LAYING THE FOUNDATION FOR CARDIOMETABOLIC DISORDERS

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FUNCTIONAL MEDICINE
Continuing Education

DISCLOSURES

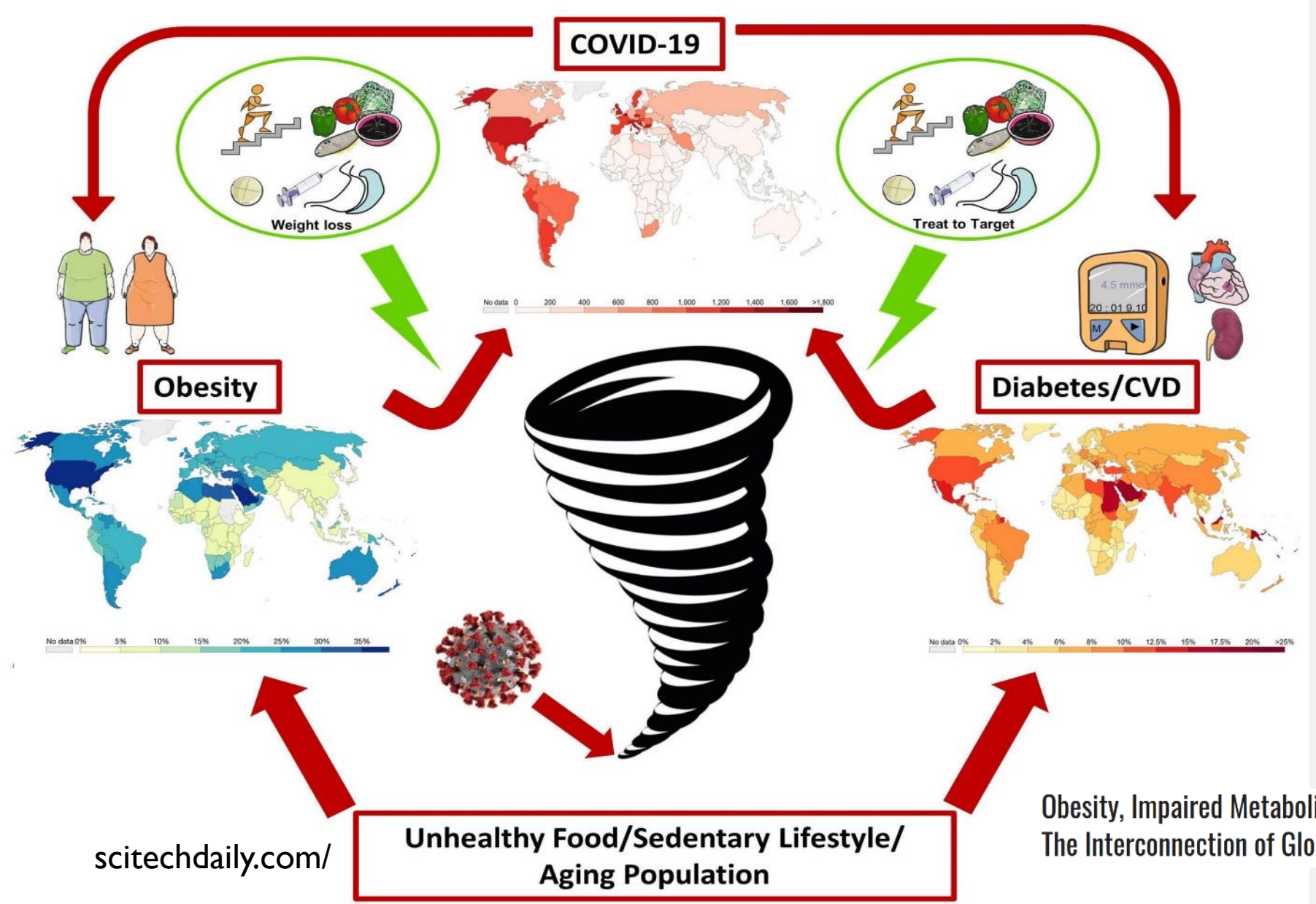
Dr. Guilliams is a paid consultant for:

- Orthomolecular Products & KD Nutra

OBJECTIVES

- Overview the genesis of the term and discipline that defines "cardiometabolic".
- Define the primary connecting points between dysregulation of metabolism and cardiovascular pathophysiology.
- Point toward leverage points in which lifestyle and nutritional solutions can greatly reduce cardiometabolic risk.
- Observe the relationship between cardiometabolic risk and vulnerabilities to acute viral infections such as Covid.

A VIRAL PANDEMIC- EXPOSING A METABOLIC PANDEMIC



scitechdaily.com/

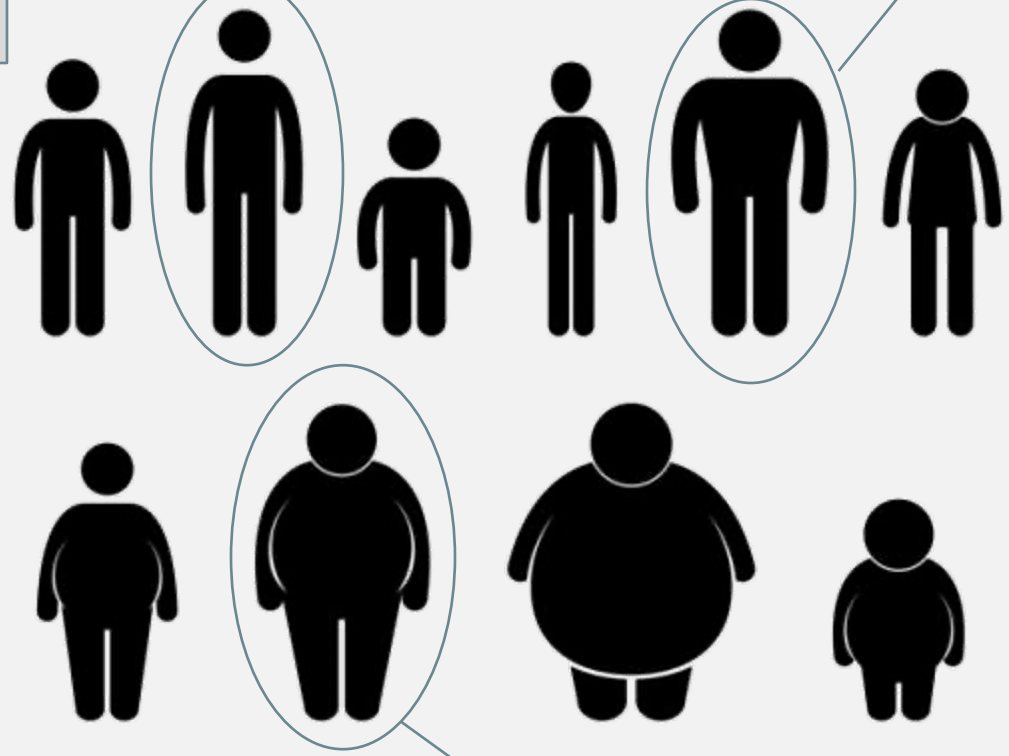
Obesity, Impaired Metabolic Health and COVID-19: The Interconnection of Global Pandemics

THE TYPE OF MEDICINE YOU PRACTICE IS GREATLY INFLUENCED BY HOW YOU MEASURE RISK?

EPIDEMIOLOGY ASKS WHO IS AT RISK? RELATIVELY SPEAKING….

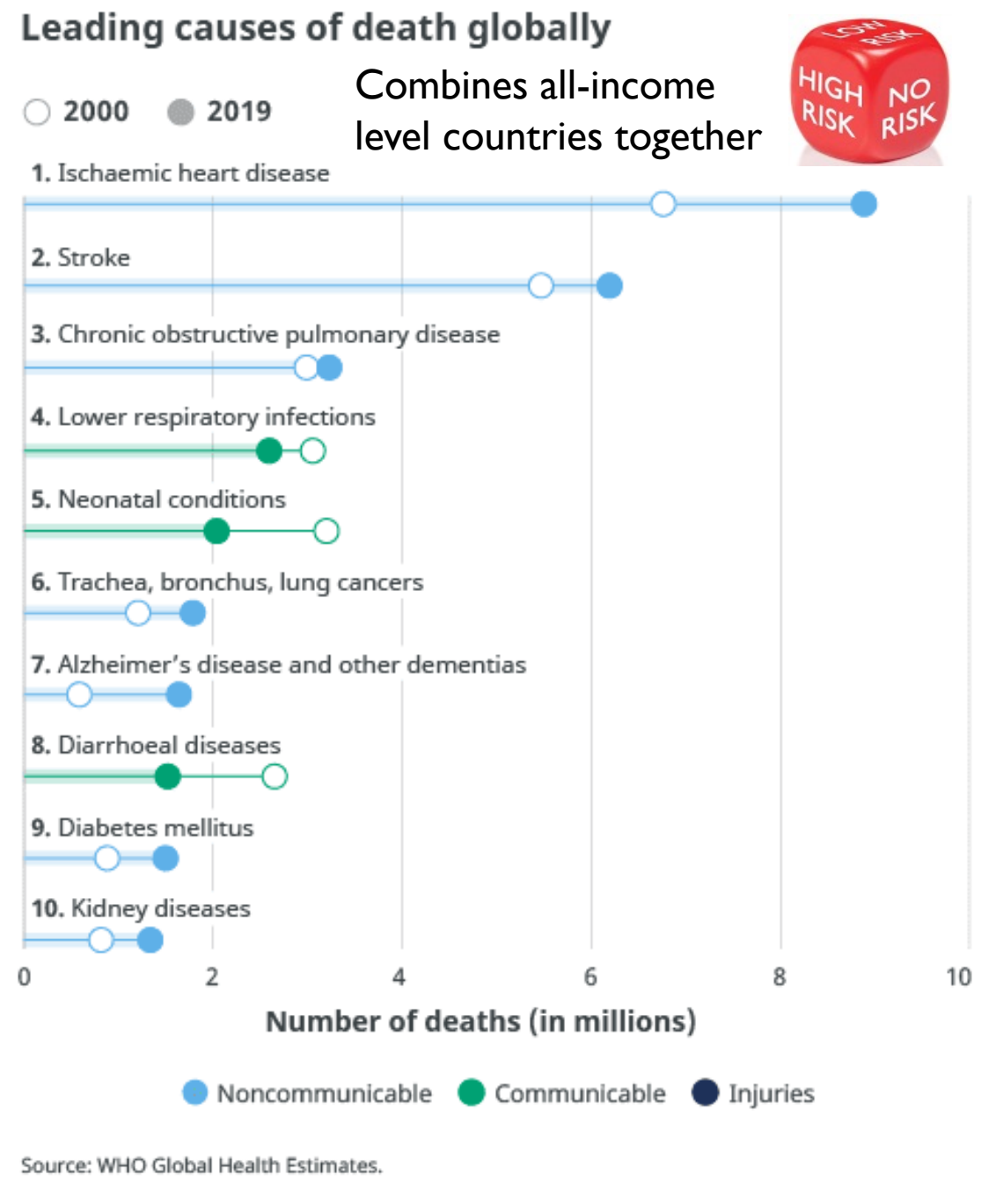
3/100 event in 10 years

15/100 event in 10 years



30/100 event in 10 years

BUT YOU NEED TO KNOW WHO NEEDS IMMEDIATE INTERVENTION?



RISK OF MORTALITY…..

