Hyperinsulinemia Consequences

Benjamin Bikman, Ph.D.
Professor
Cell Biology and Physiology
Brigham Young University

Why does hyperinsulinemia matter?

What is insulin resistance?

Some cells fail to fully respond to insulin

Insulin levels are high

There is no “insulin resistance” without hyperinsulinemia

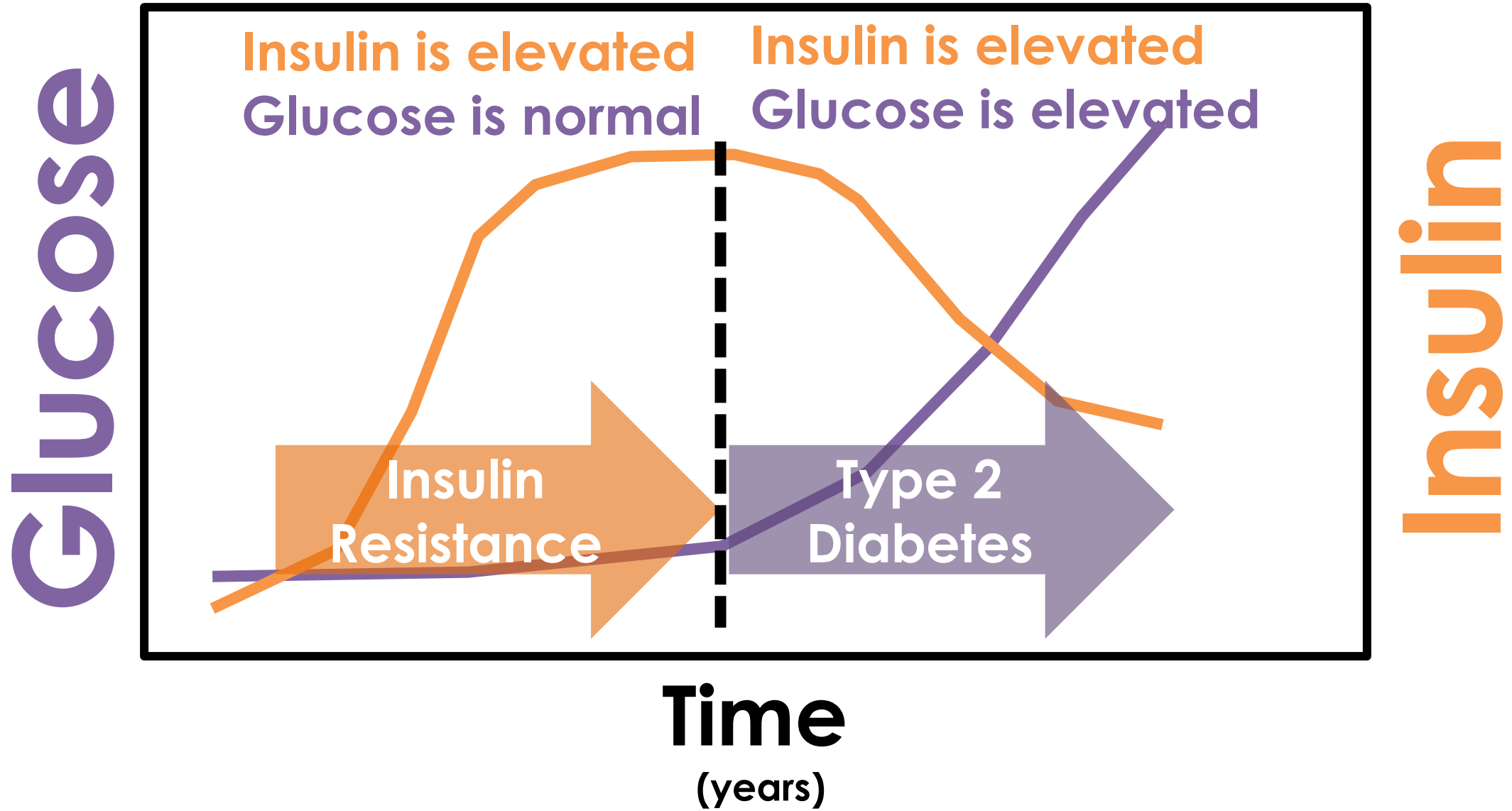

Heart Disease
Diabetes
Cancer
Body Fat
Insulin Resistance
Fatty Liver
Migraines
PCOS
Dementia
Erectile Dysfunction

