

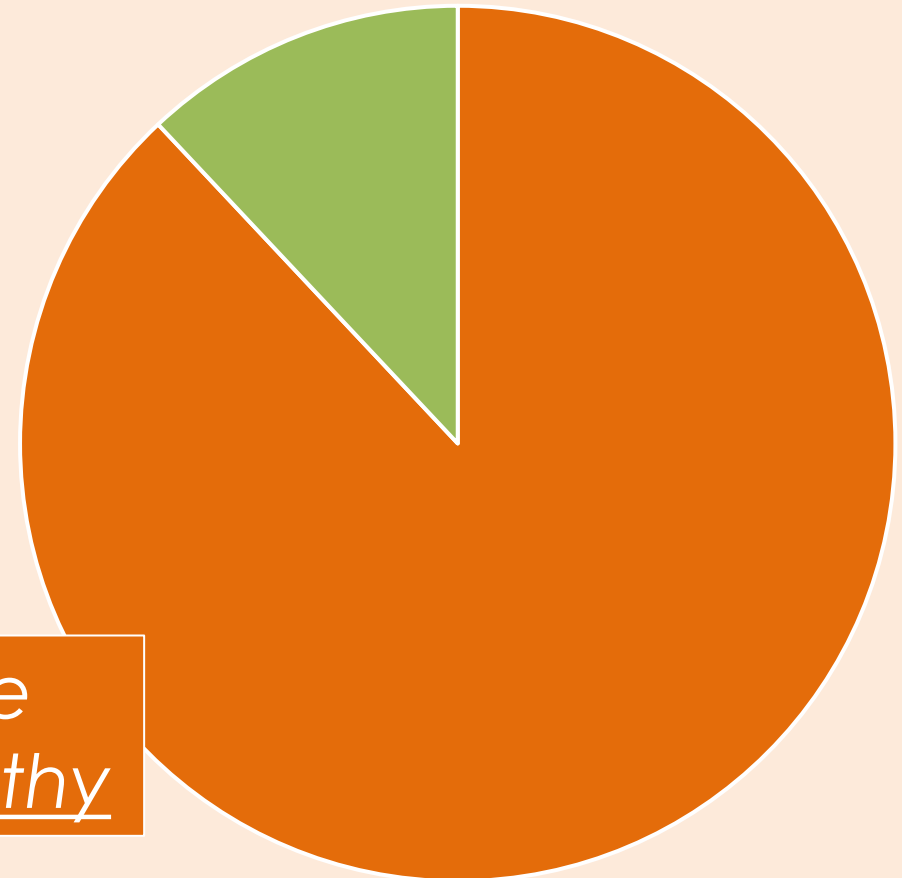
Insulin Resistance: Role in Cognitive Decline

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Prevalence of Optimal Metabolic Health in American Adults: National Health and Nutrition Examination Survey 2009-2016

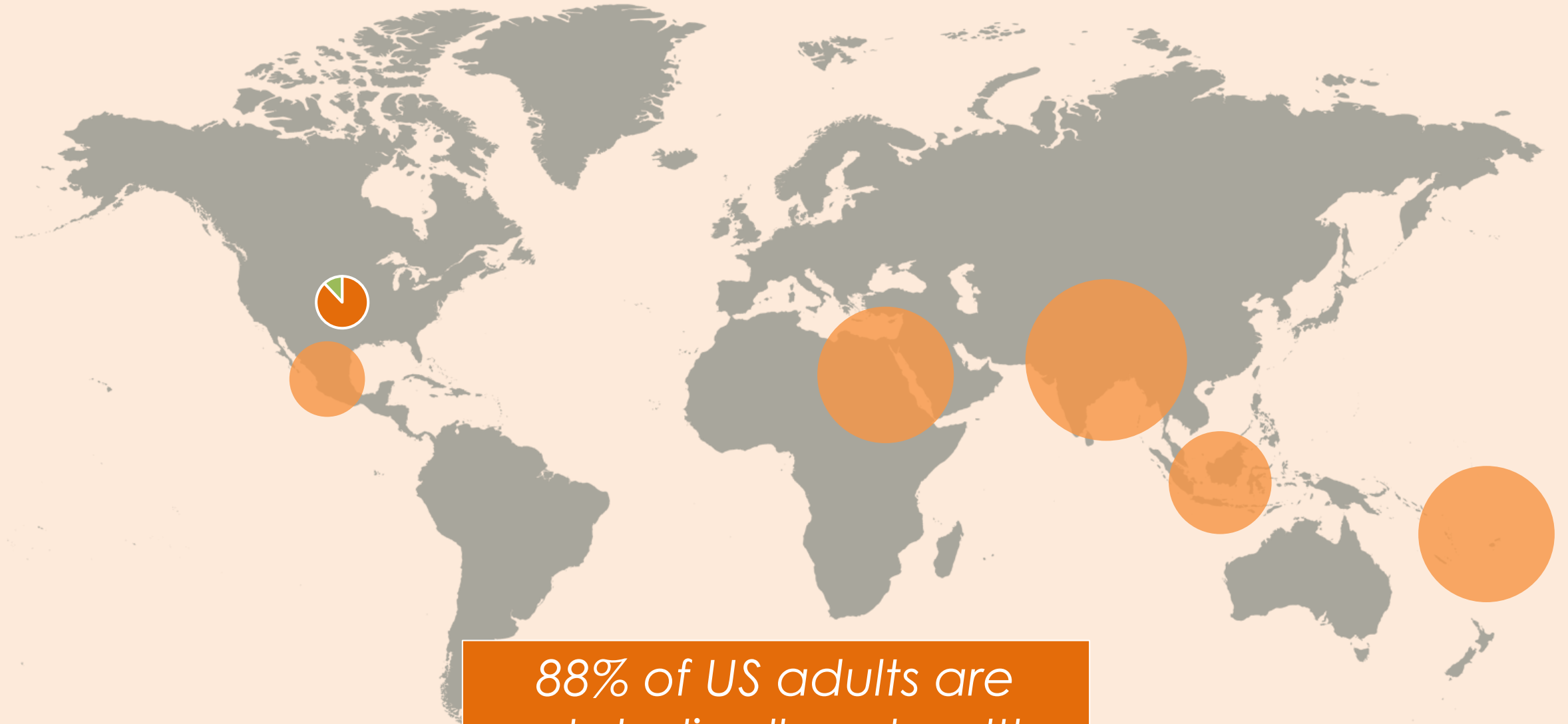
*“Prevalence of **metabolic health** in American adults is **alarmingly low**, even in **normal weight** individuals.”*