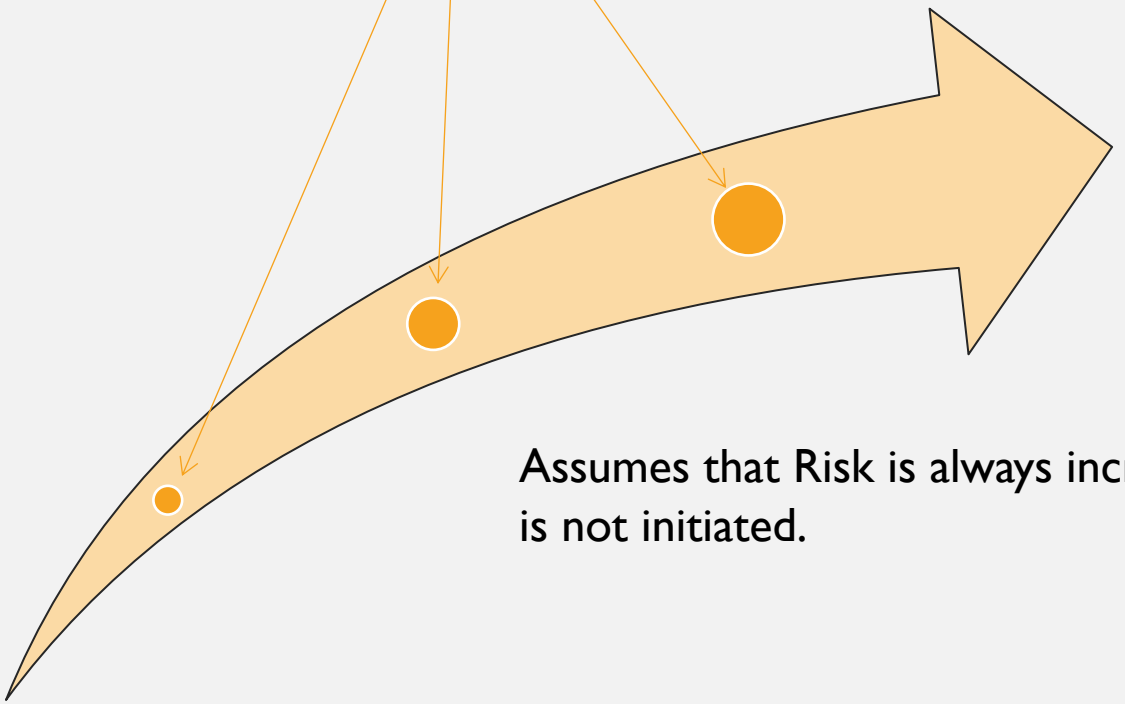
Note the rise in metabolic related disease over the past decade compared to the lowering of communicable diseases (Pre-Covid).

While Alzheimer's disease is a multifactorial condition, it should be viewed within the larger sphere of metabolic diseases greatly influenced by the cardiometabolic pathophysiology

PROJECTING FUTURE RISK AND NEED FOR INTERVENTION- THE OLD MODEL

A single point in time

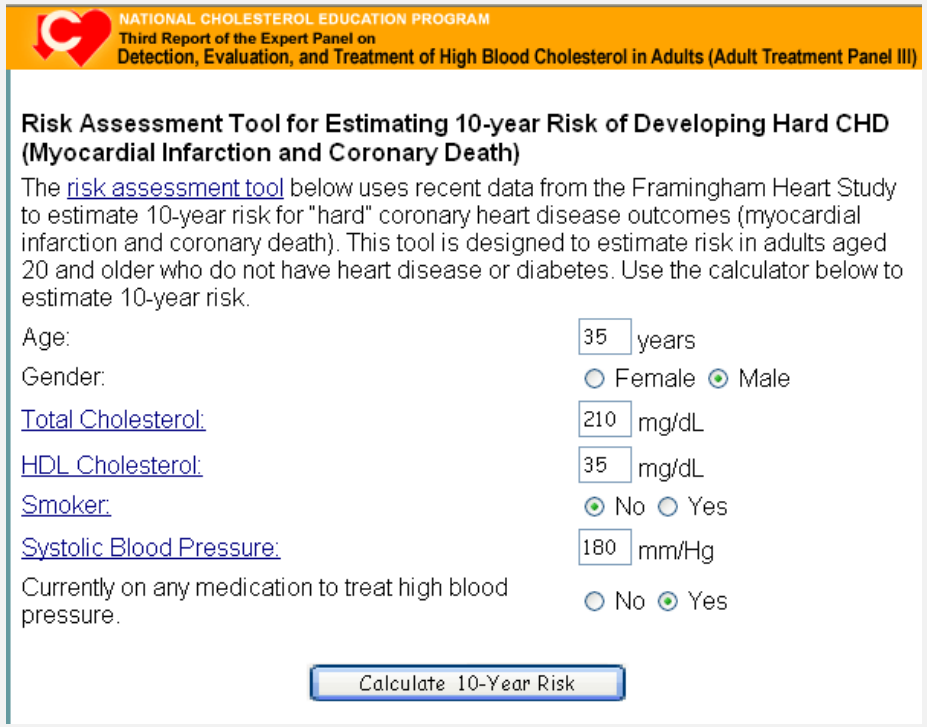
Based on current biomarkers, age, sex etc.- patient has X% chance of an event in the next Y years.



Assumes that Risk is always increasing if Intervention is not initiated.

RISK CALCULATION USING THIS MODEL

- 35 year old male
- BMI 30
- TG 350
- TC 210
- HDL-C 35
- LDL-C 145
- FBG- 107
- Non-smoker
- Elevated blood pressure/meds
- Risk?



NATIONAL CHOLESTEROL EDUCATION PROGRAM
Third Report of the Expert Panel on
Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

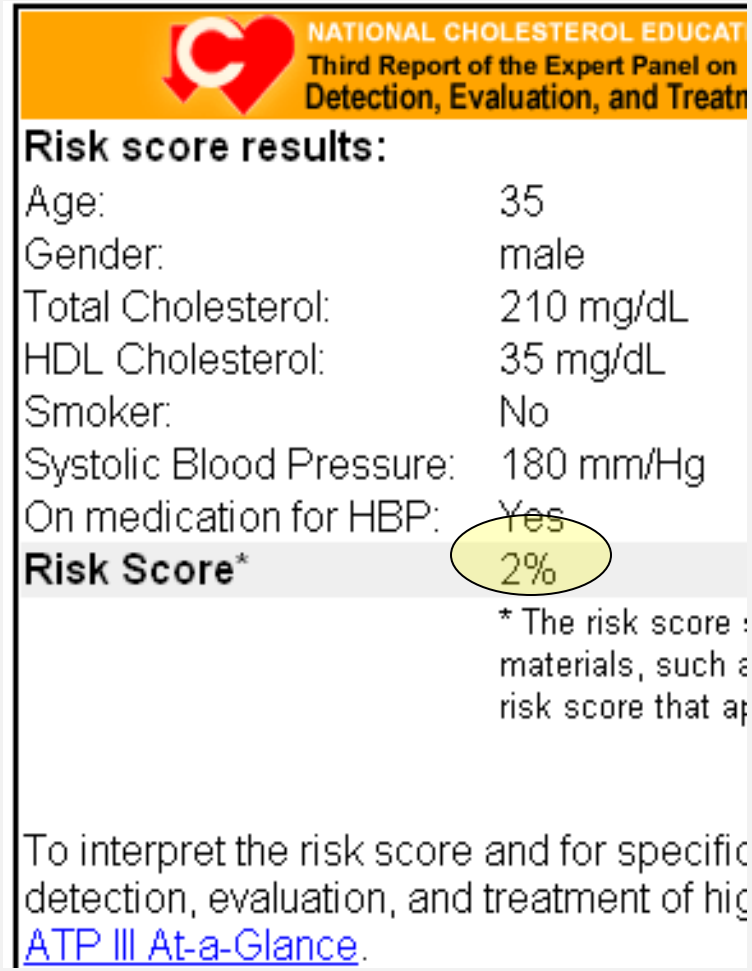
Risk Assessment Tool for Estimating 10-year Risk of Developing Hard CHD (Myocardial Infarction and Coronary Death)

The risk assessment tool below uses recent data from the Framingham Heart Study to estimate 10-year risk for "hard" coronary heart disease outcomes (myocardial infarction and coronary death). This tool is designed to estimate risk in adults aged 20 and older who do not have heart disease or diabetes. Use the calculator below to estimate 10-year risk.

Age:	35 years
Gender:	○ Female ◉ Male
Total Cholesterol:	210 mg/dL
HDL Cholesterol:	35 mg/dL
Smoker:	◉ No ○ Yes
Systolic Blood Pressure:	180 mm/Hg
Currently on any medication to treat high blood pressure.	○ No ◉ Yes

Calculate 10-Year Risk

LOW 10 YEAR RISK?



NATIONAL CHOLESTEROL EDUCAT
Third Report of the Expert Panel on
Detection, Evaluation, and Treatm

Risk score results:

Age:	35
Gender:	male
Total Cholesterol:	210 mg/dL
HDL Cholesterol:	35 mg/dL
Smoker:	No
Systolic Blood Pressure:	180 mm/Hg
On medication for HBP:	Yes
Risk Score*	2%

* The risk score
materials, such a
risk score that ap

To interpret the risk score and for specific
detection, evaluation, and treatment of hig
ATP III At-a-Glance.

- 35 year old male
- BMI 30
- TG 350
- TC 210
- HDL-C 35
- LDL-C 145
- FBG- 107
- Non-smoker
- Elevated blood pressure/meds

THE OLD "TWO-SILO" APPROACH

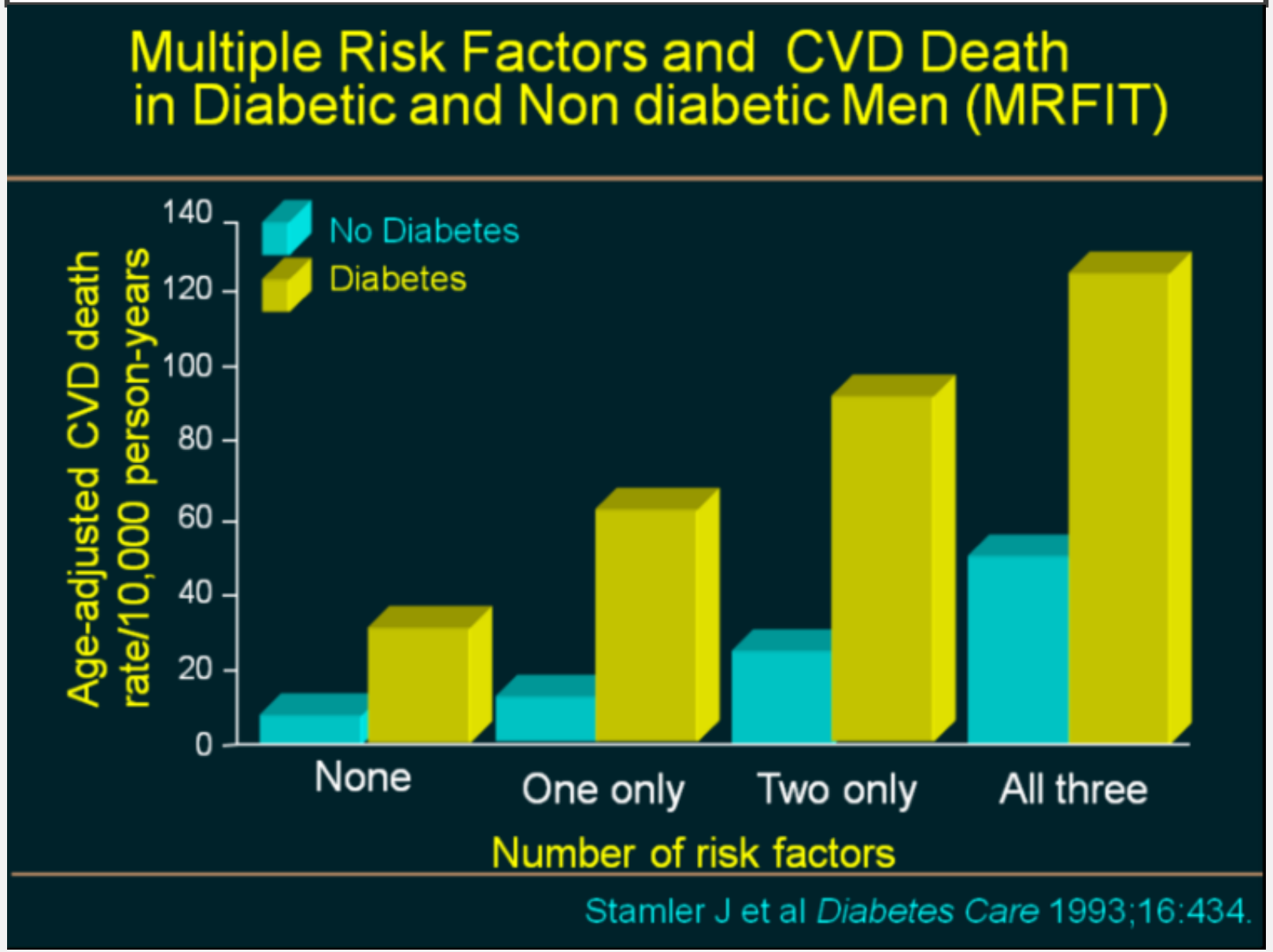
Cardiovascular Disease

- Disease of the Heart and Blood Vessel
- Causes: Hardening or Blocking of the Blood Vessels
- Treated by Cardiologist
- "American Heart Association"