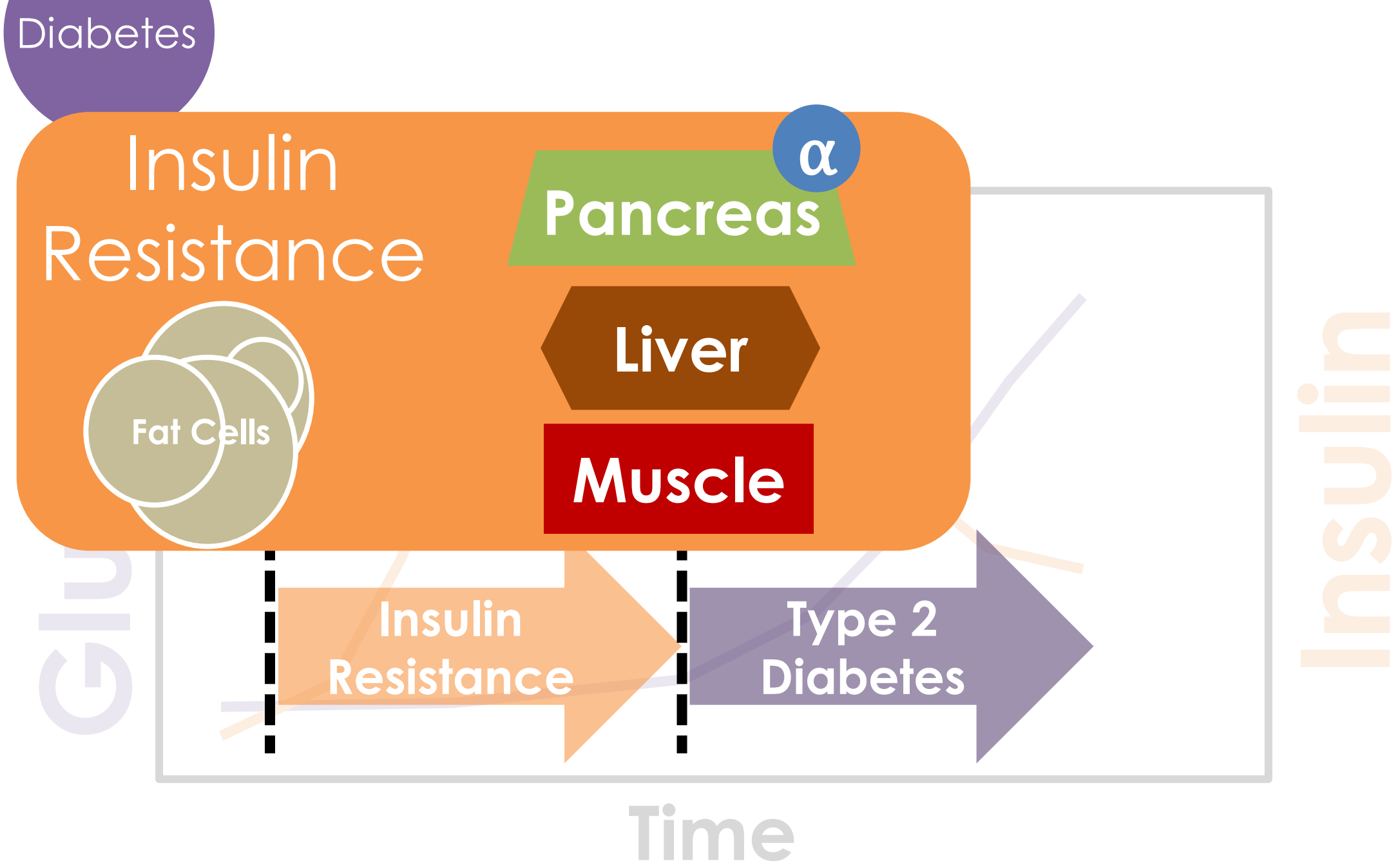

Diabet
II
Insulin
Resistance

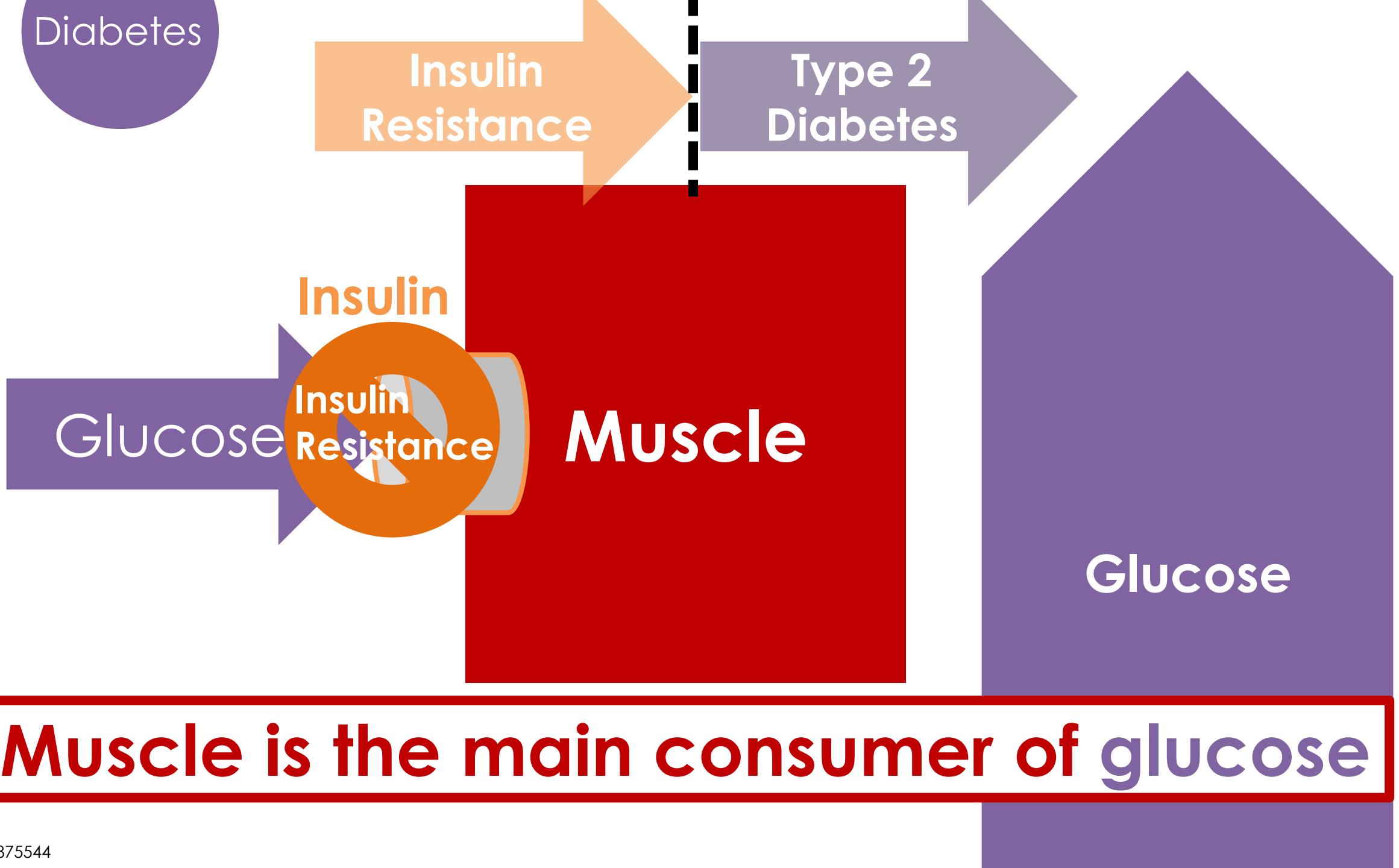

Diabetes II
Insulin Resistance

Diabetes

In true T2DM, insulin never goes to zero…

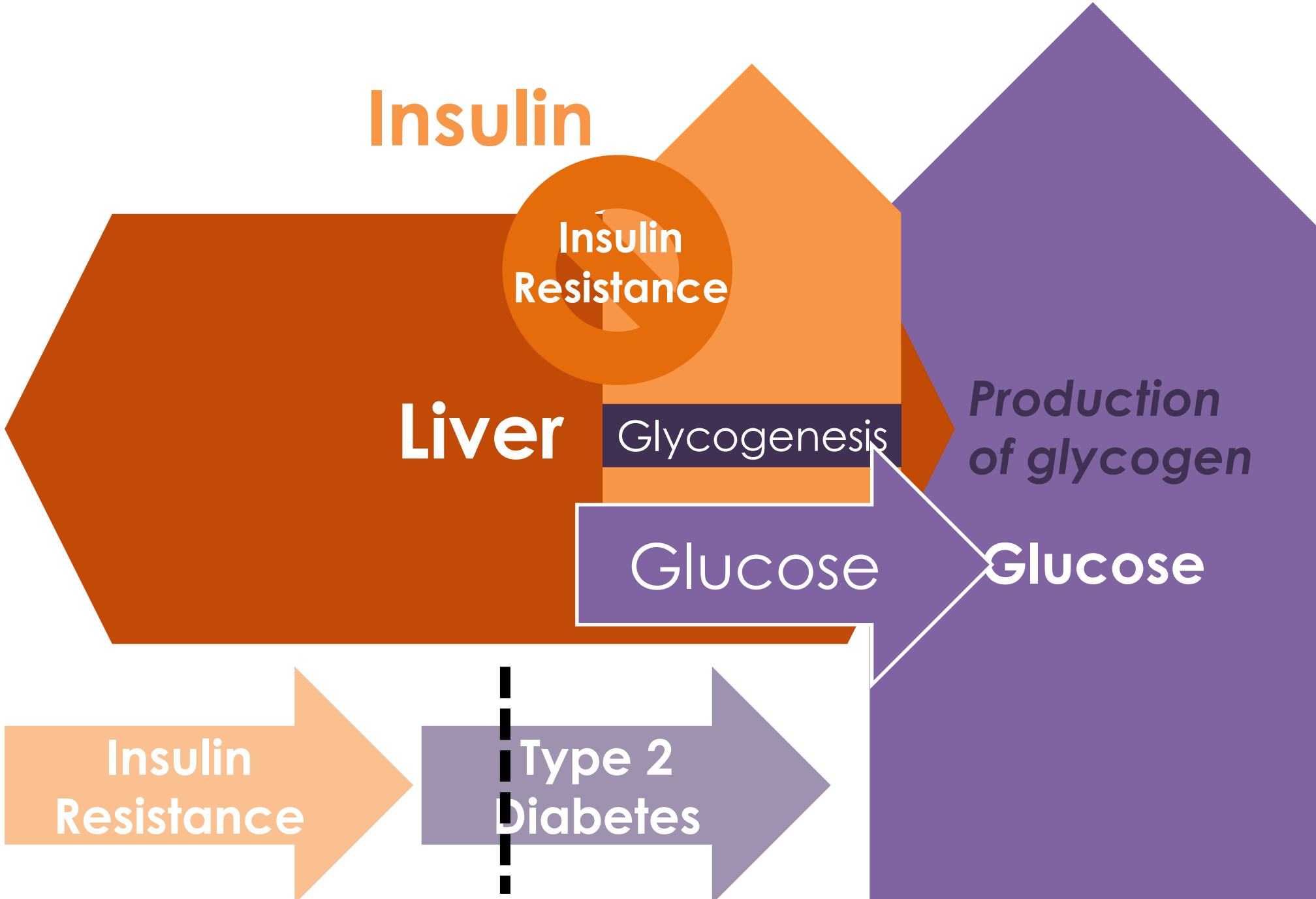



Diabetes
Insulin Resistance
Fat Cells
α
Pancreas
Liver
Muscle
Insulin Resistance
Type 2 Diabetes
Glu
Insulin
Time