88% of US adults are metabolically unhealthy

Citations for your
convenience

PMID: 30484738



*88% of US adults are
metabolically unhealthy*

What is metabolic health?



**Metabolic
Syndrome**

88% of US adults are
metabolically unhealthy

Waist Circumference



Glucose



Blood Pressure



Metabolic Syndrome

Triglycerides



HDL Cholesterol



Waist Circumference **X**

X Glucose

Blood Pressure **X**

**Insulin
Resistance**

X Triglycerides

HDL Cholesterol **X**



What is insulin resistance?



What is insulin resistance?

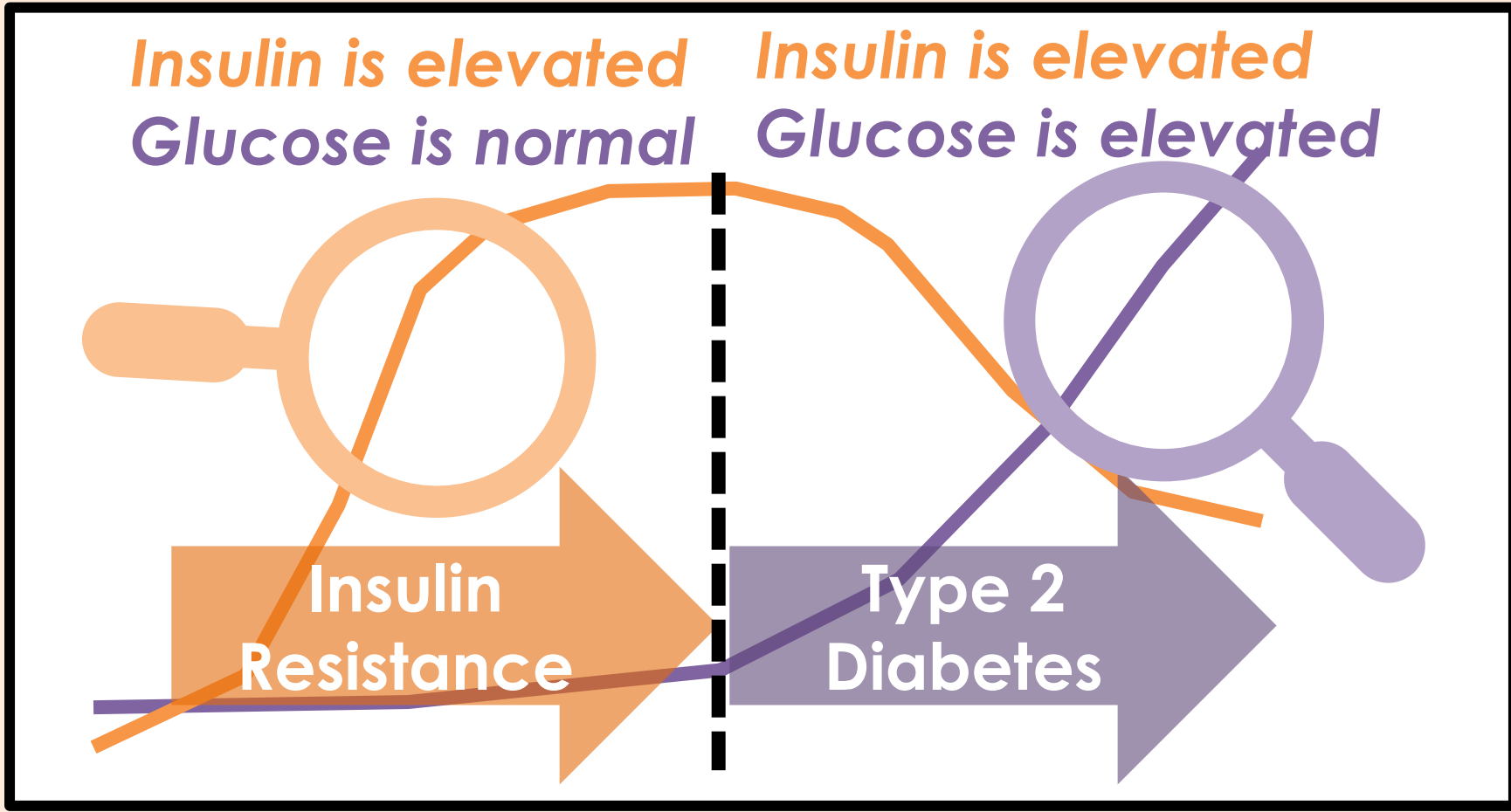


Some cells fail to fully respond to insulin

Insulin levels are high

What is insulin resistance?

