[c]	–	0.10	0.01

Mithoefer

	30 mg MDMA plus psychotherapy (n=7)	75 mg MDMA plus psychotherapy (n=7)	125 mg MDMA plus psychotherapy (n=12)
Primary efficacy measure			
Mean CAPS-IV total score			
Baseline	87·4 (14·1)	82·4 (17·3)	89·7 (17·3)
After two experimental sessions of MDMA	76·0 (23·4)	24·1 (17·2)	45·3 (33·8)
Change†	−11·4 (12·7)	−58·3 (9·8)	−44·3 (28·7)
p value‡	NA	0·0005	0·004

10
ω–3 FATTY ACIDS
and
ISCHEMIC HEART DISEASE

ω–3 Fatty Acids Involved in Human Physiology

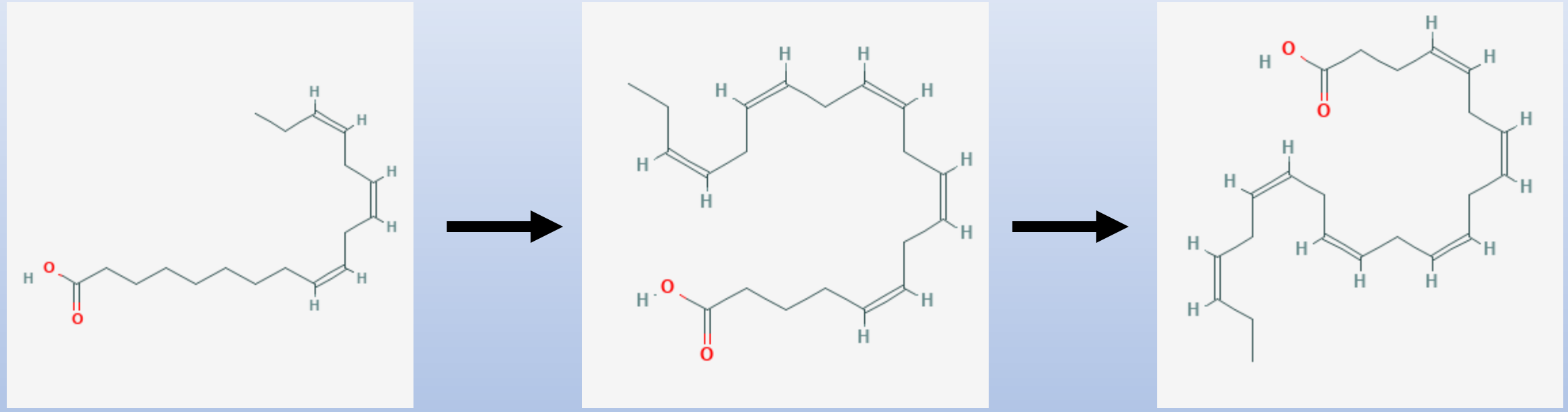
α-linolenic acid (ALA) in walnut, flaxseed, hemp oils

eicosapentaenoic acid (EPA) in fish, squid, krill

docosahexaenoic acid (DHA) in fish, squid, krill

Added to statin therapy to reduce cardiovascular events

Human Metabolism



ALA EPA DHA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of n–3 Fatty Acid Supplements in Diabetes Mellitus

JAMA Cardiology | Original Investigation

Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks

Meta-analysis of 10 Trials Involving 77 917 Individuals

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Marine n–3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer

CONCLUSIONS

Supplementation with n–3 fatty acids did not result in a lower incidence of major cardiovascular events or cancer than placebo. (Funded by the National Institutes of Health and others; VITAL ClinicalTrials.gov number, NCT01169259.)

CONCLUSIONS

Among patients with diabetes without evidence of cardiovascular disease, there was no significant difference in the risk of serious vascular events between those who were assigned to receive n–3 fatty acid supplementation and those who were assigned to receive placebo. (Funded by the British Heart Foundation and others;

Findings This meta-analysis of 10 trials involving 77 917 participants demonstrated that supplementation with marine-derived omega-3 fatty acids for a mean of 4.4 years had no significant association with reductions in fatal or nonfatal coronary heart disease or any major vascular events.

Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis

MitsuhiroYokoyama, Hideki Origasa, Masunori Matsuzaki, Yuji Matsuzawa, Yasushi Saito, Yuichi Ishikawa, Shinichi Oikawa, Jun Sasaki, Hitoshi Hishida, Hiroshige Itakura, Toru Kita, Akira Kitabatake, Noriaki Nakaya, Toshiie Sakata, Kazuyuki Shimada, Kunio Shirato, for the Japan EPA lipid intervention study (JELIS) Investigators

Yokoyama M et al. Lancet 2007

Japan EPA Lipid Intervention Study (JELIS)

- **open label**, randomized
- 1800 mg eicosapentaenoic acid (EPA)
- 18,645 subjects followed for 4.6 years
- 19% relative reduction in major coronary events

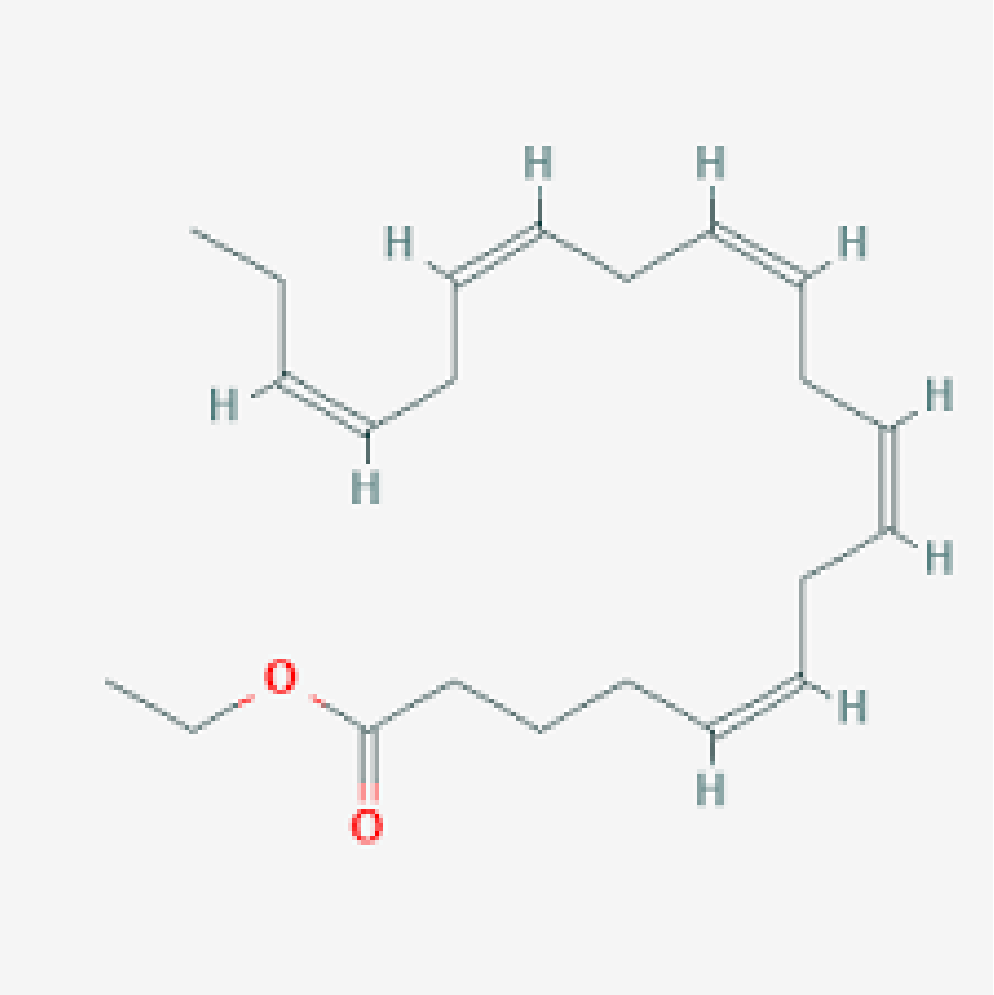
REDUCE-IT

The NEW ENGLAND JOURNAL of MEDICINE

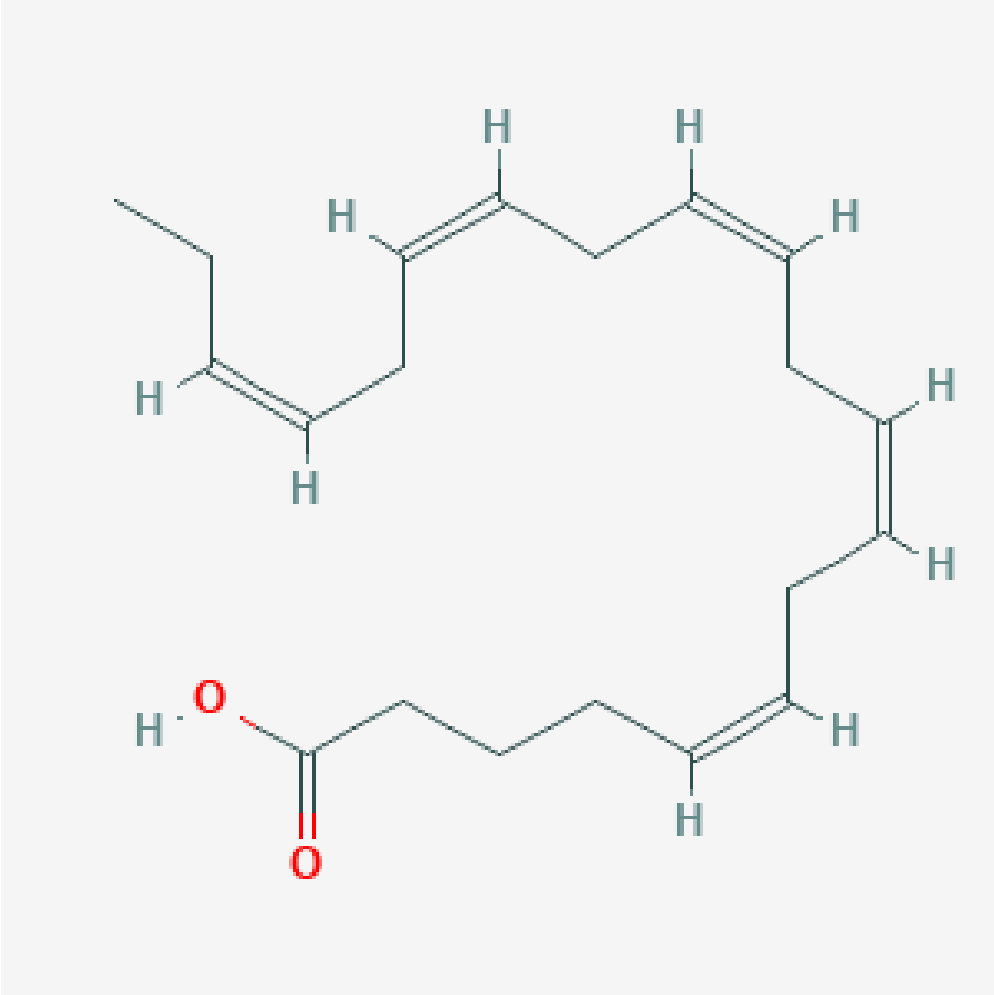
ESTABLISHED IN 1812 JANUARY 3, 2019 VOL. 380 NO. 1