PMID: 19875544

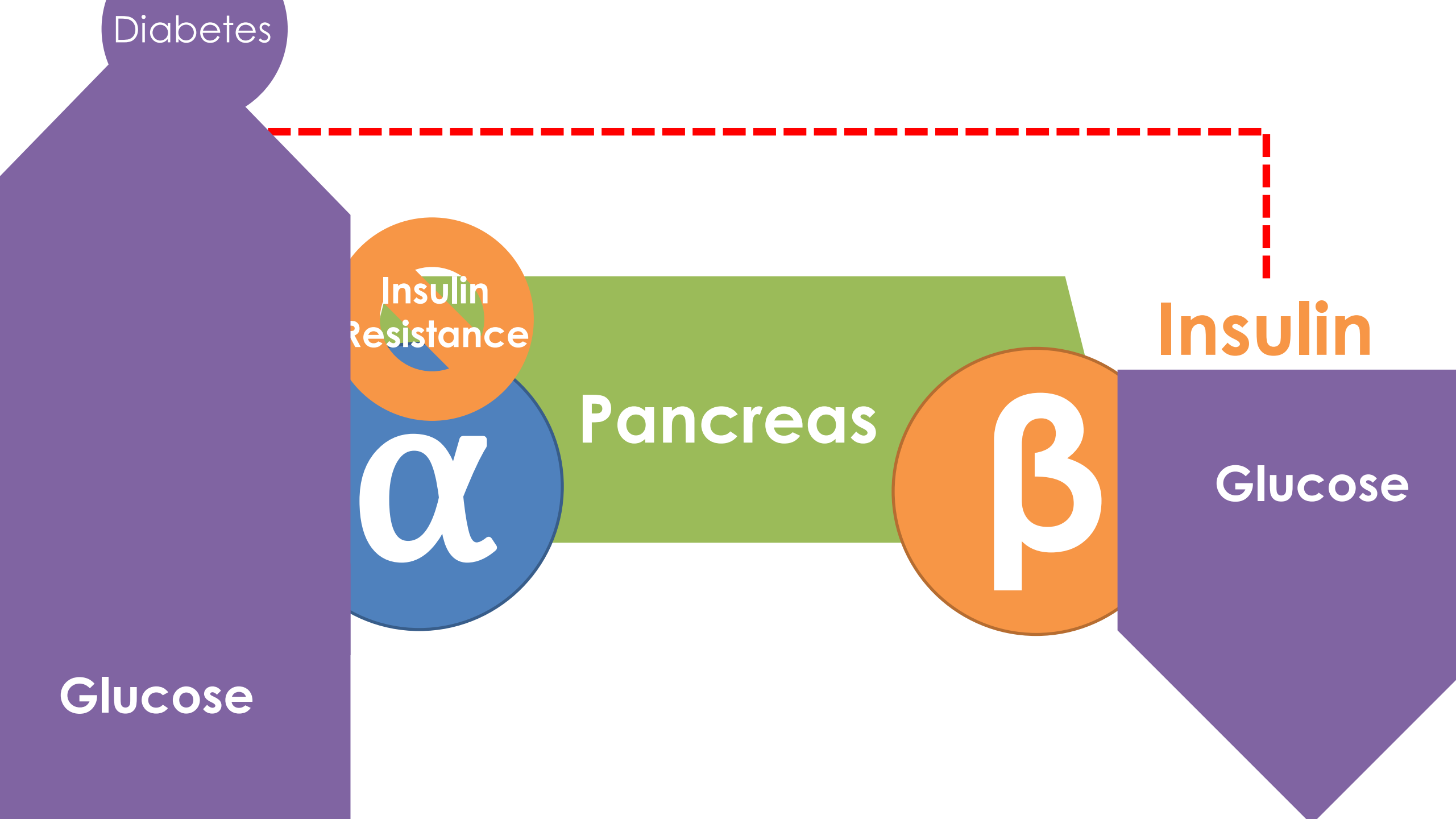
Diabetes

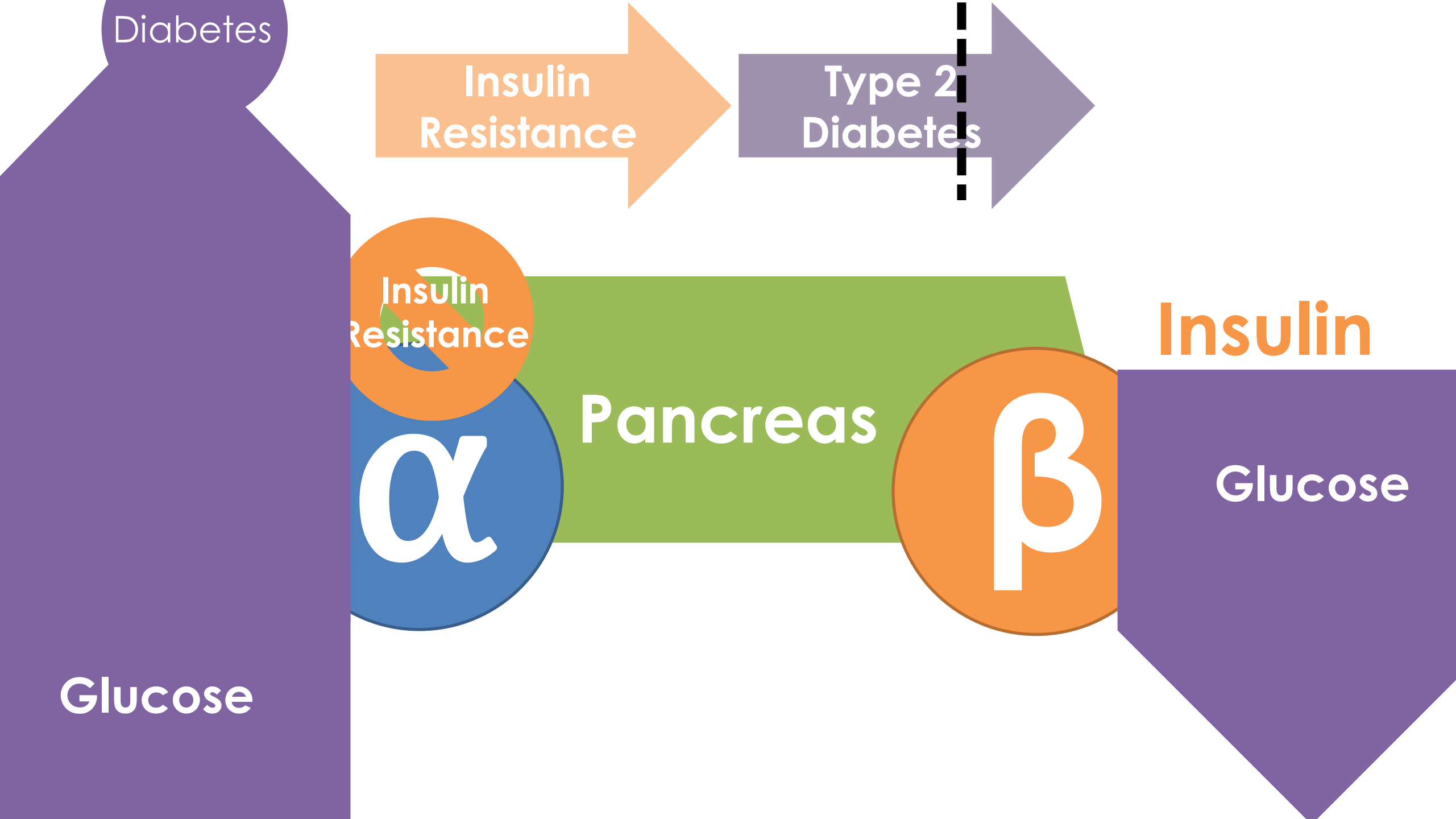


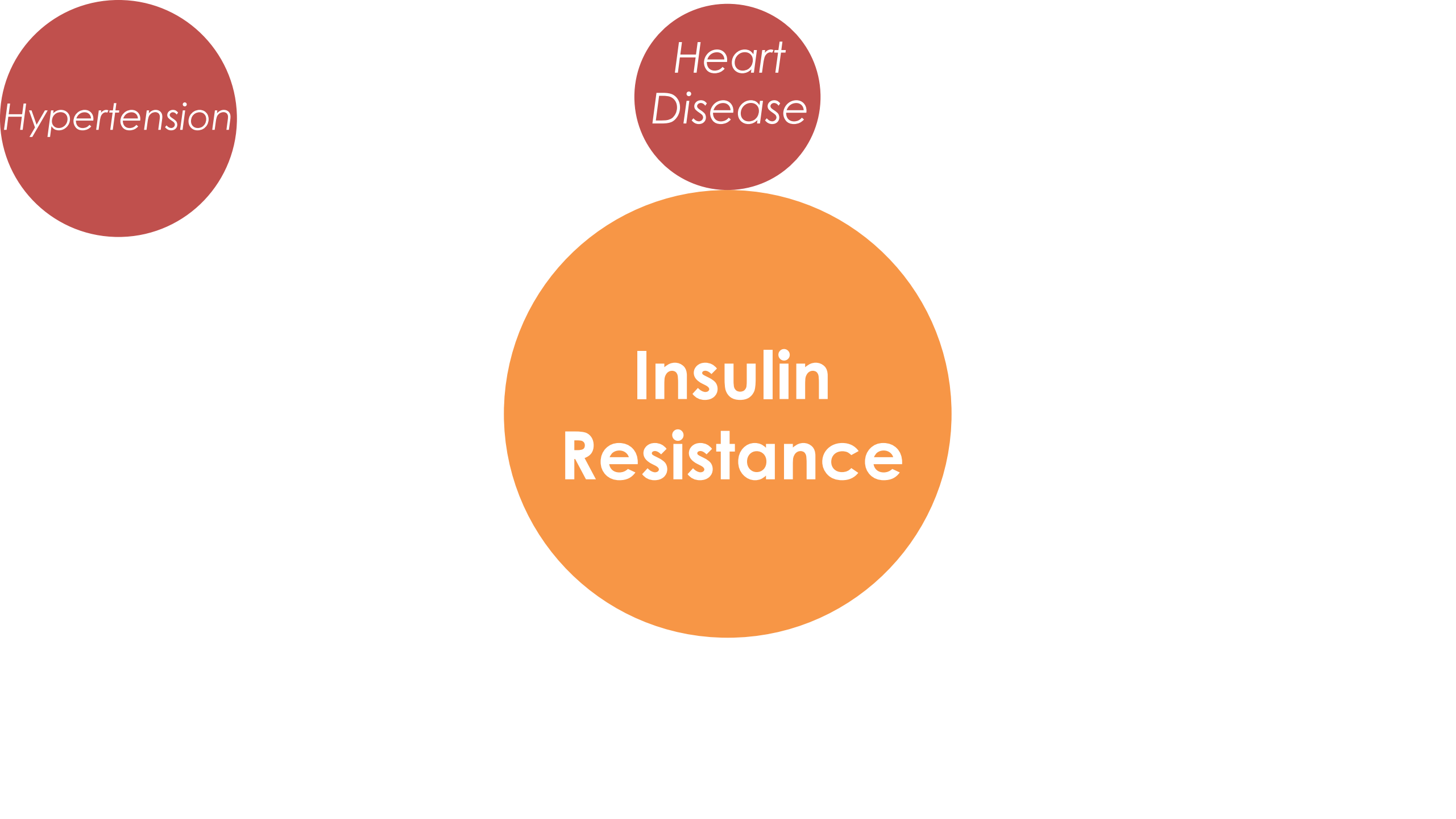
PMID: 20133650

Diabetes

PMID: 10414926


Diabetes
Insulin Resistance
α
Pancreas
β
Insulin
Glucose
Glucose


Diabetes
Insulin Resistance
Type 2 Diabetes
Insulin Resistance
α
Pancreas
β
Insulin
Glucose
Glucose