Glucose



Insulin

Time
(years)

Where does insulin resistance come from?



**Insulin
Resistance**

Fast

Slow

Inflammation

Insulin

Fat cells

Stress

Resistance

Hyperinsulinemia

Insulin

Is it common to have high insulin?

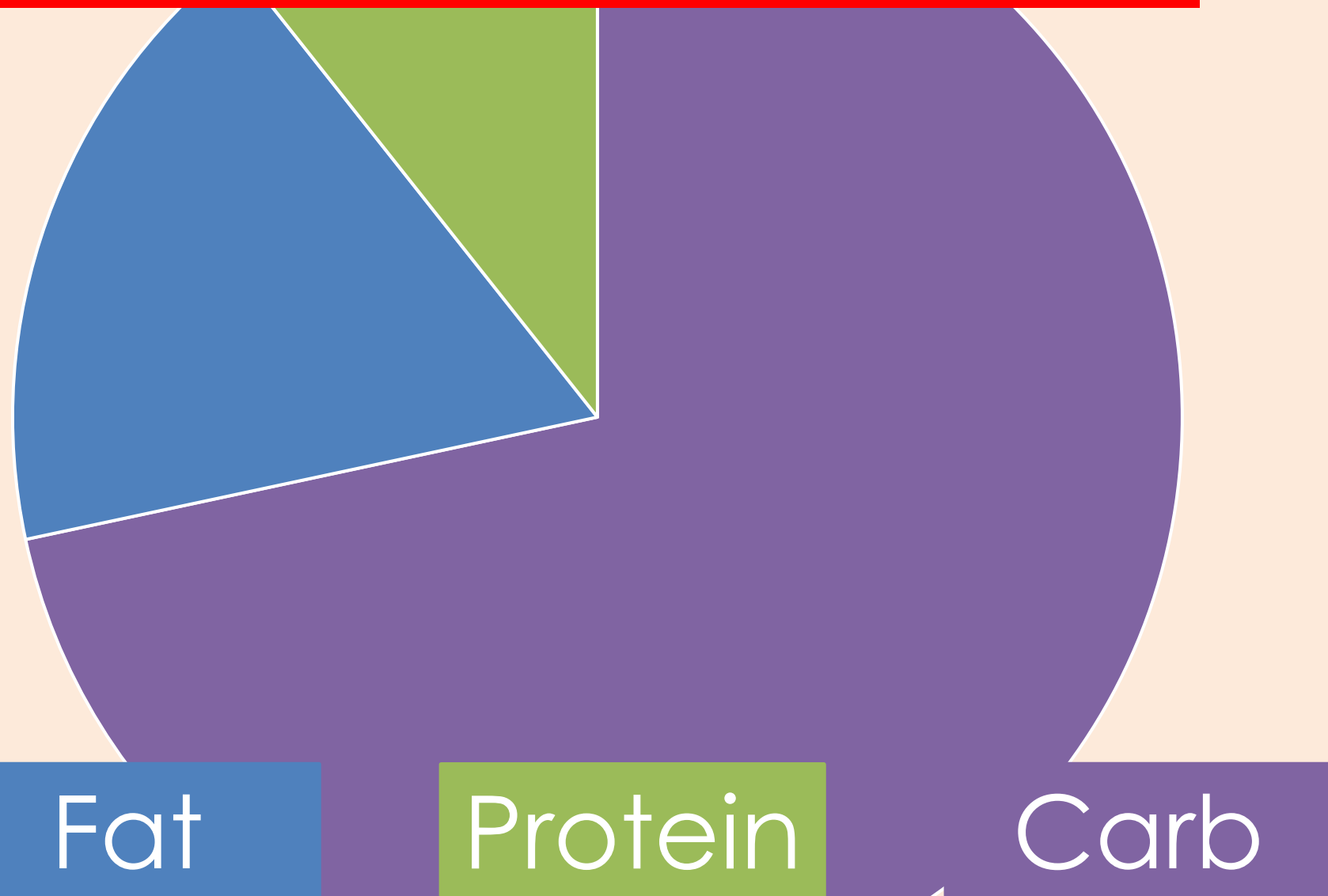