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Bhatt DL et al. NEJM 2019



icosapent ethyl

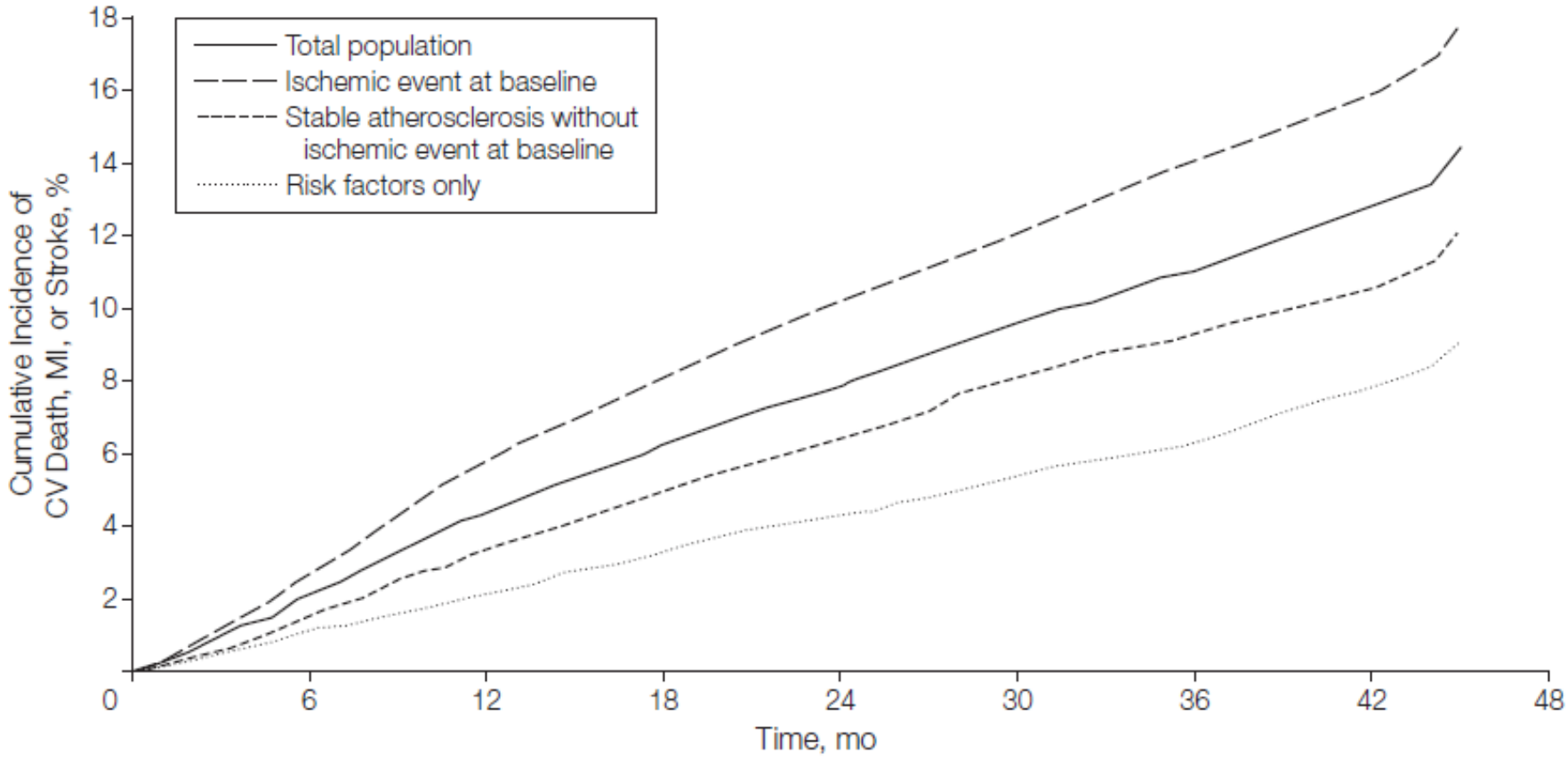


eicosapentaenoic

We already have very potent statins!

Why do we need to be studying fatty acids?