Hypertension
Heart Disease
Insulin Resistance

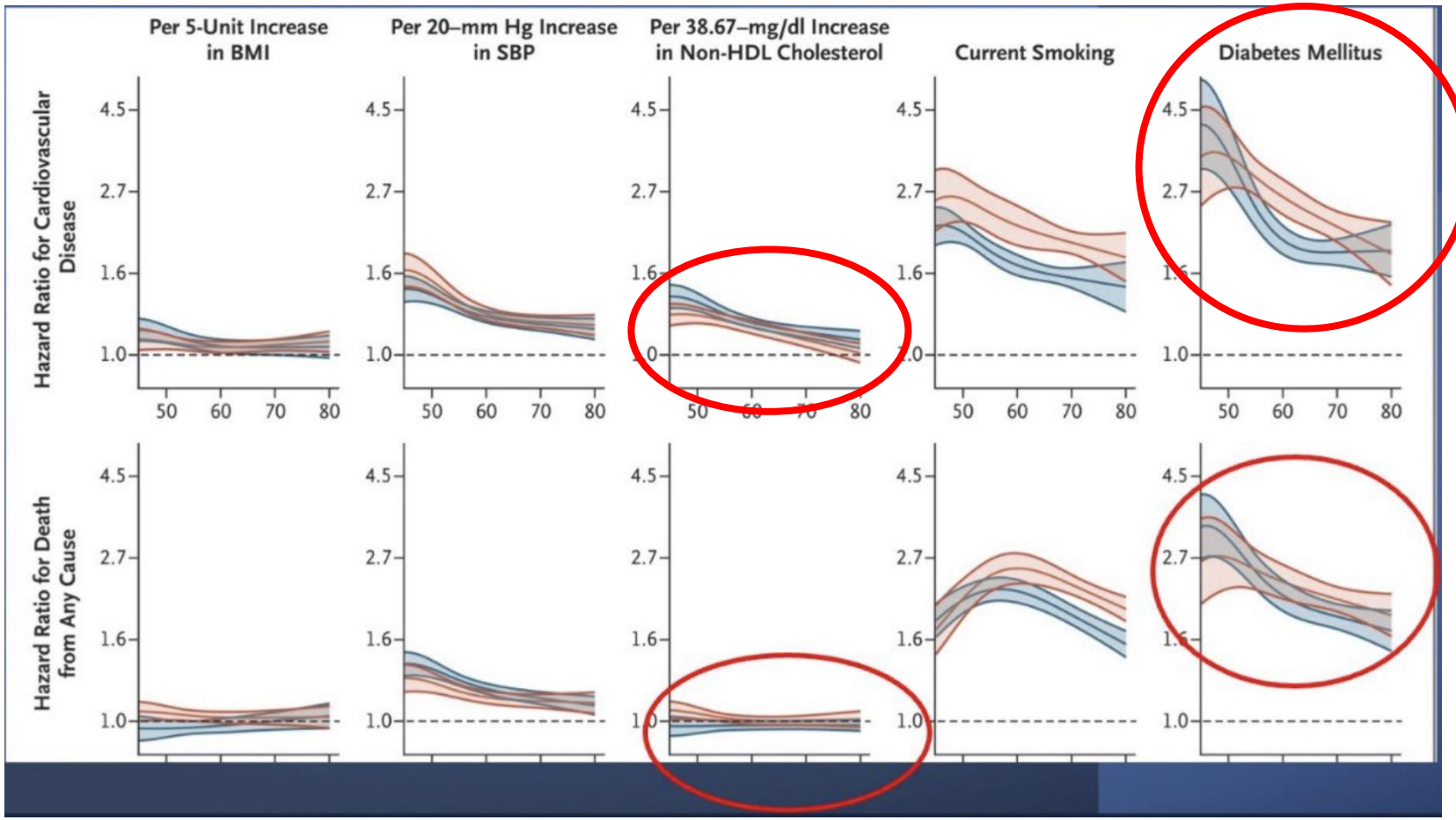
Hypertension

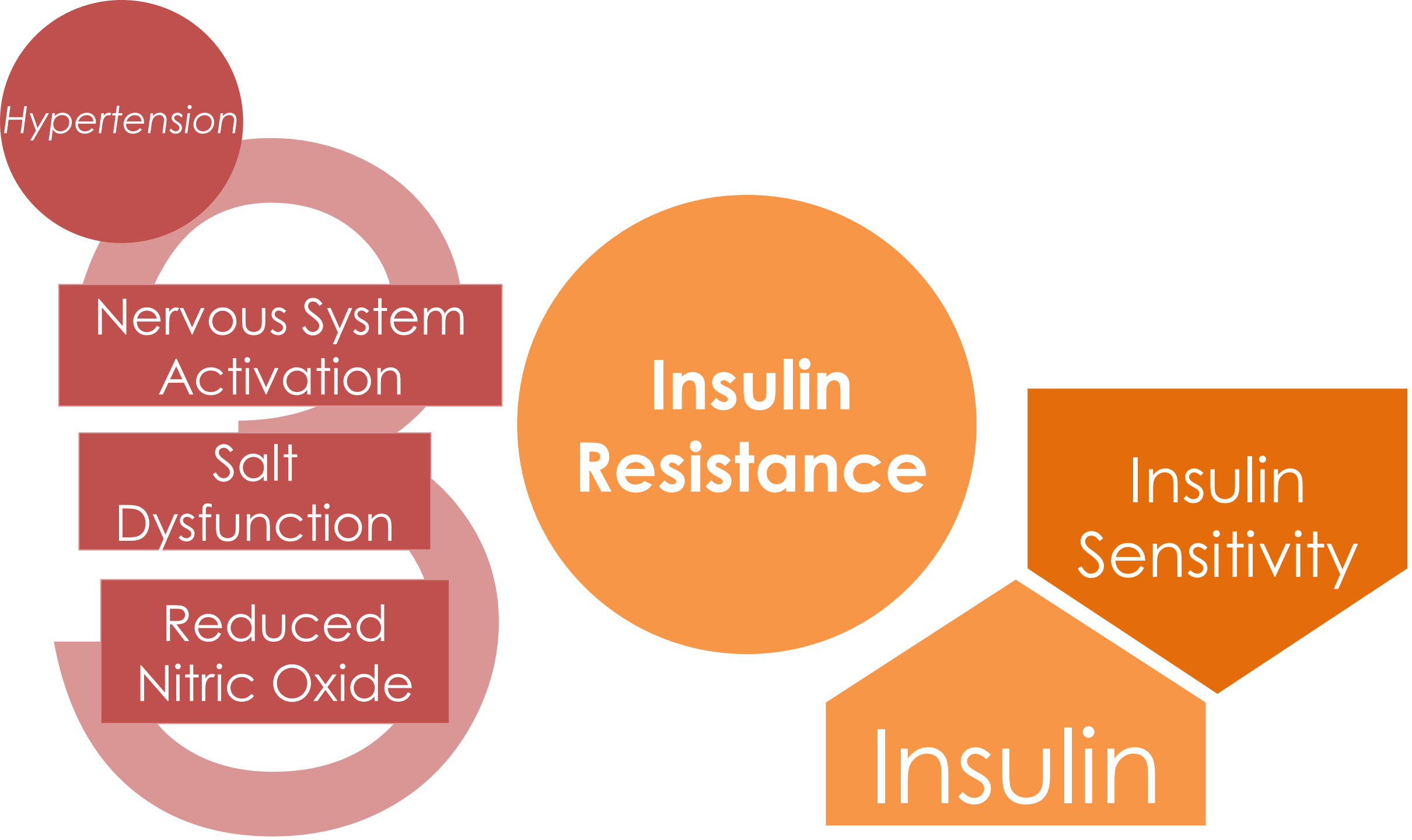
Heart Disease

Global Effect of Modifiable Risk Factors on Cardiovascular Disease and Mortality

The Global Cardiovascular Risk Consortium*

October 5, 2023
N Engl J Med 2023; 389:1273-1285
DOI: 10.1056/NEJMoa2206916



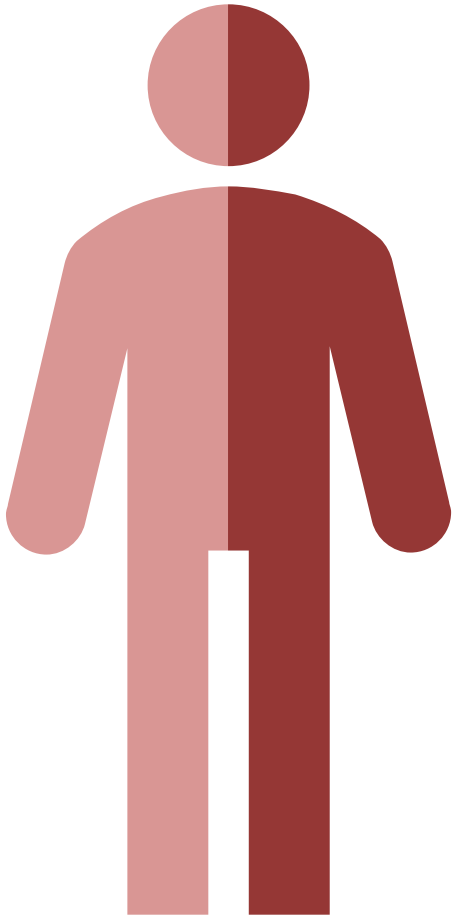

Hypertension
Nervous System Activation
Salt Dysfunction
Reduced Nitric Oxide
Insulin Resistance
Insulin Sensitivity
Insulin

Hypertension

Insulin increases activation of the **sympathetic nervous system**

Parasympathetic

"Rest and Digest"



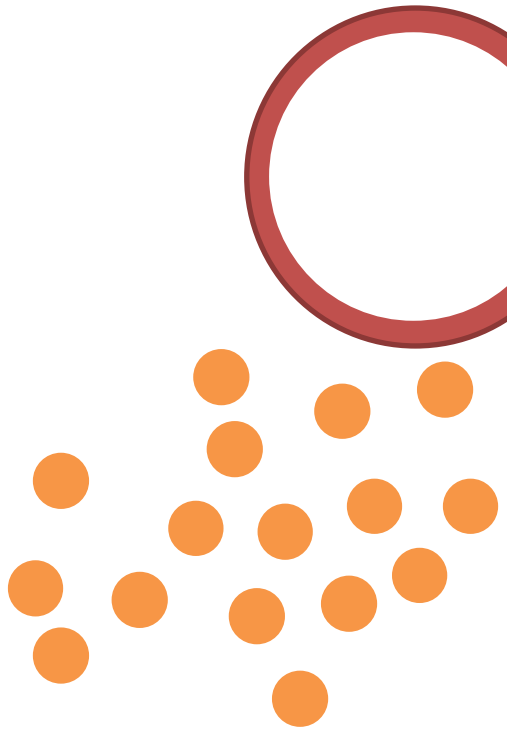
Sympathetic

"Fight or Flight"