Insulin
Resistance

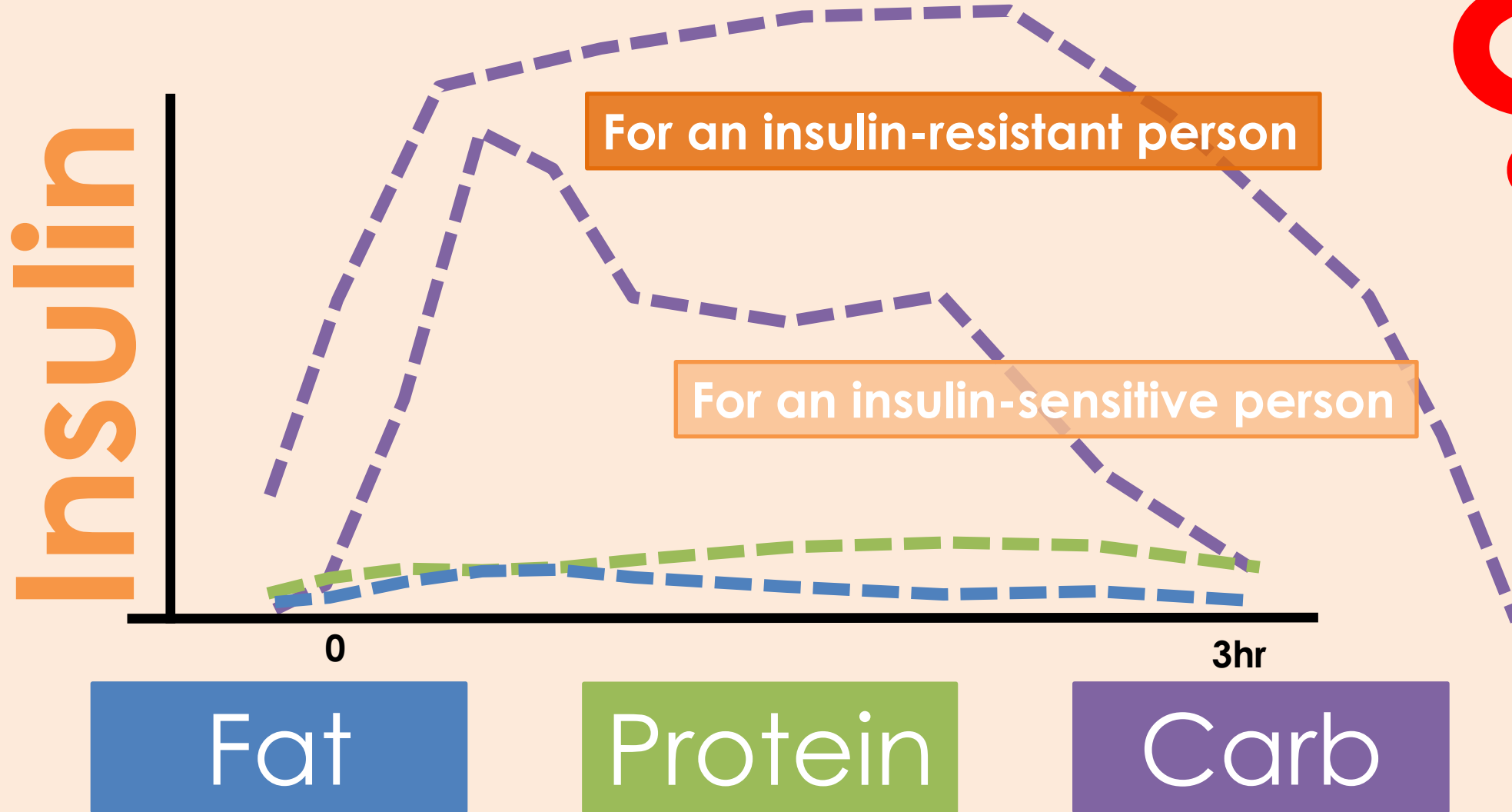
Insulin

PMID: 27340034 PMID: 2249650
PMID: 18430774 PMID: 31990657
PMID: 29455245 PMID: 24949486
PMID: 18569016 PMID: 7851681

Is it common to have high insulin?



Is it common to have high insulin?