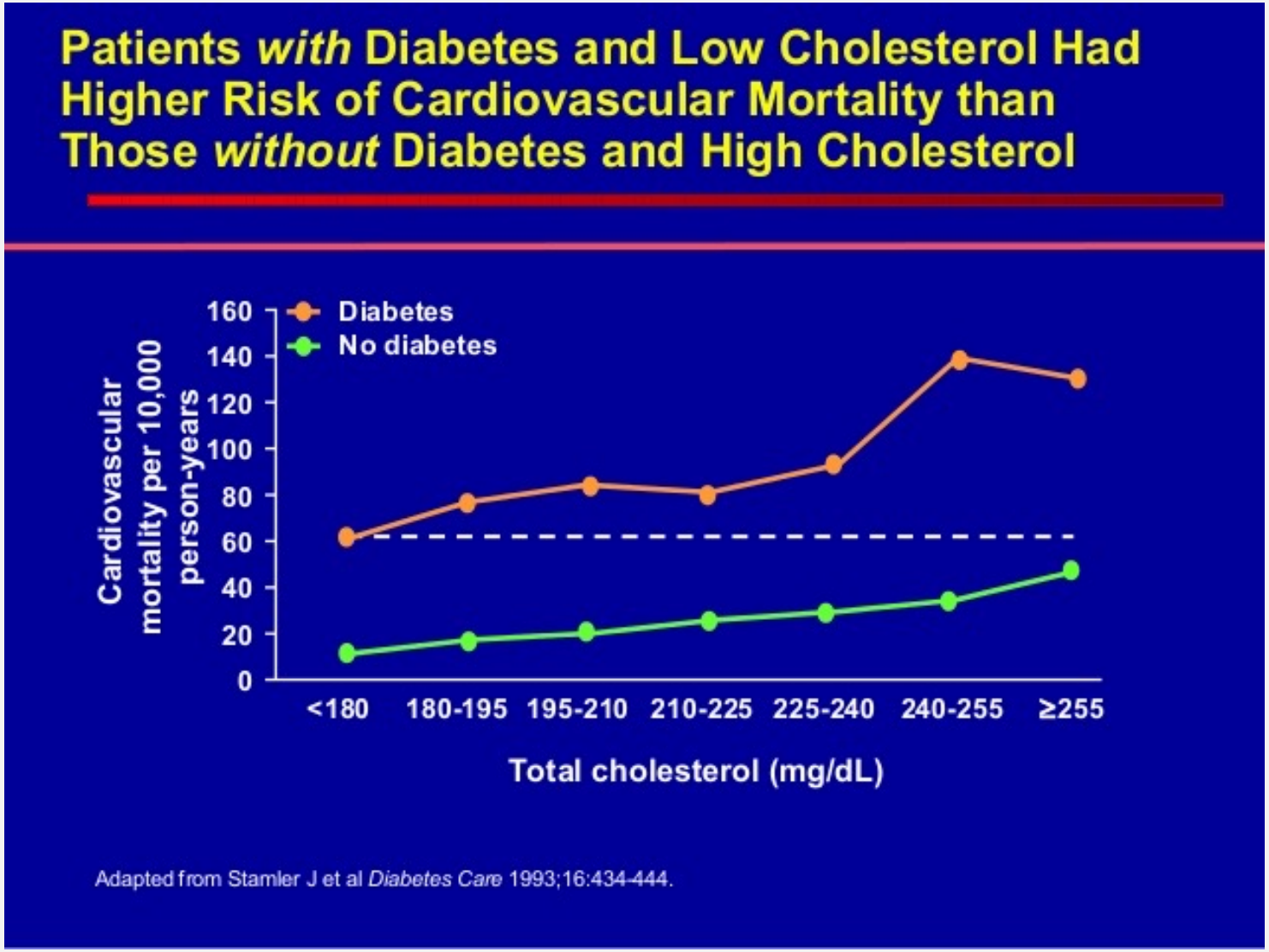
Diabetes

- Disease of the Pancreas
- Causes: Low insulin output
  - Type 1: autoimmune (juvenile)
  - Type 2: Adult-onset
- Treated by Endocrinologist
- "American Diabetes Association"

WE HAVE KNOWN FOR DECADES THAT DIABETES INCREASES CVD DEATH



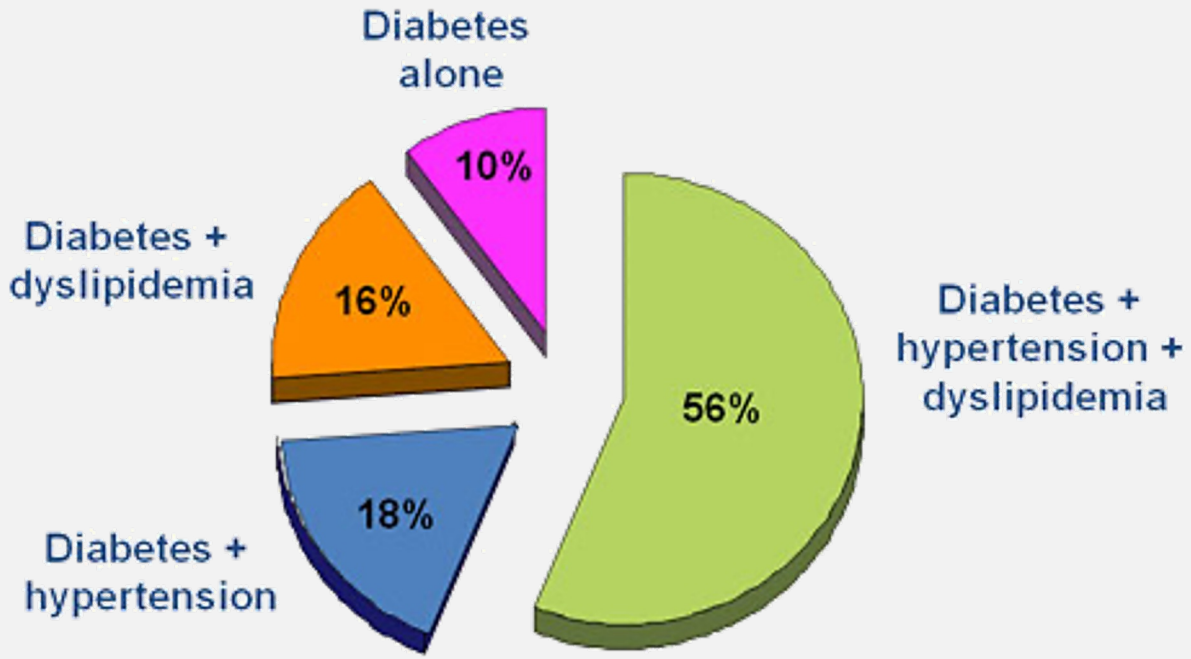
MUCH MORE THAN TOTAL CHOLESTEROL



THEN CAME THE CO-MORBID DISEASE APPROACH

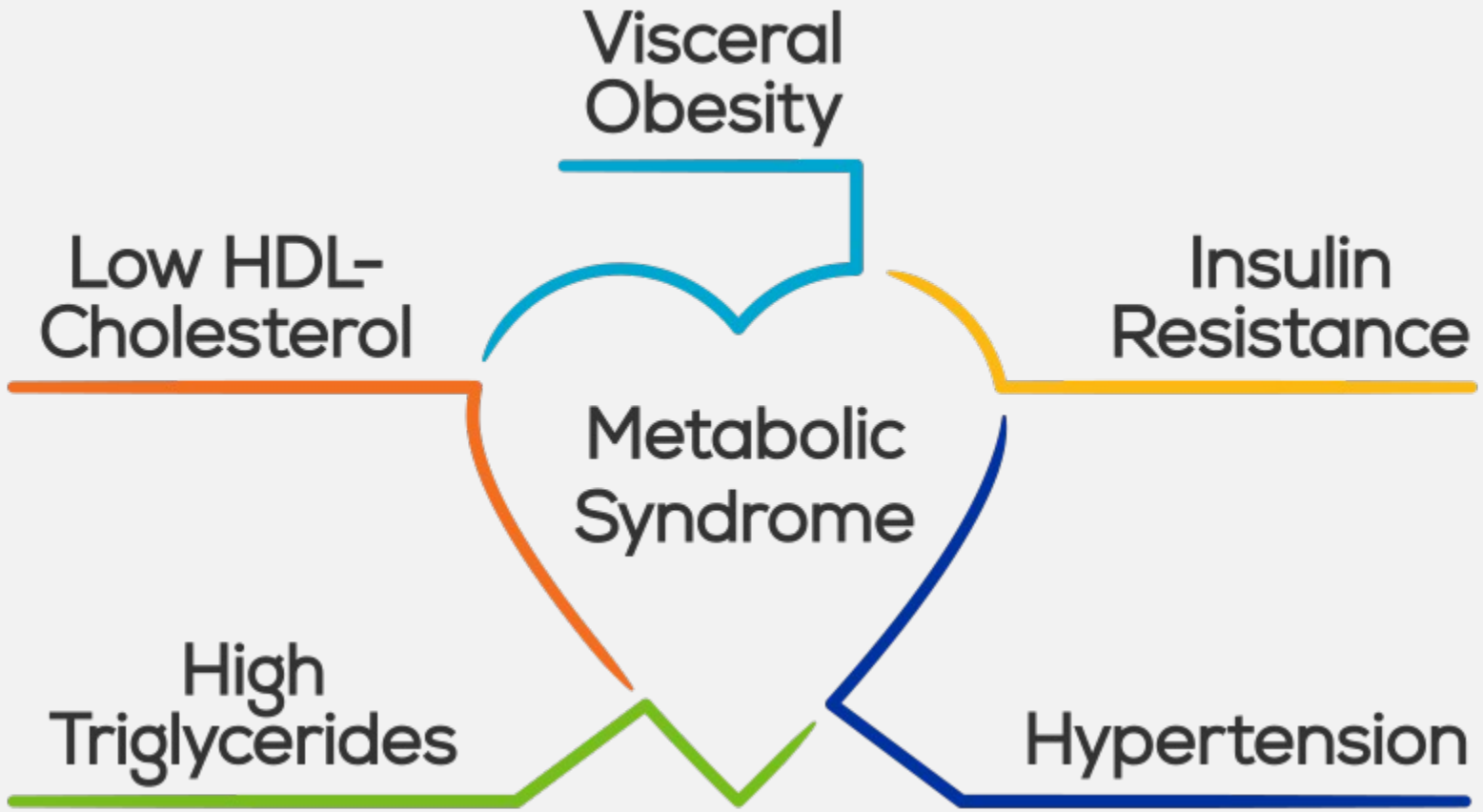
≥50% of persons with diabetes have concomitant hypertension and dyslipidemia