Hypertension

Insulin increases activation of the **sympathetic nervous system**

"Fight or Flight"



=

Increased blood pressure

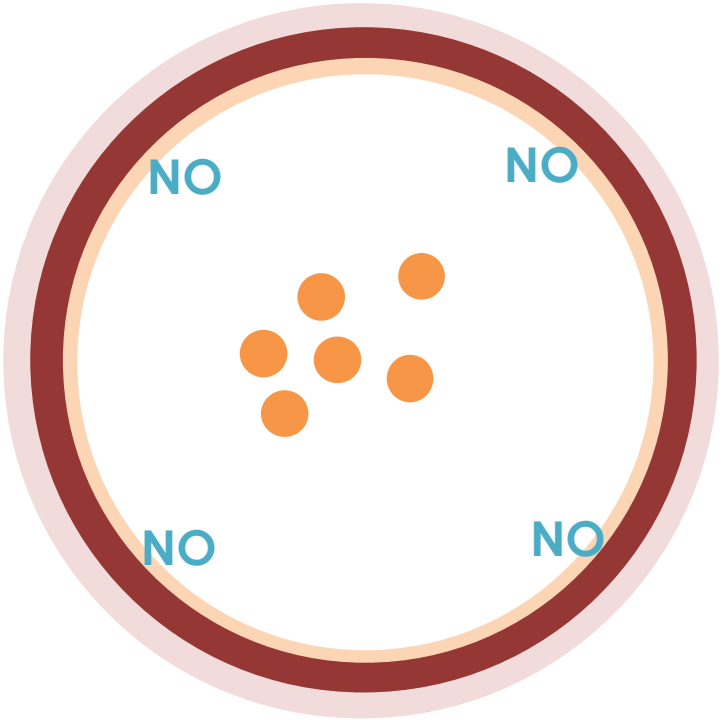
Hypertension

Insulin-resistant endothelial cells fail to release **nitric oxide**

*Nitric oxide (**NO**) is a potent vasodilator*

Insulin sensitive

Insulin resistant



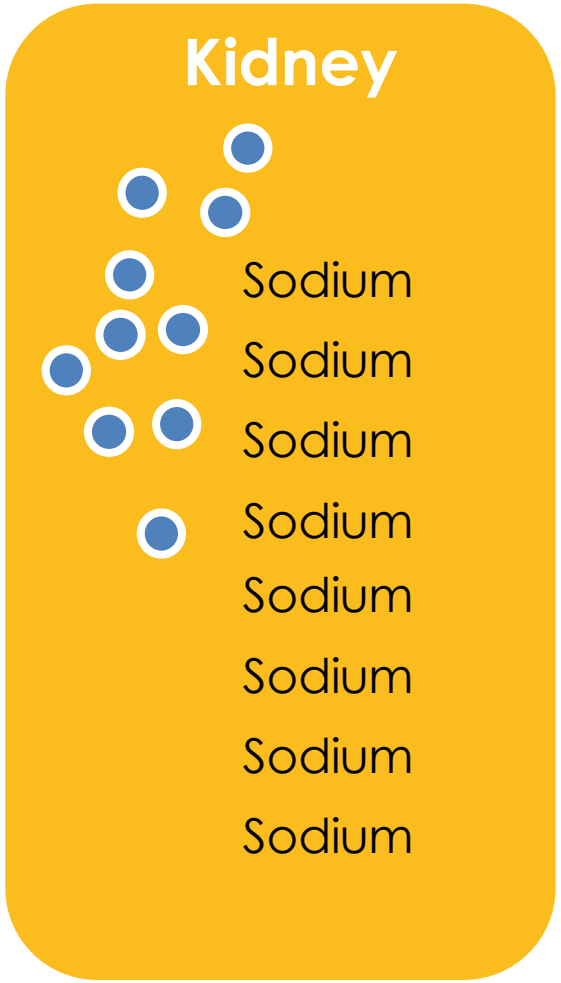
Blood Vessel

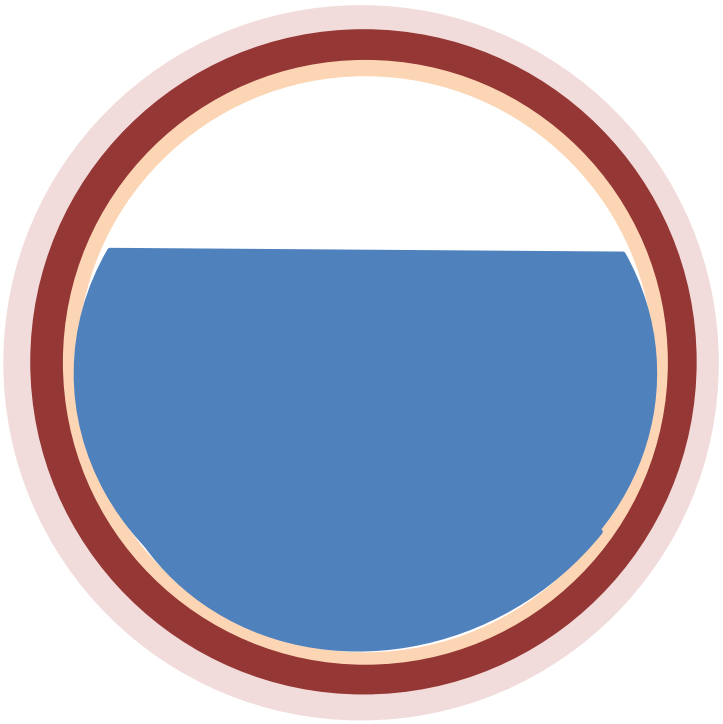
=

Increased blood pressure

Hypertension

Insulin increases kidney salt reabsorption





=

Increased blood pressure

Insulin increases kidney salt reabsorption

Dietary sodium intake and mortality: the National Health and Nutrition Examination Survey (NHANES 1)