For an insulin-resistant person

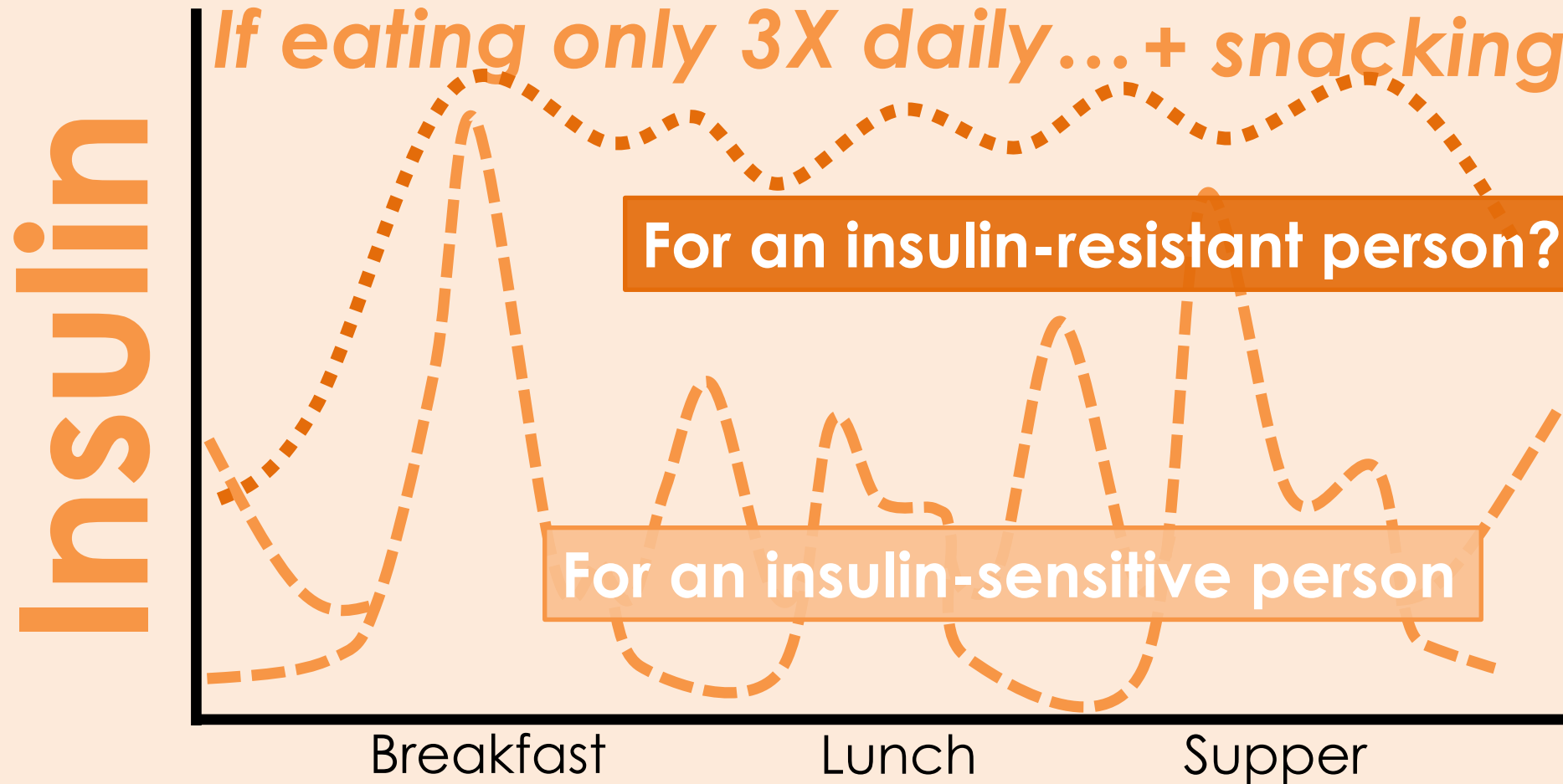
For an insulin-sensitive person

Fat

Protein

Carb

Is it common to have high insulin?



**Insulin
Resistance**

Migraines

Depression

Dementia

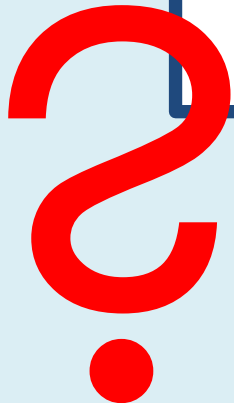
Alzheimer's Disease

- 6th leading cause of death
- Loss of memory
- Loss of motor function



Classic view: Caused by **plaques** in the brain

But do the plaques **cause** the disease
or simply **accompany** the disease?





Problems

- Many people with plaques have normal cognition
- Drugs that reduce plaques don't help



Classic view: Caused by **plaques** in the brain

2. Drugs that reduce plaques don't help

Anti-plaque drugs: A love story...

2020: FDA calls a special panel to review an anti-plaque drug

Panel: "The drug reduces plaques, but does not improve the disease"

Approve!

FDA: "...treatment with [the drug] was clearly shown in all trials to substantially **reduce amyloid beta plaques**. This reduction in plaques is reasonably **likely** to result in clinical benefit."

Dementia



2. Drugs that reduce plaques don't help

BLOTS ON A FIELD?

A neuroscience image sleuth finds signs of fabrication in scores of Alzheimer's articles, threatening a reigning theory of the disease *By Charles Piller*

“You can't cheat to cure a disease. Biology doesn't care.”

Matthew Schrag, Vanderbilt University

Is the plaque-based theory of AD based on faulty data?



Alternate view: Caused by **fuel** disruption

Glucose



Alternate view: Caused by **fuel** disruption

Association between features of the insulin resistance syndrome and Alzheimer's disease independently of apolipoprotein e4 phenotype: cross sectional population-based study



Statistically significant variables that correlated with Alzheimer's disease

- Age
- Education
- Apo E4

Journal of Diabetes Science and Technology

Volume 2, Issue 6, November 2008

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REVIEW ARTICLE

Alter

Association betw
and Alzheimer's
phenotype: cross

Alzheimer's Disease Is Type 3 Diabetes—Evidence Reviewed

Suzanne M. de la Monte, M.D., M.P.H.¹⁻³ and Jack R. Wands, M.D.³

Statistically significant variables that correlated
with Alzheimer's disease

- Age
- Education
- Apo E4

- Abnormal **glucose** tolerance
- Fasting plasma **glucose**
- Two-hour plasma **glucose**
- Fasting **insulin**
- Two-hour **insulin**