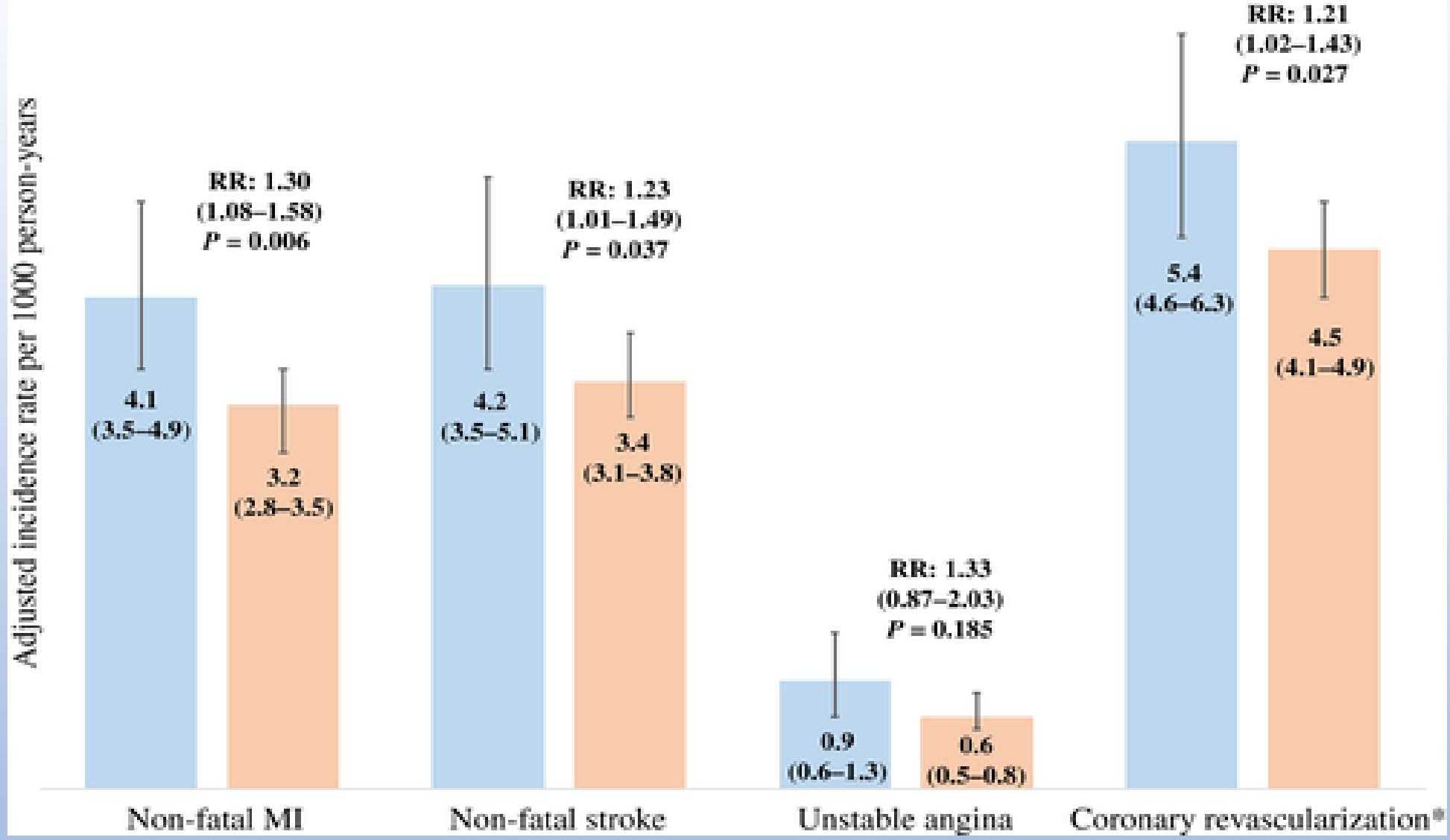
Figure 2. Kaplan-Meier Cumulative Incidence Curves for the Composite End Point of Cardiovascular Death, Myocardial Infarction, or Stroke in the Entire Population With 4-Year Follow-up and Key Subgroups



No. at risk								
Total population	45 227	44 038	42 252	40 422	34 666	32 567	29 338	25 417
Ischemic event at baseline	21 890	21 159	20 143	19 220	16 455	15 498	13 977	12 210
Stable atherosclerosis without ischemic event at baseline	15 264	14 947	14 402	13 809	11 910	11 192	10 103	8835
Risk factors only	8073	7932	7707	7382	6301	5877	5258	4372

Only first events are included. CV indicates cardiovascular; MI, myocardial infarction.