*"…these results **do not support current recommendations for routine reduction of sodium** consumption, nor do they justify advice to…decrease its concentration in the diet."*

PMID: 9519949

Insulin increases kidney salt reabsorption

Dietary sodium intake and subsequent risk of cardiovascular disease in overweight adults

Quartiles of salt consumption	1	2 (~50%)	3 (~2X)	4 (~4X)
Stroke mortality		NS	NS	NS
CVD mortality		NS	NS	NS
All cause mortality		NS	NS	NS

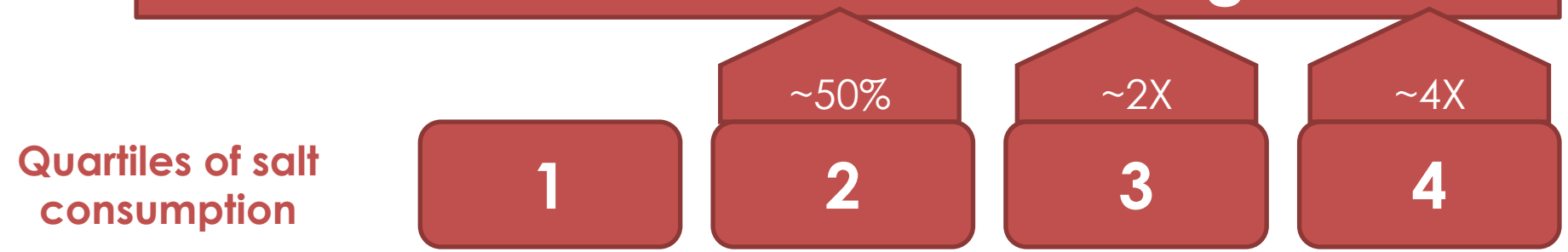
Nonoverweight subjects

PMID: 10591385

Hypertension

Insulin increases kidney salt reabsorption

Dietary sodium intake and subsequent risk of cardiovascular disease in overweight adults



- Stroke mortality
- CVD mortality
- All cause mortality

Overweight subjects

PMID: 10591385

Hypertension

Insulin increases kidney salt reabsorption

VS

Nonoverweight subjects

Overweight subjects

Hypertension

?

Low-salt diet increases insulin resistance in healthy subjects

What happens to insulin with salt restriction?

PMID: 31357547


Insulin
Resistance
Dementia

Dementia

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

2

Problems

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

PMID: 30103319
PMID: 34103732

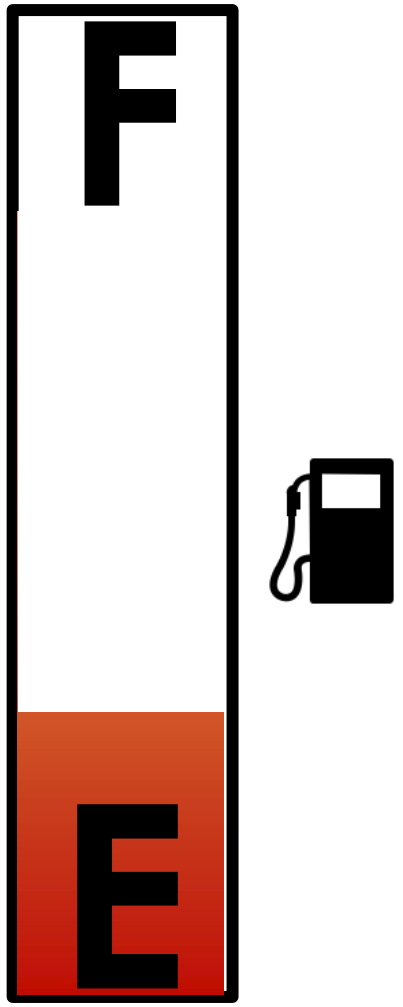
Dementia

Alternate view: Caused by **fuel** disruption

High metabolic rate
=
High demand for nutrients

Dementia

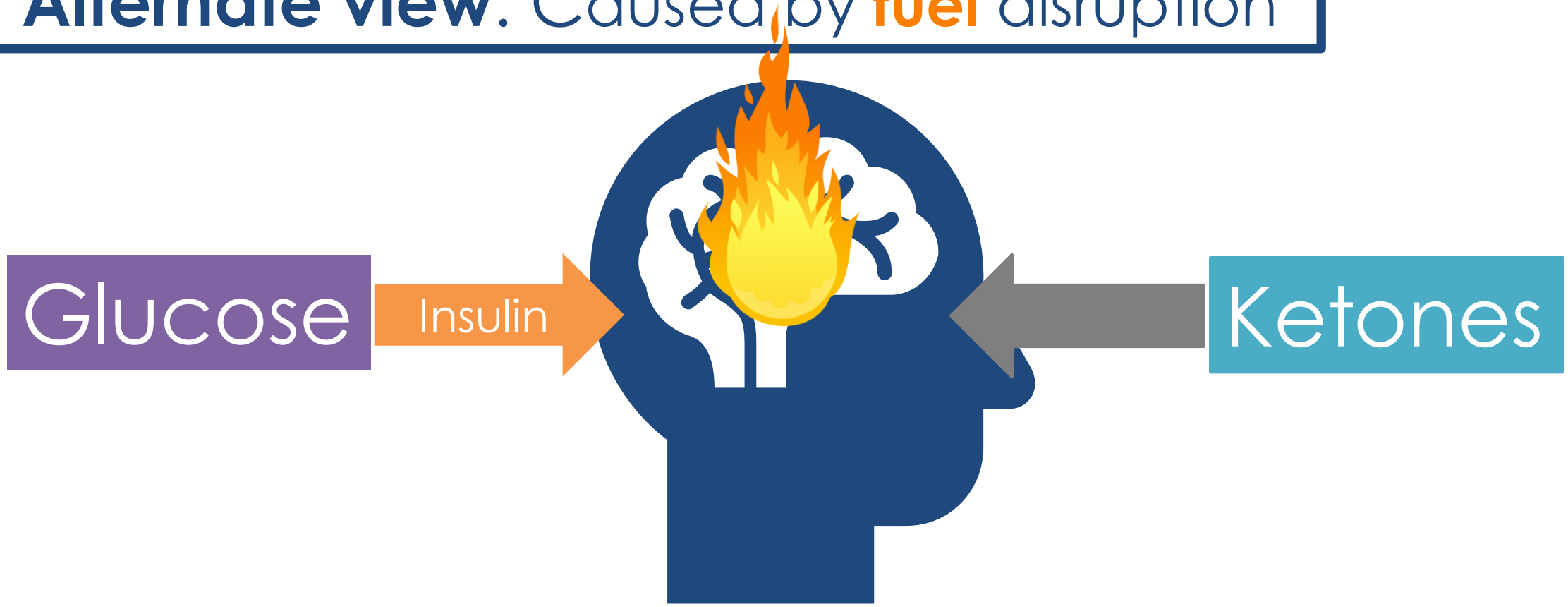
Alternate view: Caused by **fuel** disruption