Dementia

Alternate view: Caused by **fuel** disruption

Glucose

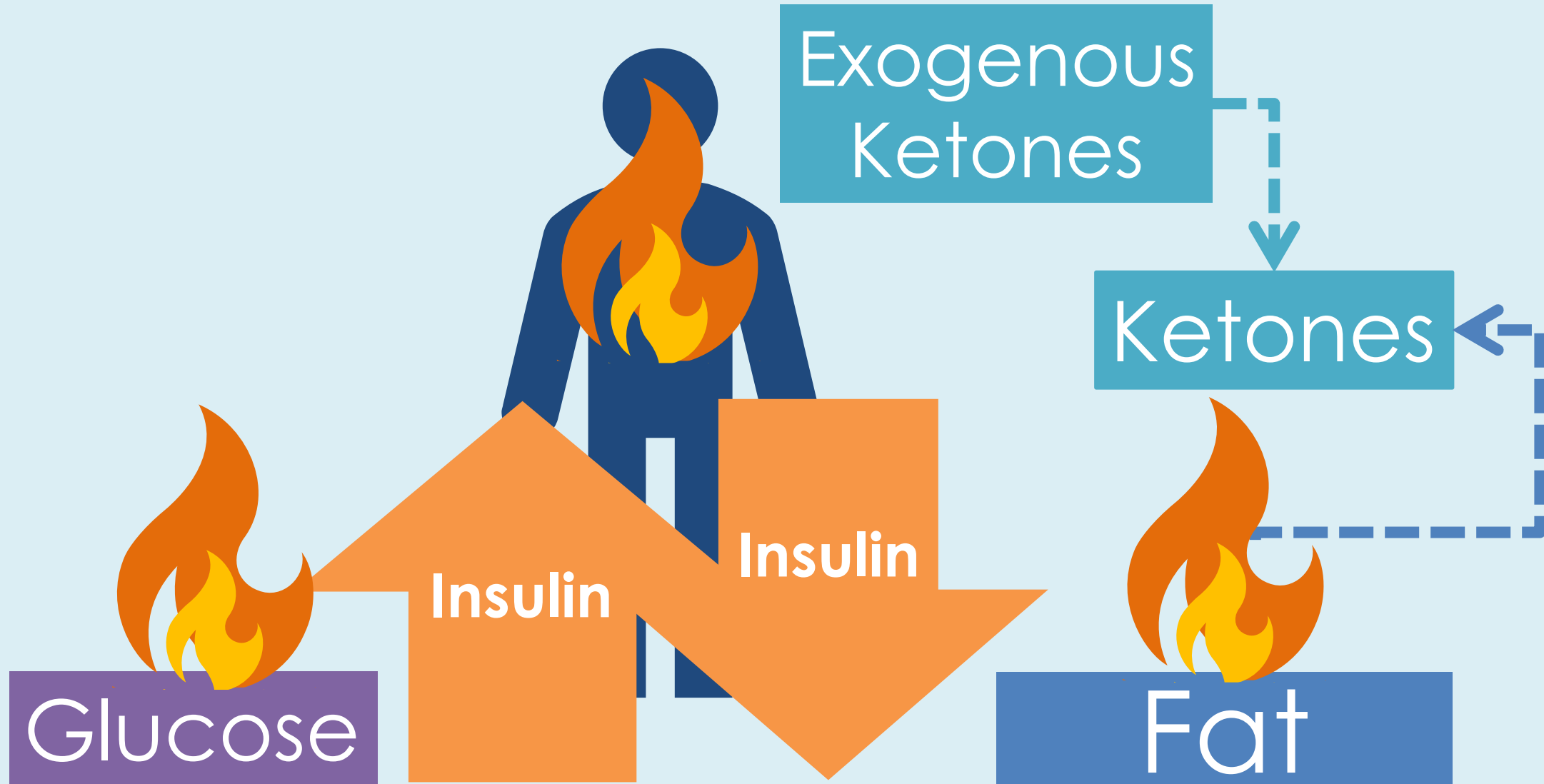
Insulin

Insulin
Resistance

Ketones

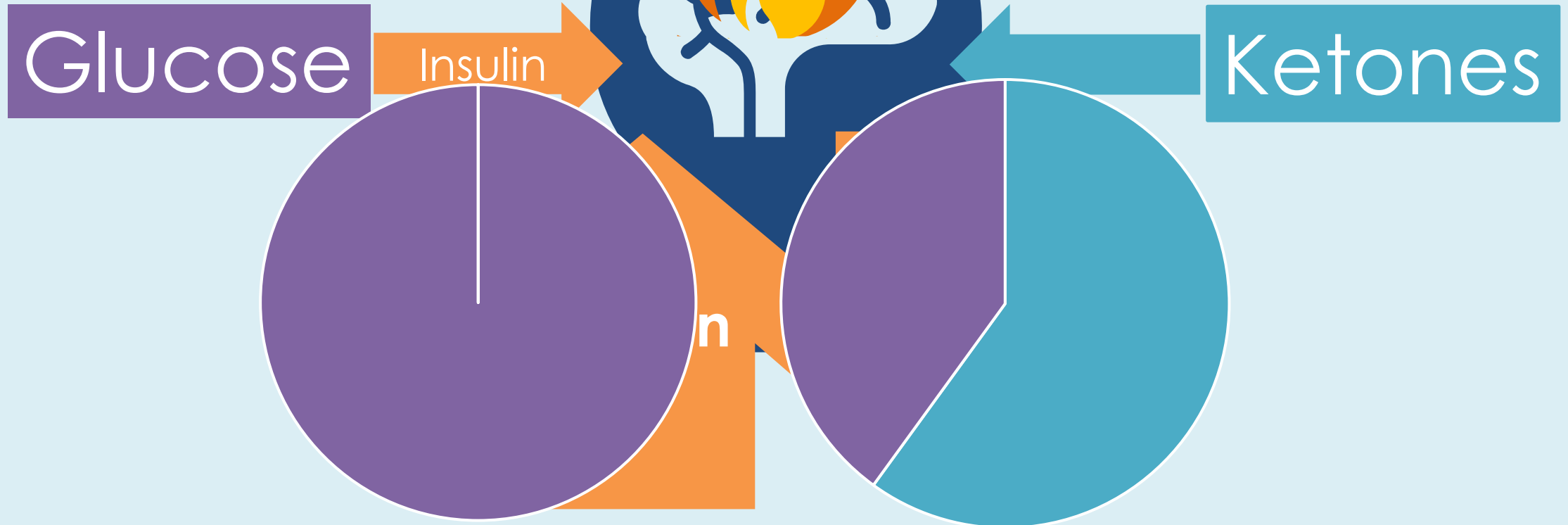


Tangent: What are ketones?



Dementia

Alternate view: Caused by **fuel** disruption



Dementia

Alternate view: Caused by **fuel** disruption



Rime of the Insulin-resistant Brain

“glucose, glucose everywhere, nor any drop to drink”

Dementia

Alternate view: Caused by **fuel** disruption

Research Article

White Matter Lipids as a Ketogenic Fuel Supply in Aging Female Brain:
Implications for Alzheimer's Disease



Lauren P. Klosinski ^a, Jia Yao ^b, Fei Yin ^b, Alfred N. Fonteh ^c, Michael G. Harrington ^c, Trace A. Christensen ^d,
Eugenia Trushina ^{d,e}, Roberta Diaz Brinton ^{a,b,f}

Ketones

*The catabolism of myelin lipids to generate ketones
"can be viewed as a systems level adaptive response to
address brain fuel and energy demand."*

Dementia

Concussion

Depression

Migraines

Glucose

Insulin

Insulin Resistance

Ketones



PMID: 29644487
PMID: 24270521
PMID: 32646634
PMID: 34166866

How can you reverse insulin resistance?