137,745 managed-care enrollees (Kaiser Permanente)

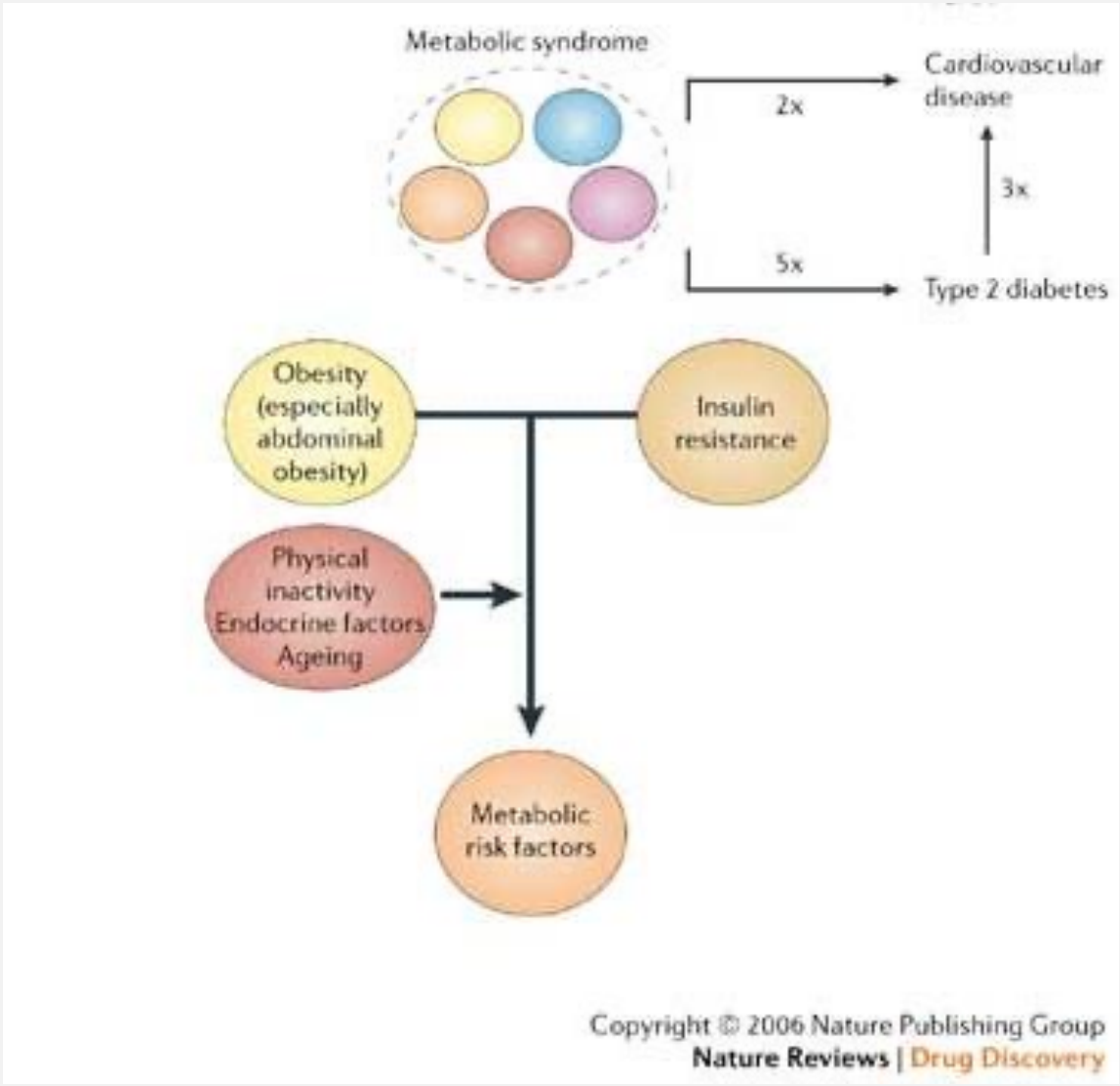


Selby JV et al. *Am J Manag Care*. 2004;10(part 2):163-70.

THEN CAME THE RISK CLUSTER APPROACH- METSYN

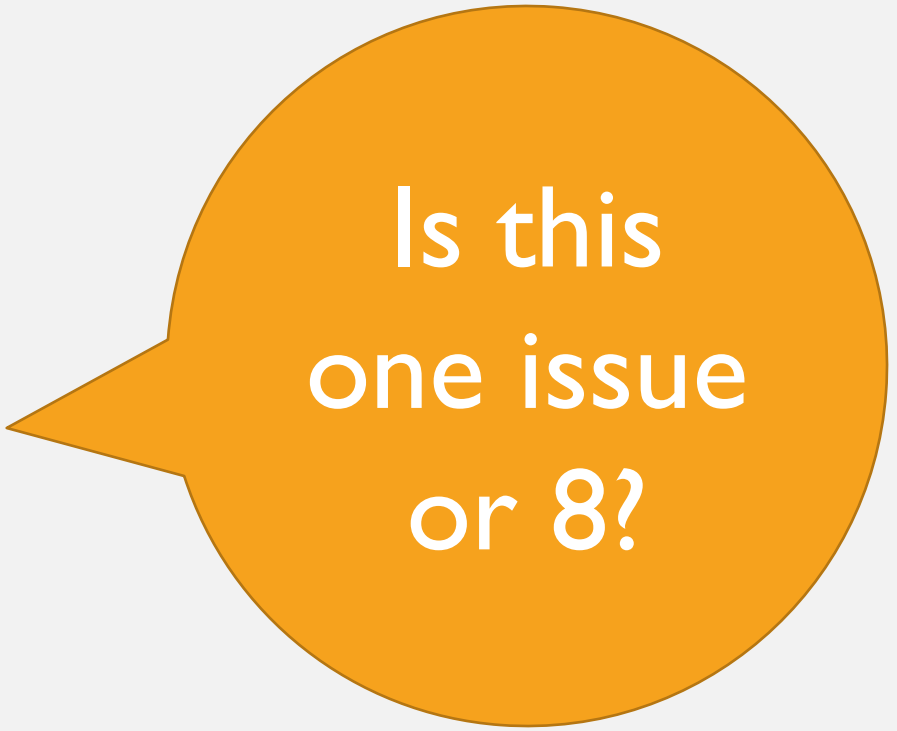


METABOLIC SYNDROME: PATTERN-BASED RISK ANALYSIS



RISK ASSESSMENT BY PATTERN RECOGNITION

- Elevated Triglycerides
- Low HDL-Cholesterol
- Elevated Fasting Insulin
- Low Serum Vitamin D
- Elevated HbA1c
- Elevated LDL particles
- Low chromium
- Elevated CRP

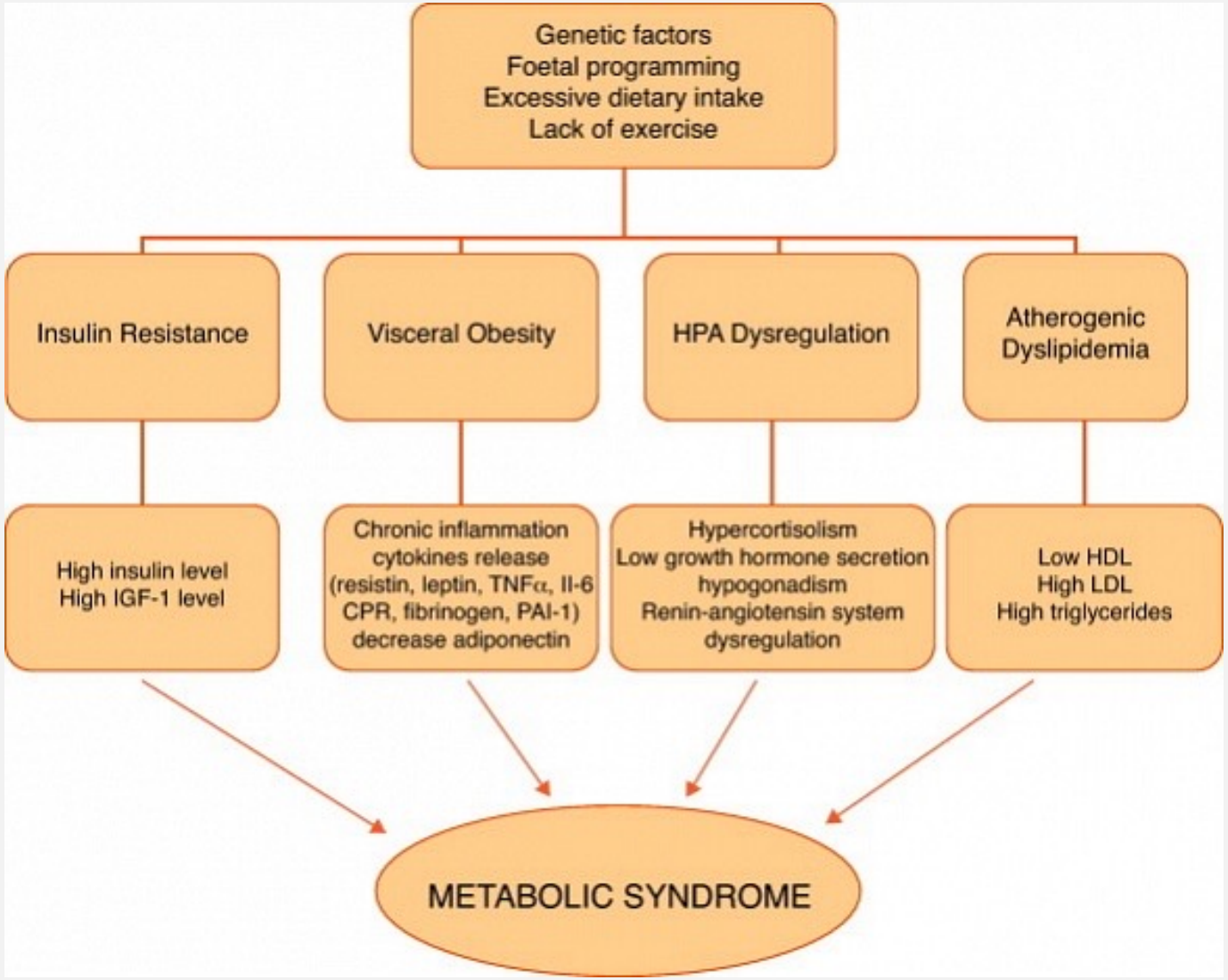


RISK ASSESSMENT VS. PATIENT SOLUTIONS

Pattern recognition & Algorithms

Simple and Targeted Therapies that empower patients

METSYN: RISK BEYOND 5 FACTORS



European Urology, Volume 61 Issue 3, March 2012, Pages 560-570

ARTICLE

The Metabolic Syndrome and Chronic Kidney Disease in U.S. Adults

Jing Chen, MD, MSc; Paul Muntner, PhD; L. Lee Hamm, MD; Daniel W. Jones, MD; Vecihi Batuman, MD; Vivian Fonseca, MD; Paul K. Whelton, MD, MSc; and Jiang He, MD, PhD

Background: The metabolic syndrome is a common risk factor for cardiovascular disease.

Objective: To examine the association between the metabolic syndrome and risk for chronic kidney disease and microalbuminuria.

Design: Cross-sectional study.

Setting: The Third National Health and Nutrition Examination Survey.

Patients: Participants 20 years of age or older were studied in the chronic kidney disease (n = 6217) and microalbuminuria (n = 6125) analyses.