PMID: 24598140

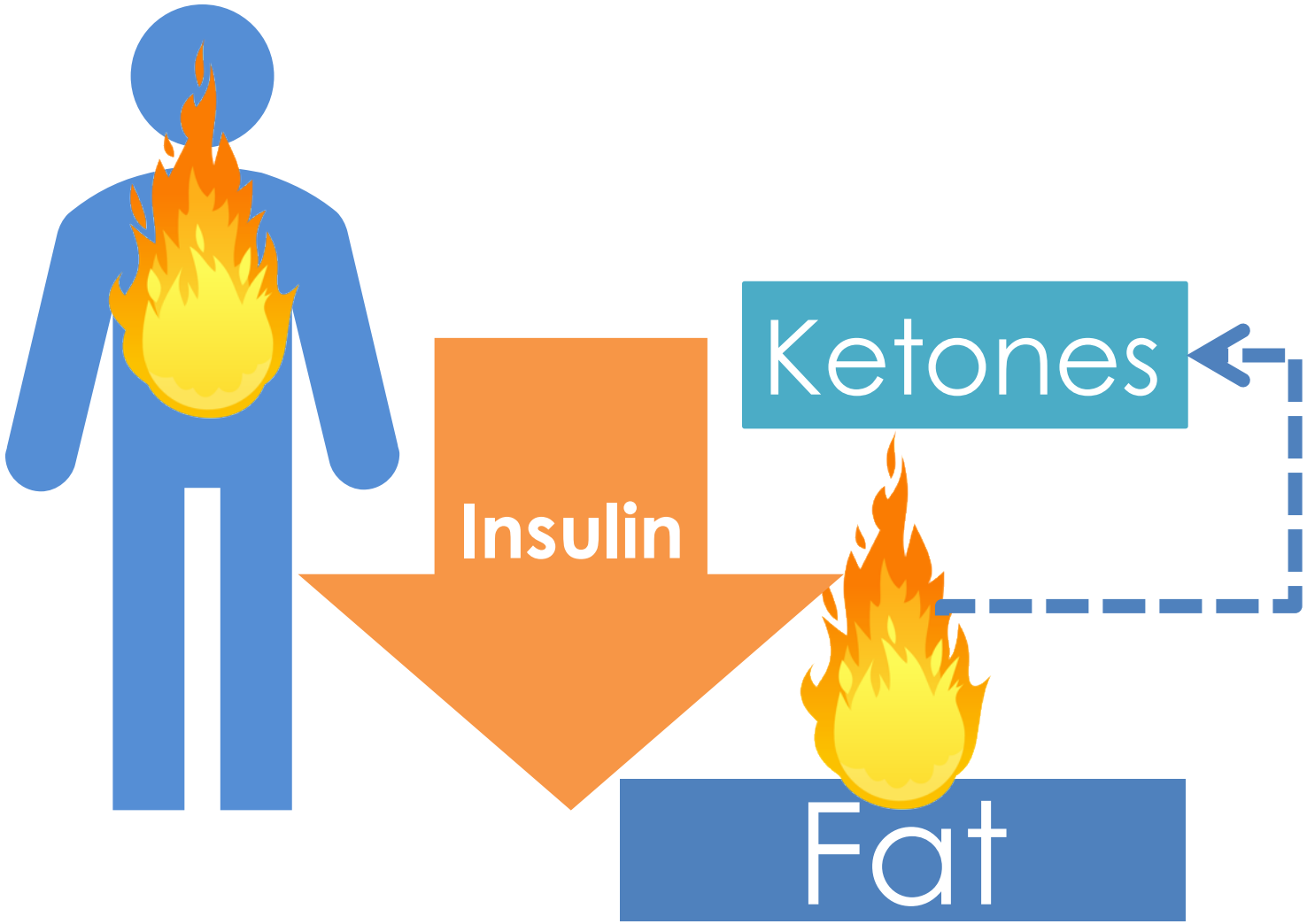
Dementia

Alternate view: Caused by **fuel** disruption



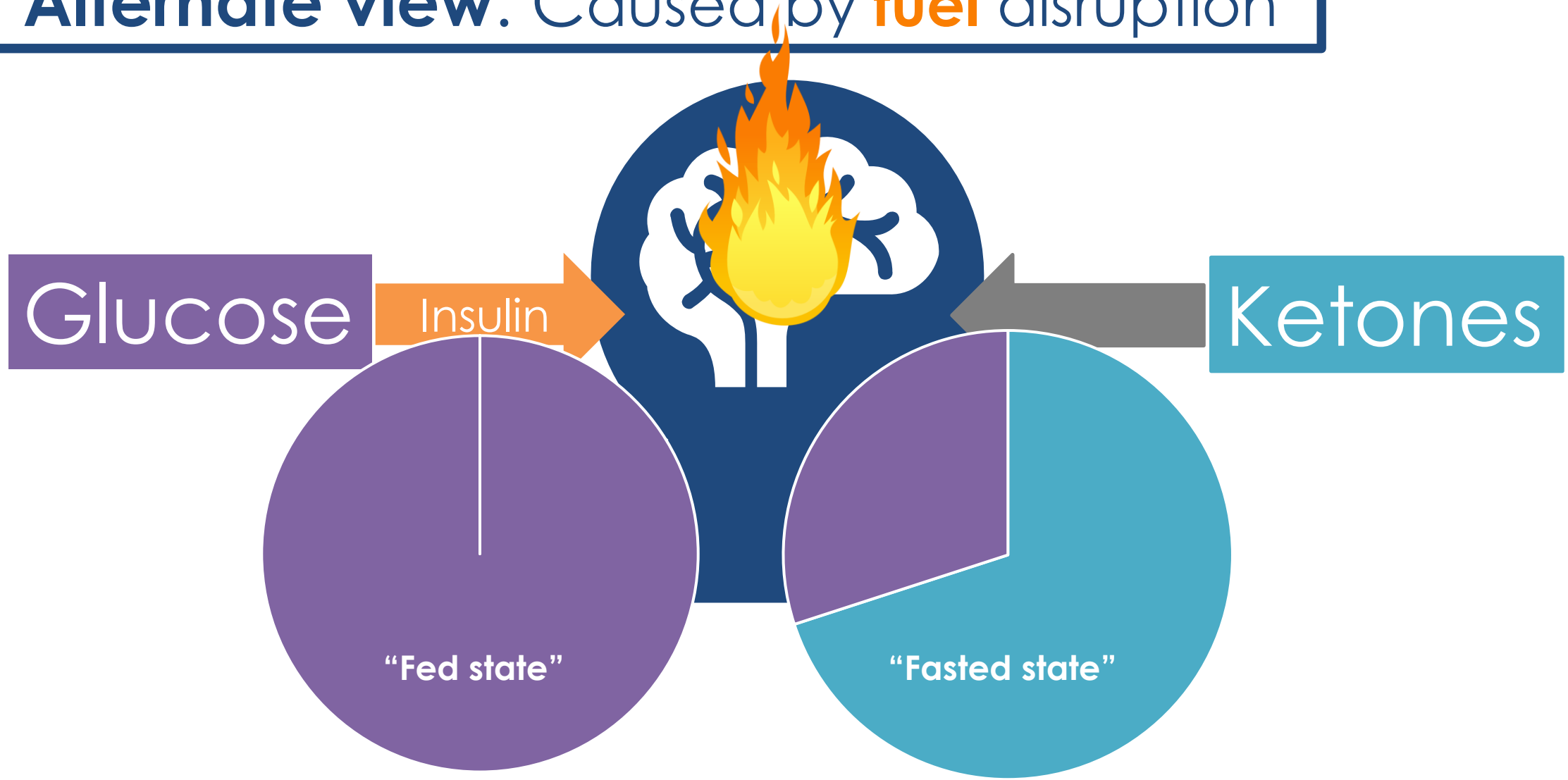
What are ketones?

Dementia



Dementia

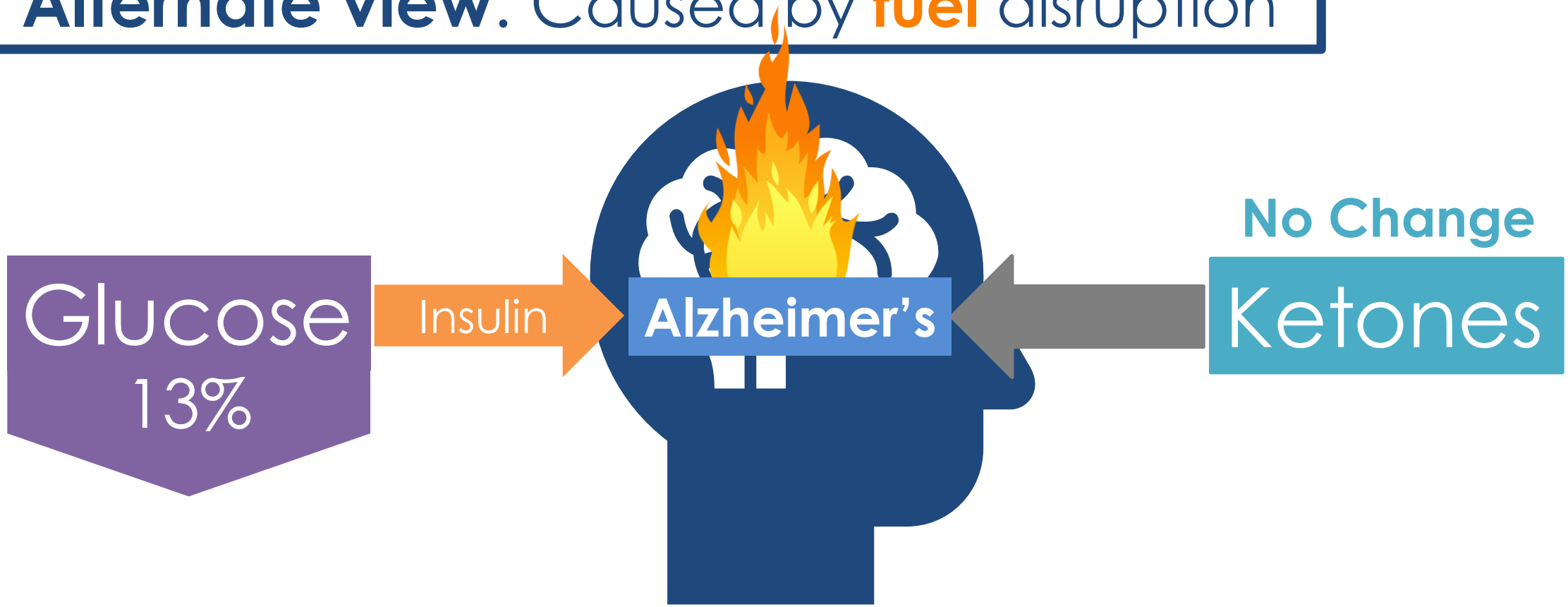
Alternate view: Caused by **fuel** disruption