Bhatt DL et al. JAMA 2010



BLUE: TG 200-499 mg/dl Orange: TG < 150 mg/dl

Nichols GA. Diabetes Obesity Metabolism 2018

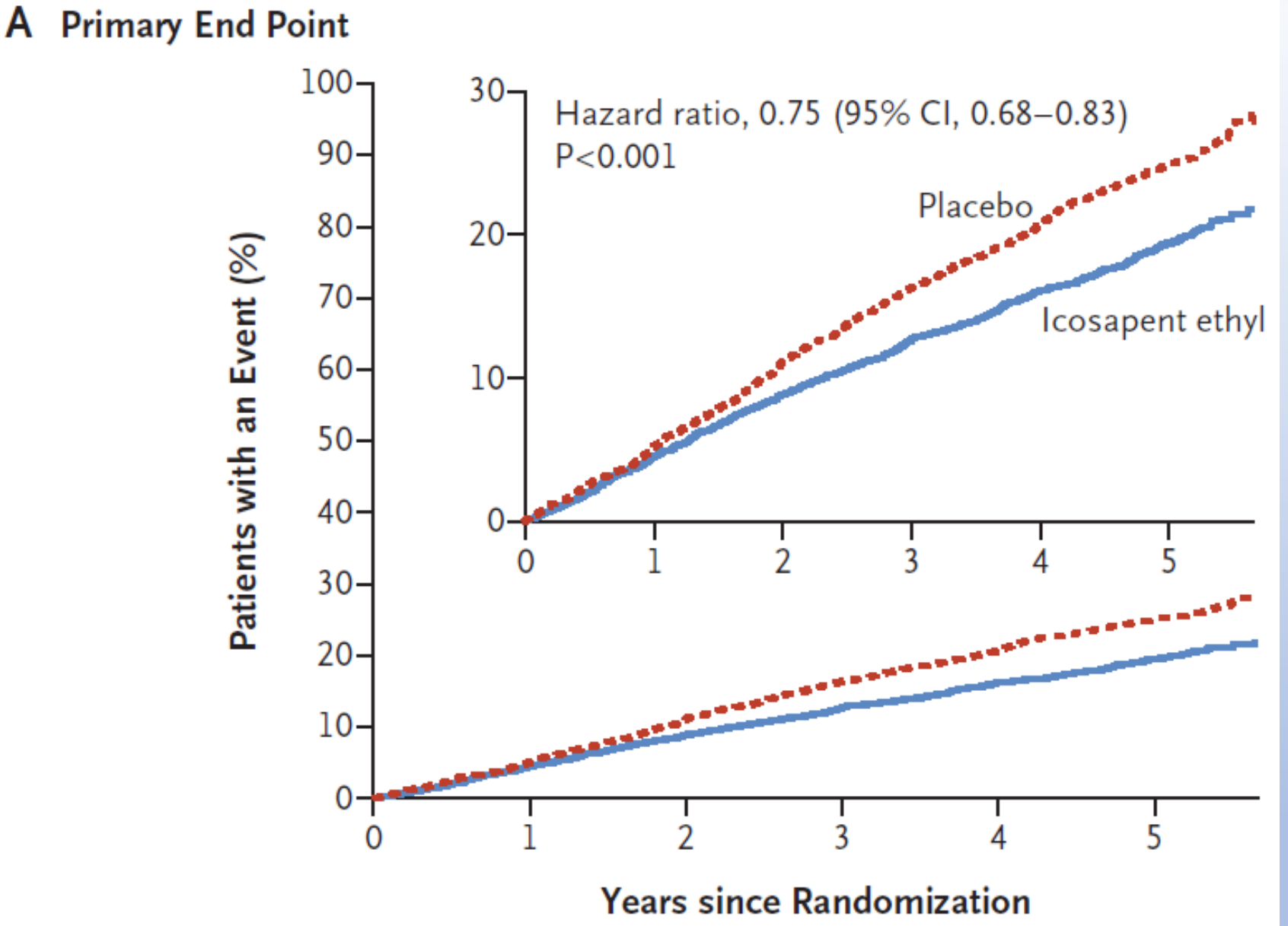
REDUCE-IT

- prospective, randomized, double-blind, placebo-controlled trial
- icosapent ethyl 2gm bid vs. placebo
- subjects: age > 45 yrs with known CAD
  age > 50 yrs with DM plus another CAD risk factor
- LDL 40 – 100 on statin therapy
- TG 150 - 499

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Icosapent Ethyl (N = 4089)	Placebo (N = 4090)
Age		
Median (IQR) — yr	64.0 (57.0–69.0)	64.0 (57.0–69.0)
≥65 yr — no. (%)	1857 (45.4)	1906 (46.6)
Male sex — no. (%)	2927 (71.6)	2895 (70.8)
White race — no. (%)†	3691 (90.3)	3688 (90.2)
Body-mass index‡		
Median (IQR)	30.8 (27.8–34.5)	30.8 (27.9–34.7)
Cardiovascular risk stratum — no. (%)		
Secondary-prevention cohort	2892 (70.7)	2893 (70.7)
Primary-prevention cohort	1197 (29.3)	1197 (29.3)
Diabetes — no. (%)		
Type 1	27 (0.7)	30 (0.7)
Type 2	2367 (57.9)	2363 (57.8)
No diabetes at baseline	1695 (41.5)	1694 (41.4)

Bhatt DL et al. New Engl J Med 2019



Composite end point of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina.

Hazard Ratio 0.75
$p < 0.001$

Bhatt DL et al.
New Engl J Med 2019

Other agents that also lower triglyceride levels, including other n−3 fatty acids, extended release niacin, fenofibrate, and cholesteryl ester transfer protein inhibitors have not been shown to reduce cardiovascular events. Why does icosapent ethyl work?

- anti-inflammatory effects
- membrane stabilization
- plaque stabilization
- anti-oxidant effects