Measurements: The metabolic syndrome was defined as the presence of 3 or more of the following risk factors: elevated blood pressure, low high-density lipoprotein cholesterol level, high triglyceride level, elevated glucose level, and abdominal obesity. Chronic kidney disease was defined as a glomerular filtration rate less than 60 mL/min per 1.73 m², and microalbuminuria was defined as a urinary albumin–creatinine ratio of 30 to 300 mg/g.

Results: The multivariate-adjusted odds ratios of chronic kidney disease and microalbuminuria in participants with the metabolic syndrome compared with participants without the metabolic syndrome were 2.60 (95% CI, 1.68 to 4.02) and 1.89 (CI, 1.34 to 2.67), respectively. Compared with participants with 0 or 1 component of the metabolic syndrome, participants with 2, 3, 4, and 5 components of chronic kidney disease had multivariate-adjusted odds ratios of 2.21 (CI, 1.16 to 4.24), 2.30 (CI, 1.40 to 7.59), 4.23 (CI, 2.05 to 8.62), and 5.85 (CI, 2.11 to 11.0), respectively. The corresponding multivariate-adjusted odds ratios of microalbuminuria for participants with 2, 3, 4, and 5 components were 1.62 (CI, 1.10 to 2.20), 2.45 (CI, 1.55 to 3.89), and 2.19 (CI, 1.56 to [illegible] respectively.

Conclusions: These findings suggest that the metabolic syndrome might be an important factor in the cause of chronic kidney disease.

Ann Intern Med 2004;140:167-174.
For author affiliations, see end of text.

Chronic kidney disease has become an important public health challenge in the United States. According to data from the third National Health and Nutrition Examination Survey (NHANES III), 8.3 million (4.6%) U.S. adults 20 years of age or older have chronic kidney disease (1). Chronic kidney disease is a major risk factor for end-stage renal disease, cardiovascular disease, and premature death (1–7). Identifying and treating risk factors for early chronic kidney disease may be the best approach to prevent and delay adverse outcomes (1).

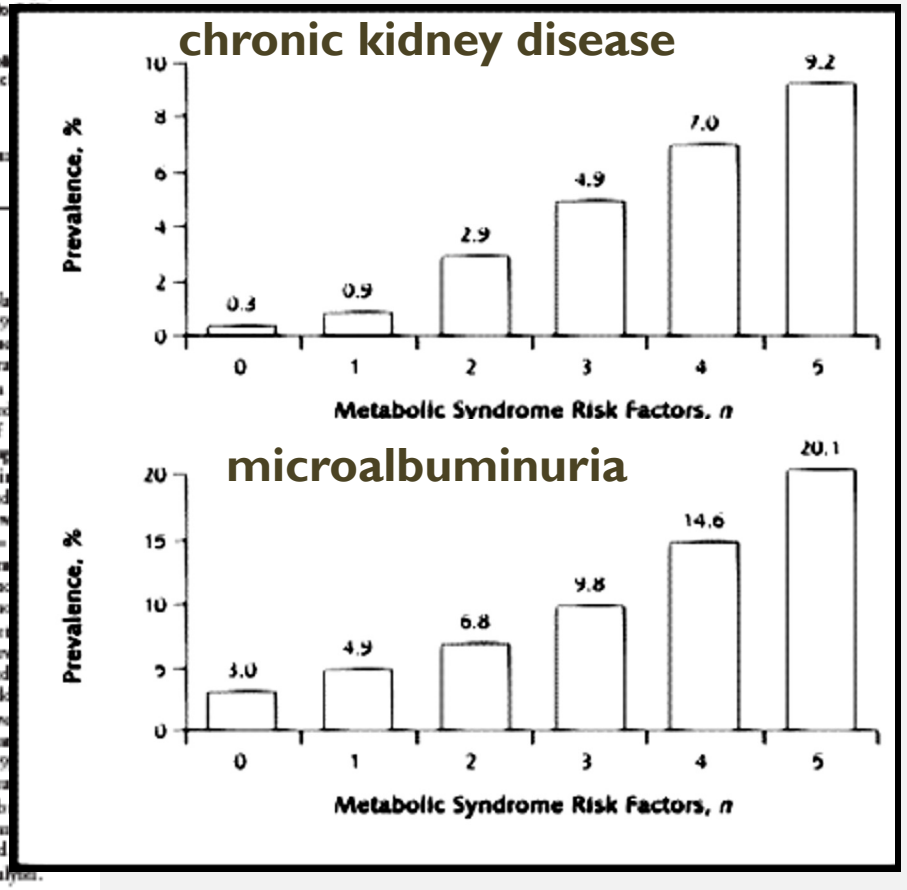
The metabolic syndrome, characterized by abdominal obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol level, high blood pressure, and high fasting glucose level, is a common disorder in the United States (8). For example, 47 million (23.7%) U.S. residents 20 years of age or older have the metabolic syndrome, according to data from NHANES III (9). With the continuous increase in the prevalence of obesity in the United States, the metabolic syndrome is expected to be even more common in the future (10). The metabolic syndrome has been associated with an increased risk for diabetes mellitus and cardiovascular disease, as well as increased mortality from cardiovascular disease and all causes (11–13). However, there are sparse data on the relationship between the metabolic syndrome and risk for chronic kidney disease (14). We examined the association between the metabolic syndrome and risk for chronic kidney disease and microalbuminuria in a large representative sample of U.S. adults who participated in the NHANES III.

METHODS

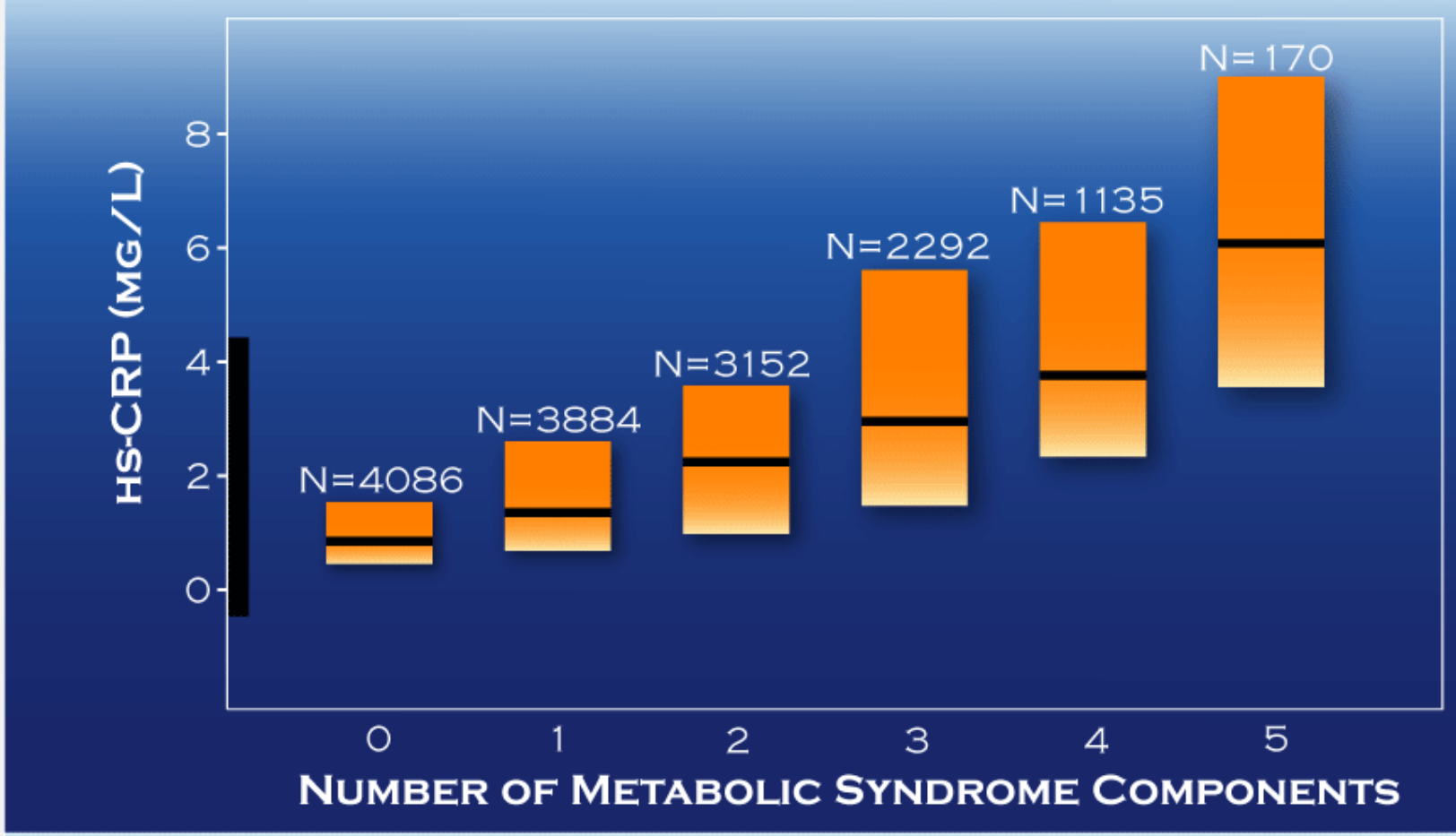
Study Participants

The NHANES III was conducted by the Na[illegible] Center for Health Statistics between 1988 and 19[illegible] detailed description of the study participants and me[illegible] has been published elsewhere (15, 16). In brief, a stra[illegible] multistage probability design was used to obtain a [illegible] sentative sample of the civilian noninstitutionalized [illegible] general population (15, 16). A subsample of [illegible] NHANES III participants who were 20 years of ag[illegible] older was randomly selected to participate in morni[illegible] in at which fasting blood specimens were obtained [illegible] ons without a fasting blood sample (n = 503), [illegible] who were pregnant (n = 120) or menstruating (n = [illegible] and 1 person with kidney failure (estimated glom[illegible] filtration rate <15 mL/min per 1.73 m²) were exc[illegible] from the current analysis. Furthermore, persons who [illegible] missing measurements for any component of the met[illegible] syndrome (plasma glucose level, HDL cholesterol le[illegible] rum triglyceride level, waist circumference, or blood [illegible] ure measurements) were excluded (n = 621). In addi[illegible] 95 persons with missing creatinine measurements we[illegible] cluded from the chronic kidney disease analyses a[illegible] persons with missing data on urinary albumin and 9[illegible] ons with clinical proteinuria (urinary albumin–crea[illegible] ratio >300 mg/g) were excluded from the microalb[illegible] uria analyses. After these exclusions, 6217 persons [illegible] included in the chronic kidney disease analyses and [illegible] persons were included in the microalbuminuria analyses.