PMID: 16848698

Dementia

Alternate view: Caused by **fuel** disruption



PMID: 25147107

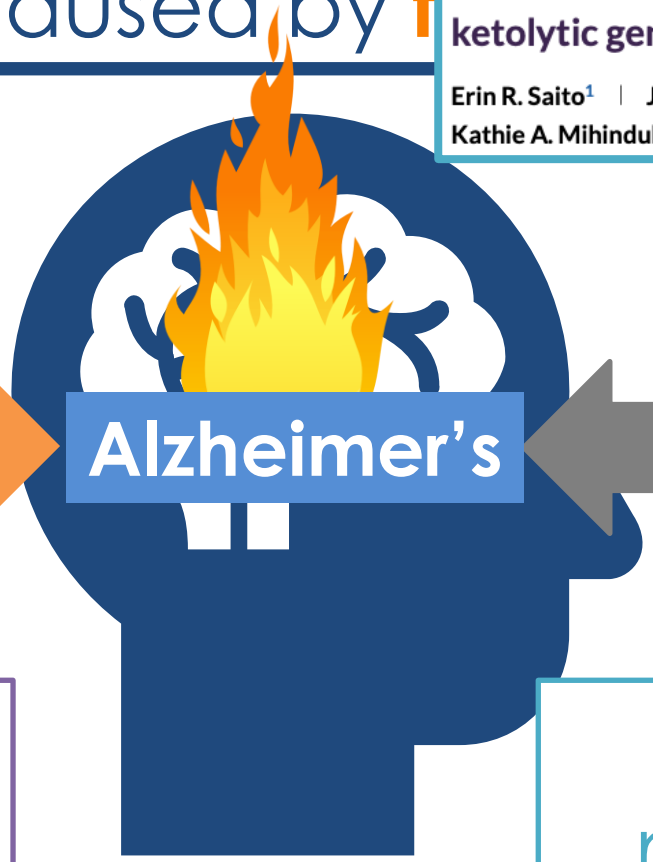
Alternate view: Caused by f

Received: 20 August 2020 | Revised: 5 January 2021 | Accepted: 17 January 2021
DOI: 10.1002/alz.12310
Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION
RESEARCH ARTICLE

Alzheimer's disease alters oligodendrocytic glycolytic and ketolytic gene expression

Erin R. Saito[1] | Justin B. Miller[2] | Oscar Harari[3] | Carlos Cruchaga[3,4,5,6] | Kathie A. Mihindukulasuriya[7] | John S. K. Kauwe[2] | Benjamin T. Bikman[1]

Glucose → Insulin → **Alzheimer's** ← Ketones



All glucose-related metabolism genes are **downregulated**

Ketone-related metabolism genes are **normal**

PMID: 25147107

Dementia

Alter

Association betv
and Alzheimer's
phenotype: cros

Journal of Diabetes Science and Technology
Volume 2, Issue 6, November 2008

REVIEW ARTICLE

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]

8

Statistically significant variables that correlated with Alzheimer's disease

- Age
- Education
- ApoE4

APOE4 inhibits insulin receptor

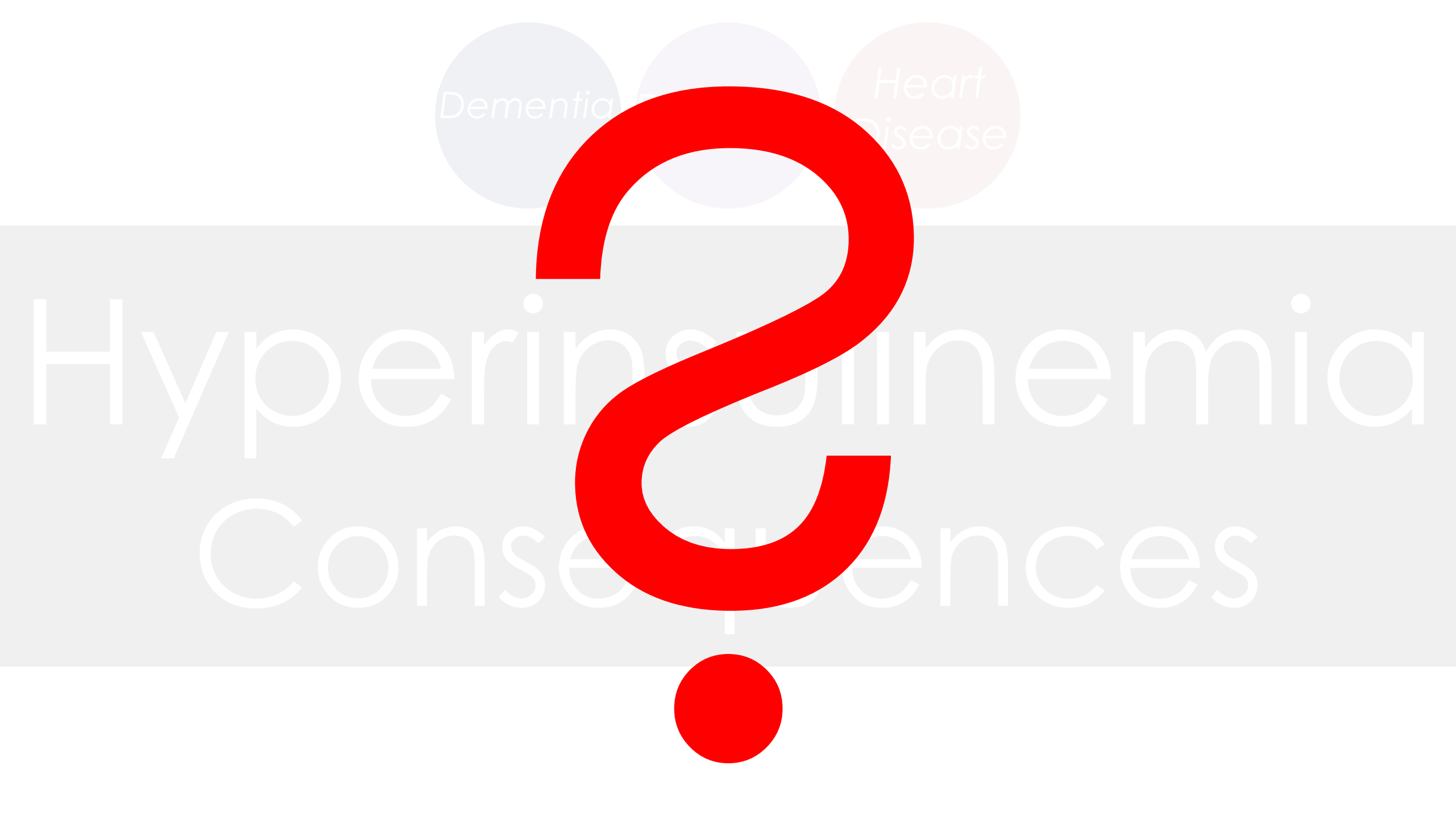
- Abnormal **glucose** tolerance
- Fasting plasma **glucose**
- Two-hour plasma **glucose**
- Fasting **insulin**
- Two-hour **insulin**

PMID: 9366728

Dementia

Alternate view: Caused by **fuel** disruption

PMID: 25147107


Dementia
Heart Disease
Hyperinsulinemia
Consequences