If it doesn't lower insulin, it won't improve insulin resistance



- Sulfonylureas
- Insulin
- GLP-1



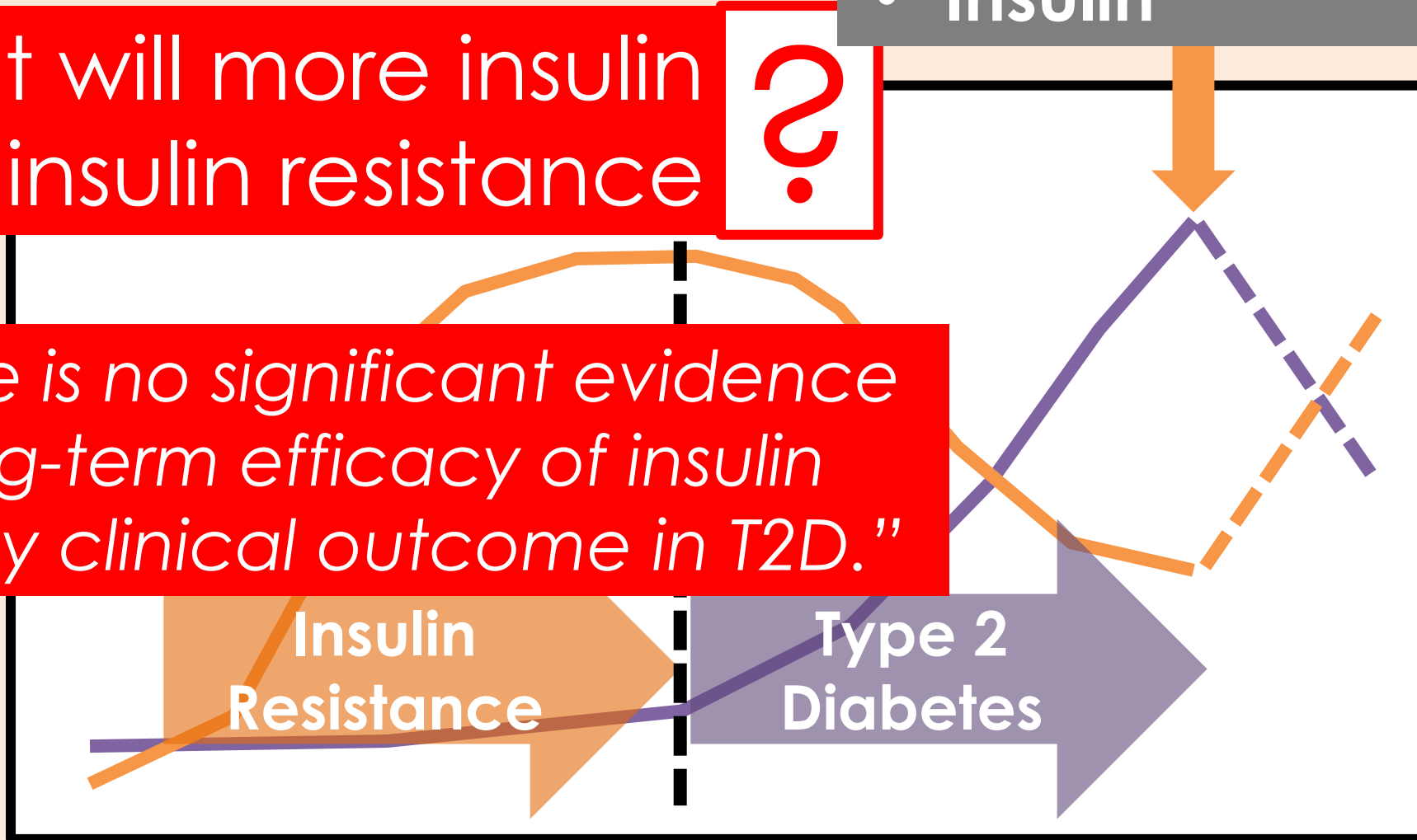
Drugs

Diet

What will more insulin do to insulin resistance?

- Sulfonylureas
- Insulin

“There is no significant evidence of long-term efficacy of insulin on any clinical outcome in T2D.”



Time

Insulin

- Sulfonylureas
- Insulin

What will more insulin do to insulin resistance

?

Increases insulin resistance

“...long-term insulin therapy increases insulin resistance...”

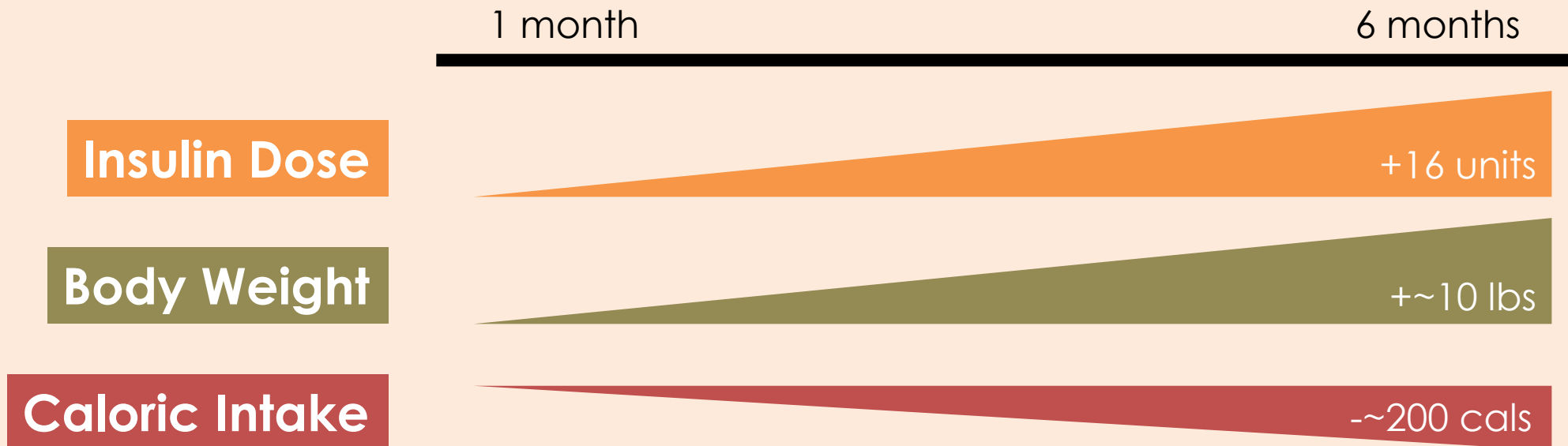
“...intensive insulin therapy increases insulin resistance...”

- Sulfonylureas
- Insulin

Body
Fat

Increases fat gain

Intensive conventional insulin therapy for type II diabetes.
Metabolic effects during a 6-mo outpatient trial



- Sulfonylureas
- Insulin

Body
Fat

Increases fat gain

Factors associated with basal metabolic rate in patients with type 2 (non-insulin-dependent) diabetes mellitus

*“Basal metabolic rate...**decreased significantly** with insulin therapy.”*

- Sulfonylureas
- Insulin

Cancer

Increases cancer mortality

Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin

*“Insulin use was associated with an adjusted **HR of cancer-related mortality of 1.9.**”*

*“Patients with type 2 diabetes exposed to sulfonylureas and exogenous insulin had a **significantly increased risk of cancer-related mortality** compared with patients exposed to metformin.”*

- Sulfonylureas
- Insulin

Heart
Disease

Increases CVD mortality

Association of Second-line Antidiabetic Medications With Cardiovascular Events Among Insured Adults With Type 2 Diabetes

“Higher cardiovascular risk was associated with use of sulfonylureas or basal insulin...”

Dementia

- Sulfonylureas
- Insulin

Increases dementia risk

Impact of pharmacological treatment of diabetes mellitus on dementia risk: systematic review and meta-analysis

“...we found differential effects across drug classes, with a signal of harm associated with insulin therapy ...”

- Sulfonylureas
- Insulin
- GLP-1



Drugs

Diet



Control
Carbs



Prioritize
Protein



Don't fear
Fat





What is insulin resistance?

Where does it come from?

How does it affect the brain?

What to do about it?



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