Ann. of Int. Med 140(3):167-174; 2004



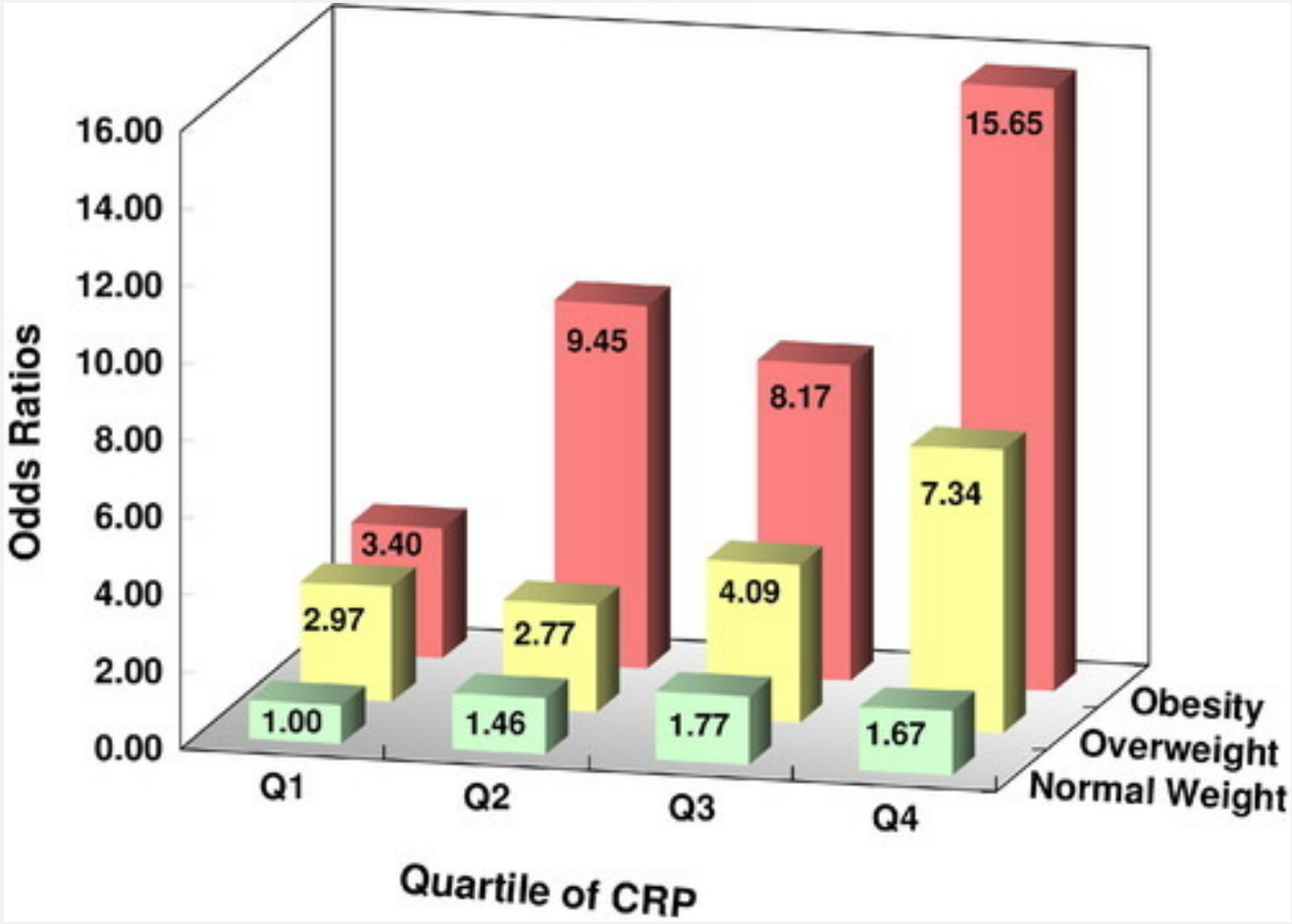
C-REACTIVE PROTEIN AND METABOLIC SYNDROME



Ridker et al. Circulation. 2003;107:391.

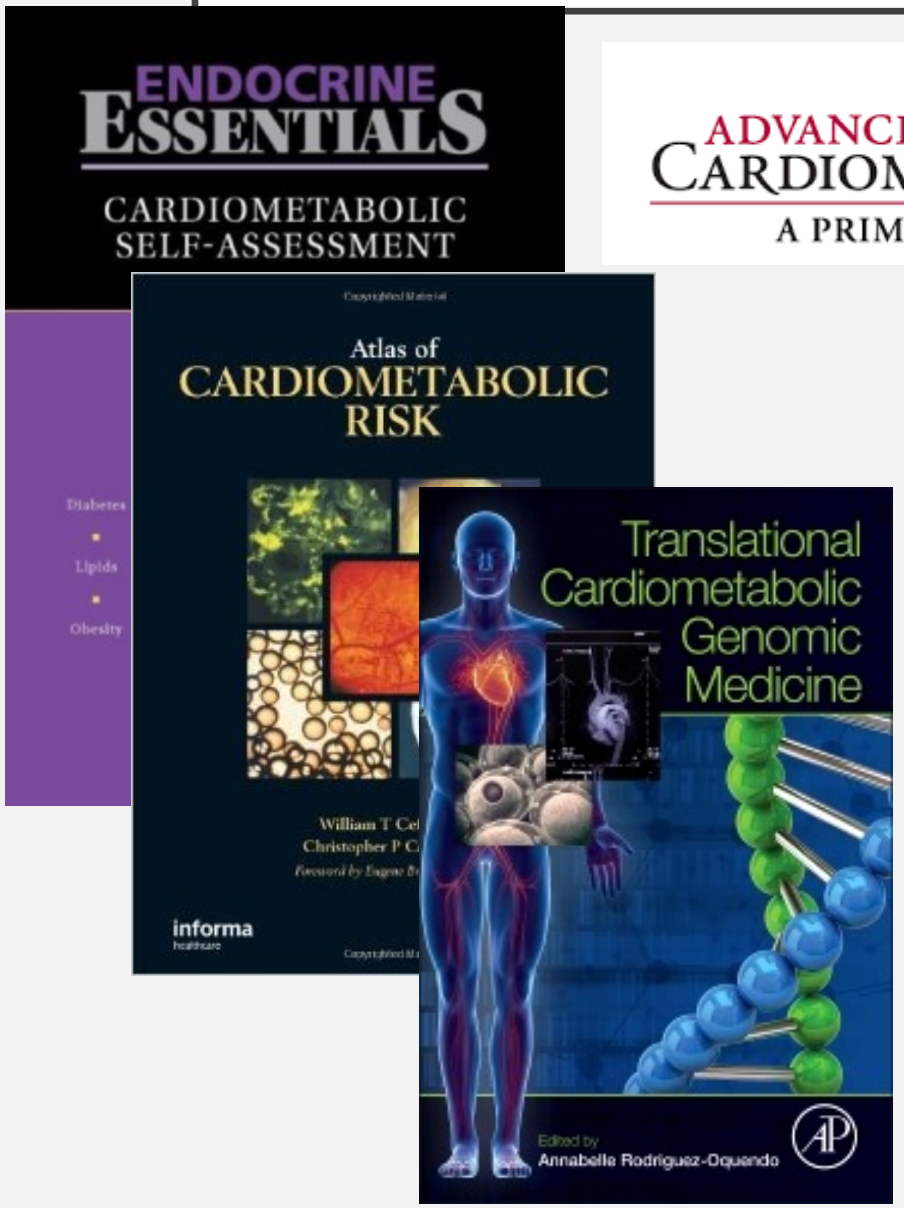
The Metabolic Syndrome Institute

OBESITY INCREASES THE RISK OF CRP



J Am Coll Cardiol. 2007 May, 49 (17) 1798–1805

A NEW NOMENCLATURE EMERGES



Joslin Diabetes Center

ADVANCES IN CARDIOMETABOLIC HEALTH

A PRIMARY CARE SUMMIT 2014

CardioMetabolic HEALTH ALLIANCE

International Chair on Cardiometabolic Risk

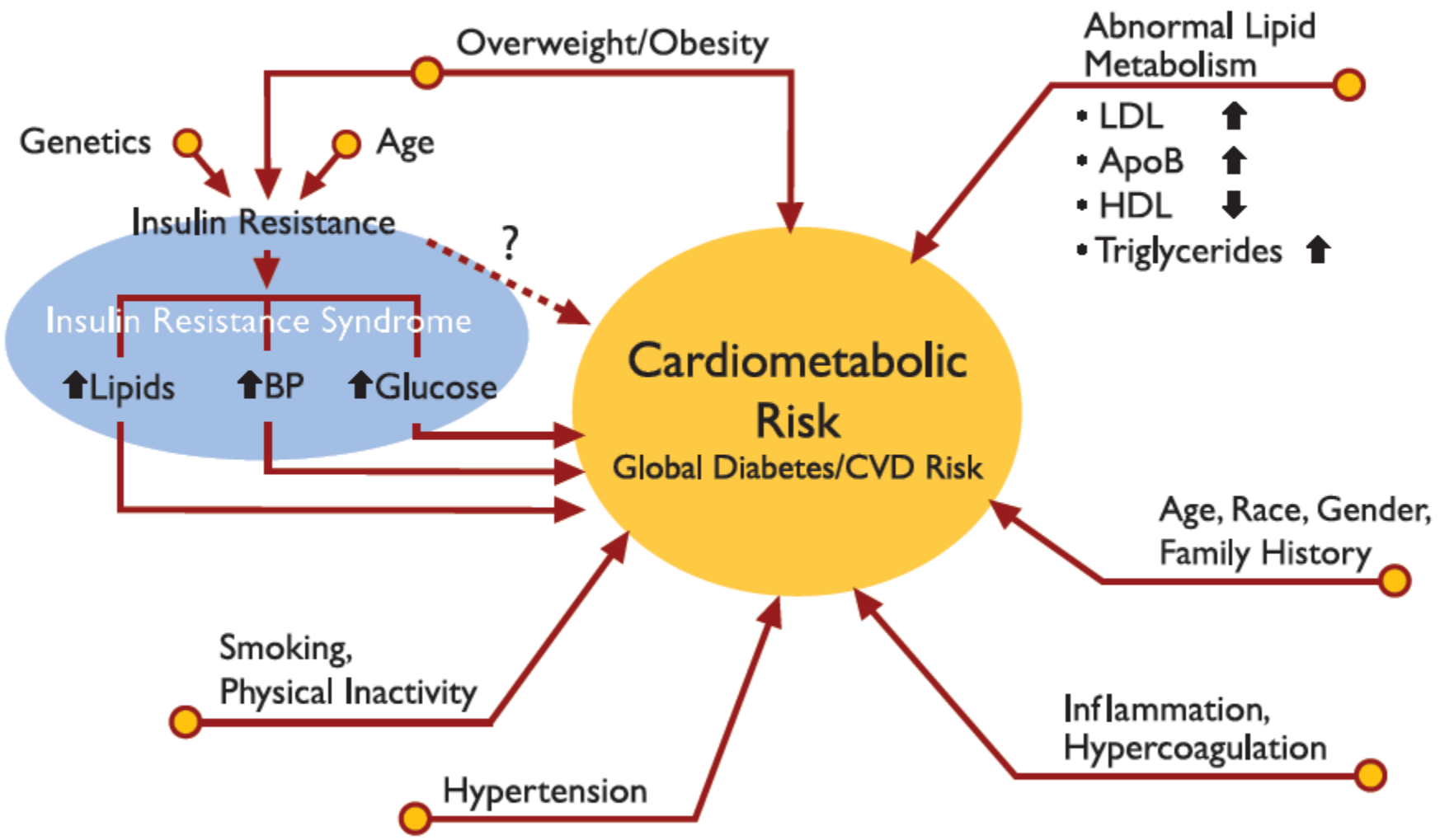
11th Annual CMHC

Cardiometabolic Health Congress

October 5 - 8, 2016 • Boston, MA

Factors Contributing to Cardiometabolic Risk

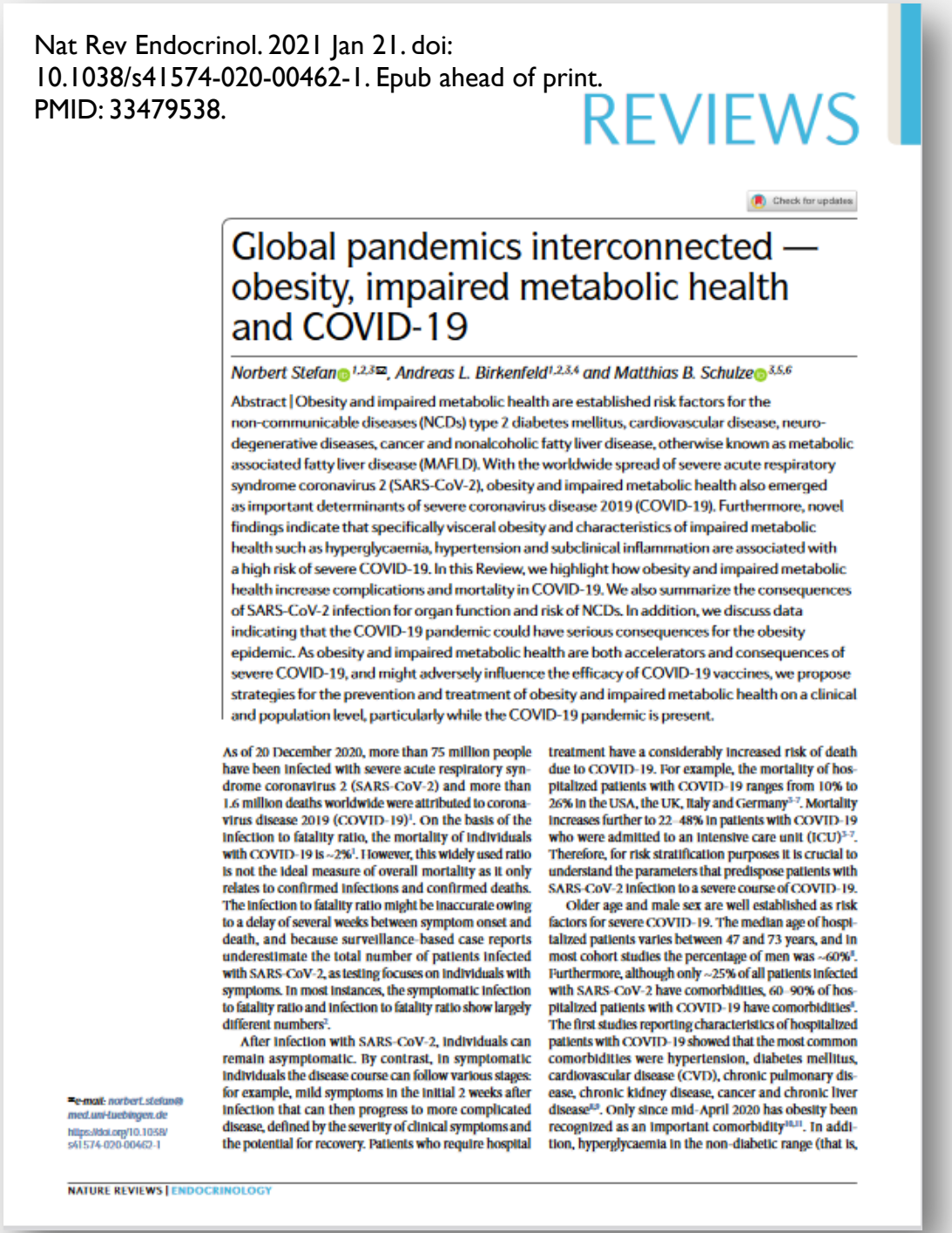
American Diabetes Association.
Cure • Care • Commitment



CARDIOMETABOLIC "DISEASE": A NOMENCLATURE FOR COMPLEX MULTIFACTORIAL METABOLIC DYSFUNCTIONS

- CM Disease is a classic challenge to the "old" diagnostic model
- CM Disease defies the silo approach to diagnostics
- CM risk factors can predict how the disease will progress
- CM risk factors can be diagnosed and treated before frank cardiovascular or glucose disposal diseases (i.e., DM) are diagnosed
- Cardiometabolic disorders are not simply Pre-DM, or Pre-CVD
- Cardiometabolic dysfunctions reduce resilience to many chronic and acute disease phenomena

Nat Rev Endocrinol. 2021 Jan 21. doi: 10.1038/s41574-020-00462-1. Epub ahead of print.
PMID: 33479538.



Check for updates

Global pandemics interconnected — obesity, impaired metabolic health and COVID-19

Norbert Stefan[1,2,3]✉, *Andreas L. Birkenfeld*[1,2,3,4] *and Matthias B. Schulze*[3,5,6]

Abstract | Obesity and impaired metabolic health are established risk factors for the non-communicable diseases (NCDs) type 2 diabetes mellitus, cardiovascular disease, neurodegenerative diseases, cancer and nonalcoholic fatty liver disease, otherwise known as metabolic associated fatty liver disease (MAFLD). With the worldwide spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), obesity and impaired metabolic health also emerged as important determinants of severe coronavirus disease 2019 (COVID-19). Furthermore, novel findings indicate that specifically visceral obesity and characteristics of impaired metabolic health such as hyperglycaemia, hypertension and subclinical inflammation are associated with a high risk of severe COVID-19. In this Review, we highlight how obesity and impaired metabolic health increase complications and mortality in COVID-19. We also summarize the consequences of SARS-CoV-2 infection for organ function and risk of NCDs. In addition, we discuss data indicating that the COVID-19 pandemic could have serious consequences for the obesity epidemic. As obesity and impaired metabolic health are both accelerators and consequences of severe COVID-19, and might adversely influence the efficacy of COVID-19 vaccines, we propose strategies for the prevention and treatment of obesity and impaired metabolic health on a clinical and population level, particularly while the COVID-19 pandemic is present.

As of 20 December 2020, more than 75 million people have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and more than 1.6 million deaths worldwide were attributed to coronavirus disease 2019 (COVID-19)[1]. On the basis of the infection to fatality ratio, the mortality of individuals with COVID-19 is ~2%[1]. However, this widely used ratio is not the ideal measure of overall mortality as it only relates to confirmed infections and confirmed deaths. The infection to fatality ratio might be inaccurate owing to a delay of several weeks between symptom onset and death, and because surveillance-based case reports underestimate the total number of patients infected with SARS-CoV-2, as testing focuses on individuals with symptoms. In most instances, the symptomatic infection to fatality ratio and infection to fatality ratio show largely different numbers[2].

After infection with SARS-CoV-2, individuals can remain asymptomatic. By contrast, in symptomatic individuals the disease course can follow various stages: for example, mild symptoms in the initial 2 weeks after infection that can then progress to more complicated disease, defined by the severity of clinical symptoms and the potential for recovery. Patients who require hospital treatment have a considerably increased risk of death due to COVID-19. For example, the mortality of hospitalized patients with COVID-19 ranges from 10% to 26% in the USA, the UK, Italy and Germany[3–7]. Mortality increases further to 22–48% in patients with COVID-19 who were admitted to an intensive care unit (ICU)[3–7]. Therefore, for risk stratification purposes it is crucial to understand the parameters that predispose patients with SARS-CoV-2 infection to a severe course of COVID-19.

Older age and male sex are well established as risk factors for severe COVID-19. The median age of hospitalized patients varies between 47 and 73 years, and in most cohort studies the percentage of men was ~60%[8]. Furthermore, although only ~25% of all patients infected with SARS-CoV-2 have comorbidities, 60–90% of hospitalized patients with COVID-19 have comorbidities[8]. The first studies reporting characteristics of hospitalized patients with COVID-19 showed that the most common comorbidities were hypertension, diabetes mellitus, cardiovascular disease (CVD), chronic pulmonary disease, chronic kidney disease, cancer and chronic liver disease[8,9]. Only since mid-April 2020 has obesity been recognized as an important comorbidity[10,11]. In addition, hyperglycaemia in the non-diabetic range (that is,

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https://doi.org/10.1038/s41574-020-00462-1

Key points

- Obesity, particularly severe obesity, is a strong and independent determinant of severe COVID-19; novel studies also suggest that visceral obesity increases the risk of complications.

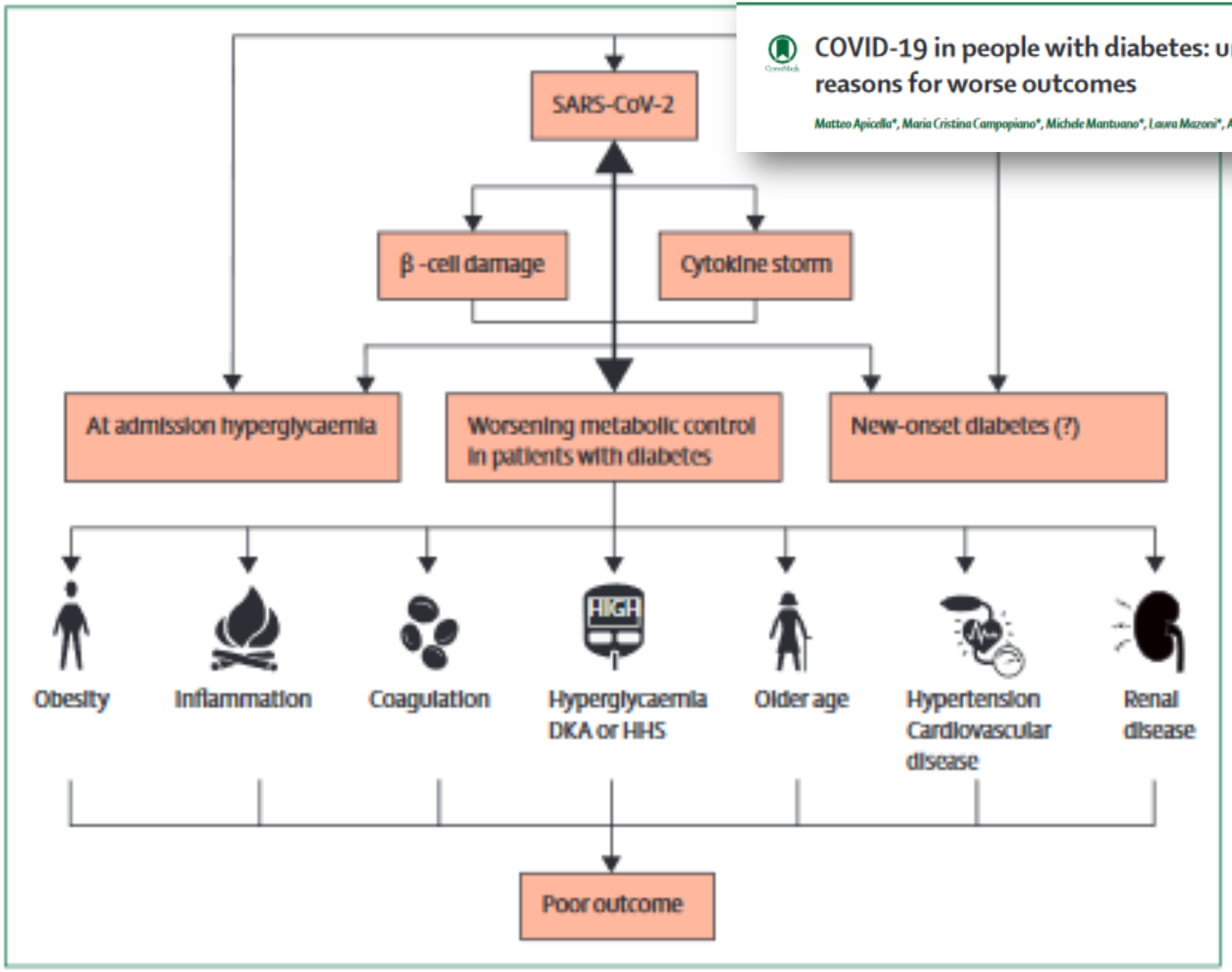
- Although diabetes mellitus is an established risk factor for severe COVID-19, evidence is increasing that hyperglycaemia in the non-diabetic also strongly predicts severe COVID-19.

- SARS-CoV-2 targets organs and tissues that are relevant for cardiometabolic health; SARS-CoV-2-induced organ or tissue dysfunction could result in an increased incidence of cardiometabolic diseases.

- Targeted interventions for metabolic pathologies could improve management of COVID-19; the SARS-CoV-2 vaccination response should be carefully evaluated in patients with obesity and/or diabetes mellitus because of a potentially reduced response.

- Weight loss and the improvement of metabolic health in people with metabolically unhealthy obesity should be implemented at the patient level and in the public health sector.

- Research to understand how diet and nutritional status modify the immune response could help explain some of the variability in COVID-19 morbidity and mortality and improve patient outcomes.



COVID-19 in people with diabetes: understanding the reasons for worse outcomes

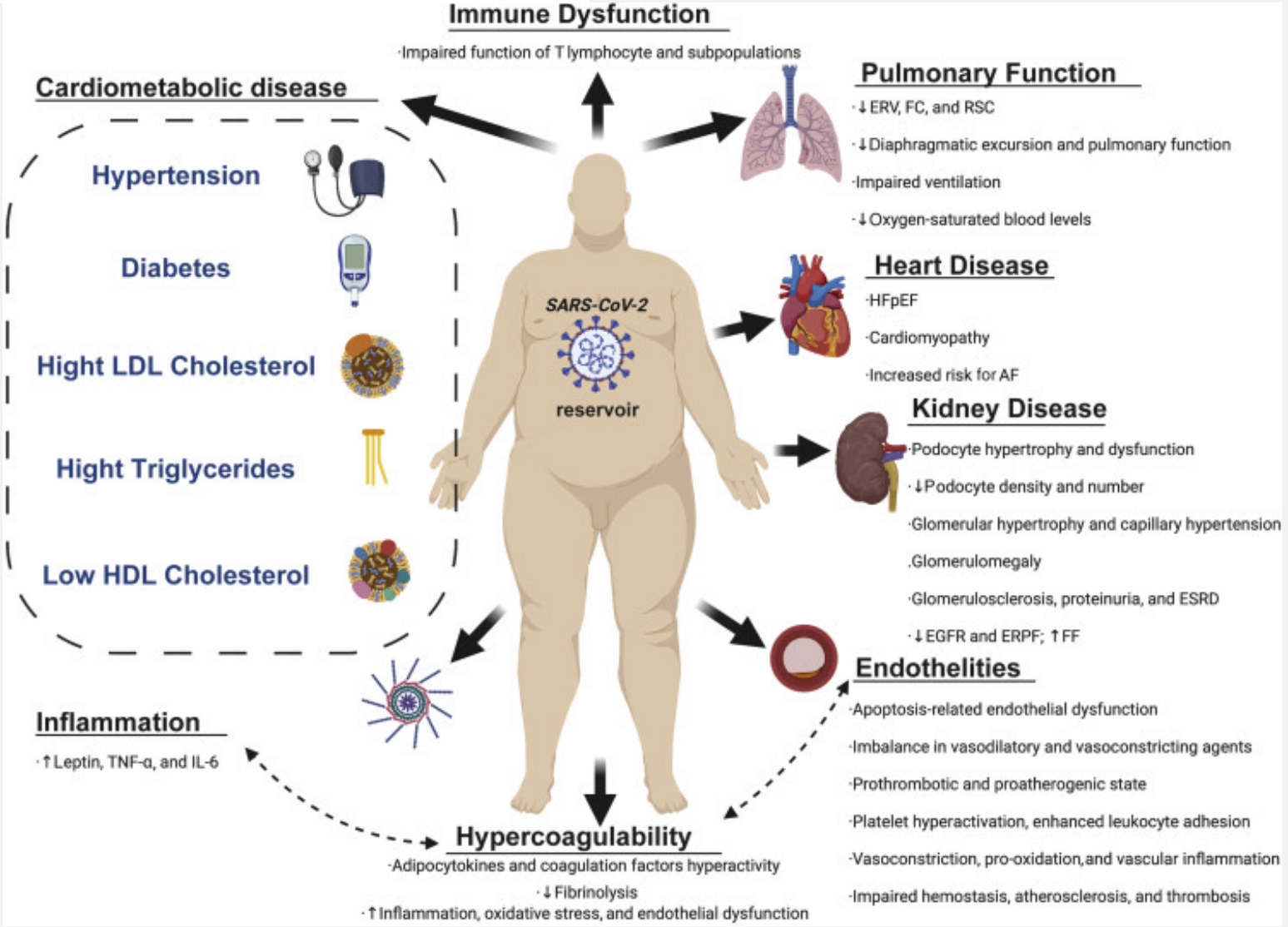
Matteo Apicella*, Maria Cristina Campopiano*, Michele Mantuano*, Laura Mazoni*, Alberto Coppelli, Stefano Del Prato

Lancet Diabetes Endocrinol. 2020 Sep; 8(9): 782–792.

MAYO CLINIC

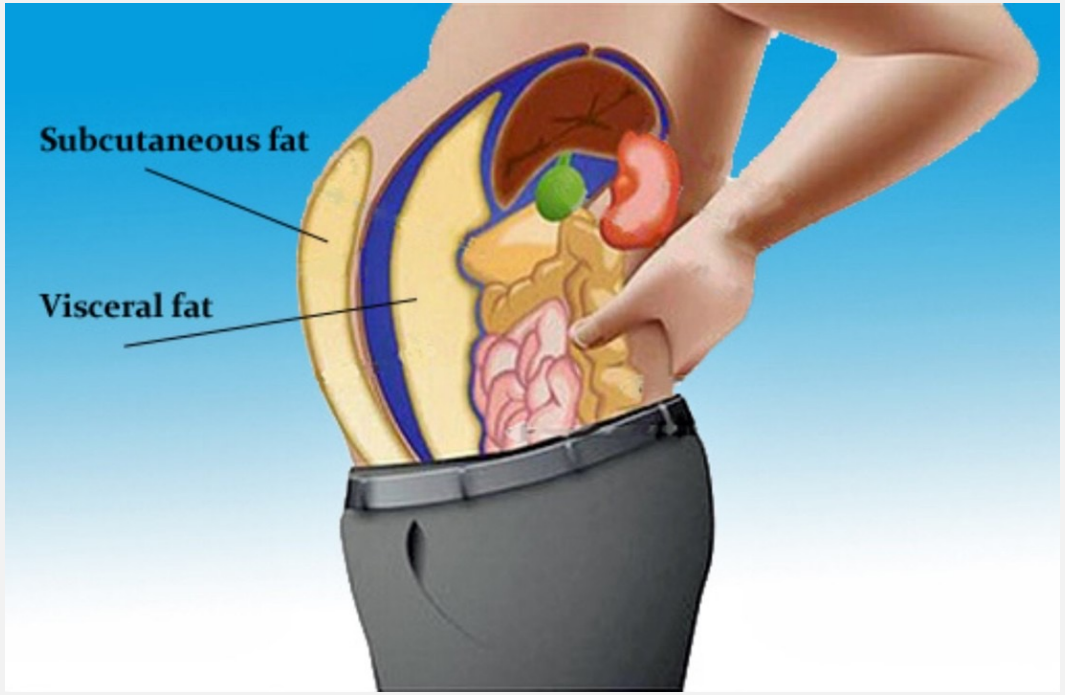
SPECIAL ARTICLE

Obesity and Outcomes in COVID-19: When an Epidemic and Pandemic Collide



FAT MASS- THE ULTIMATE BUFFER

- Nearly every metabolic buffering system uses fat mass as a buffer against immediate crisis
- Energy imbalance
- Hormone imbalance
- Toxin dilution
- Stress and emotional
- Sleep imbalances



Review
OBESITY BIOLOGY AND INTEGRATED PHYSIOLOGY

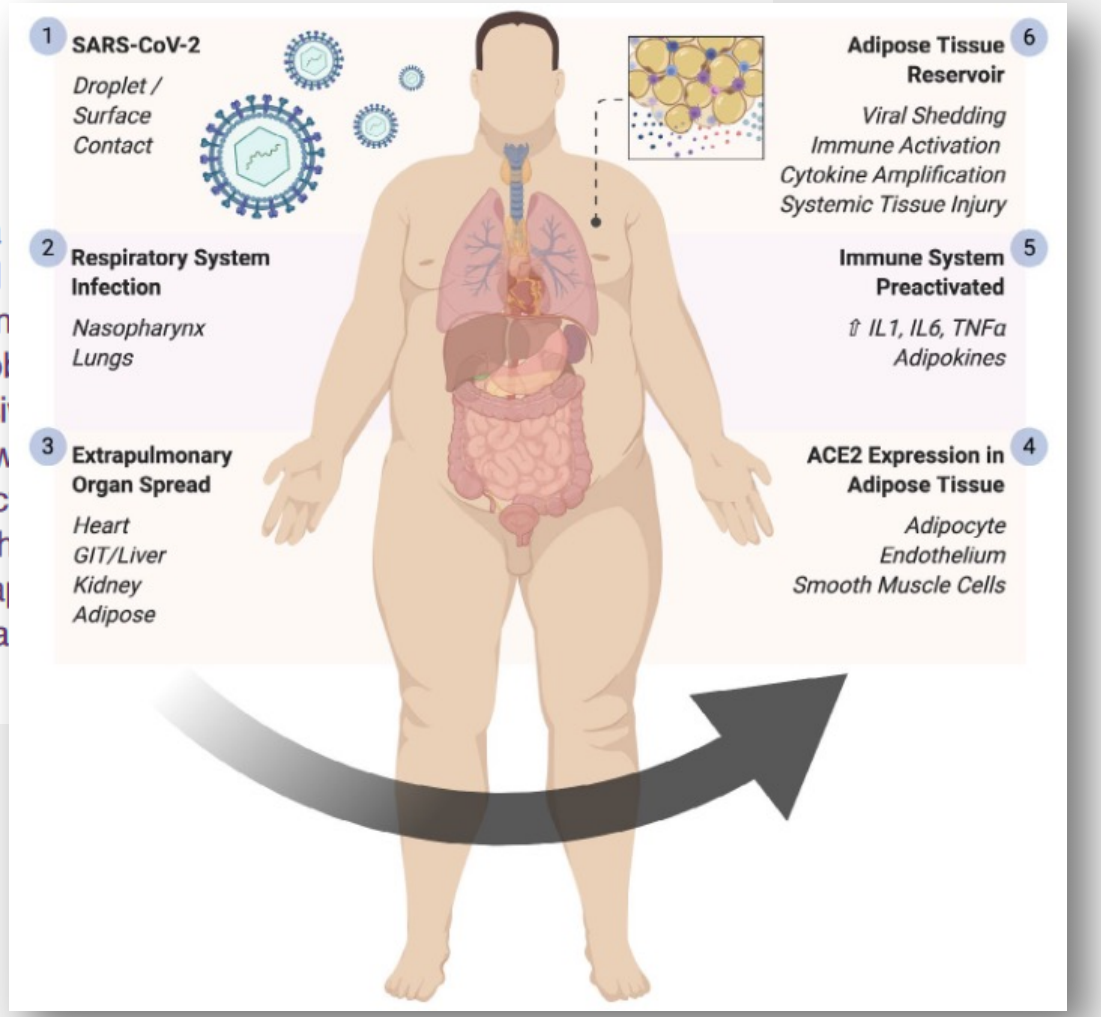
Obesity

Is Adipose Tissue a Reservoir for Viral Spread, Immune Activation, and Cytokine Amplification in Coronavirus Disease 2019?

Paul MacDaragh Ryan *and Noel M. Caplice*

Coronavirus disease 2019 (COVID-19), the worst pandemic in more than a
wide to date. Emerging predictors for poor outcomes include advanced
disease, and risk factors including hypertension, diabetes, and, more recen
driven predictors of poor COVID-19 outcomes, over and above the more ob
including cardiometabolic disease and hypoventilation syndrome in intensi
theoretical mechanistic framework whereby adipose tissue in individuals w
extensive viral spread, with increased shedding, immune activation, and c
studies to test this reservoir concept with a focus on specific cytokine path
with obesity and COVID-19. Finally, this paper underscores emerging therap
of patients in which cytokine amplification is excessive and potentially fata

Obesity (2020) **0**, 1-4.



Breaking News!

COVID-19 Death Rates 10 Times Higher in Countries Where Most Are Overweight

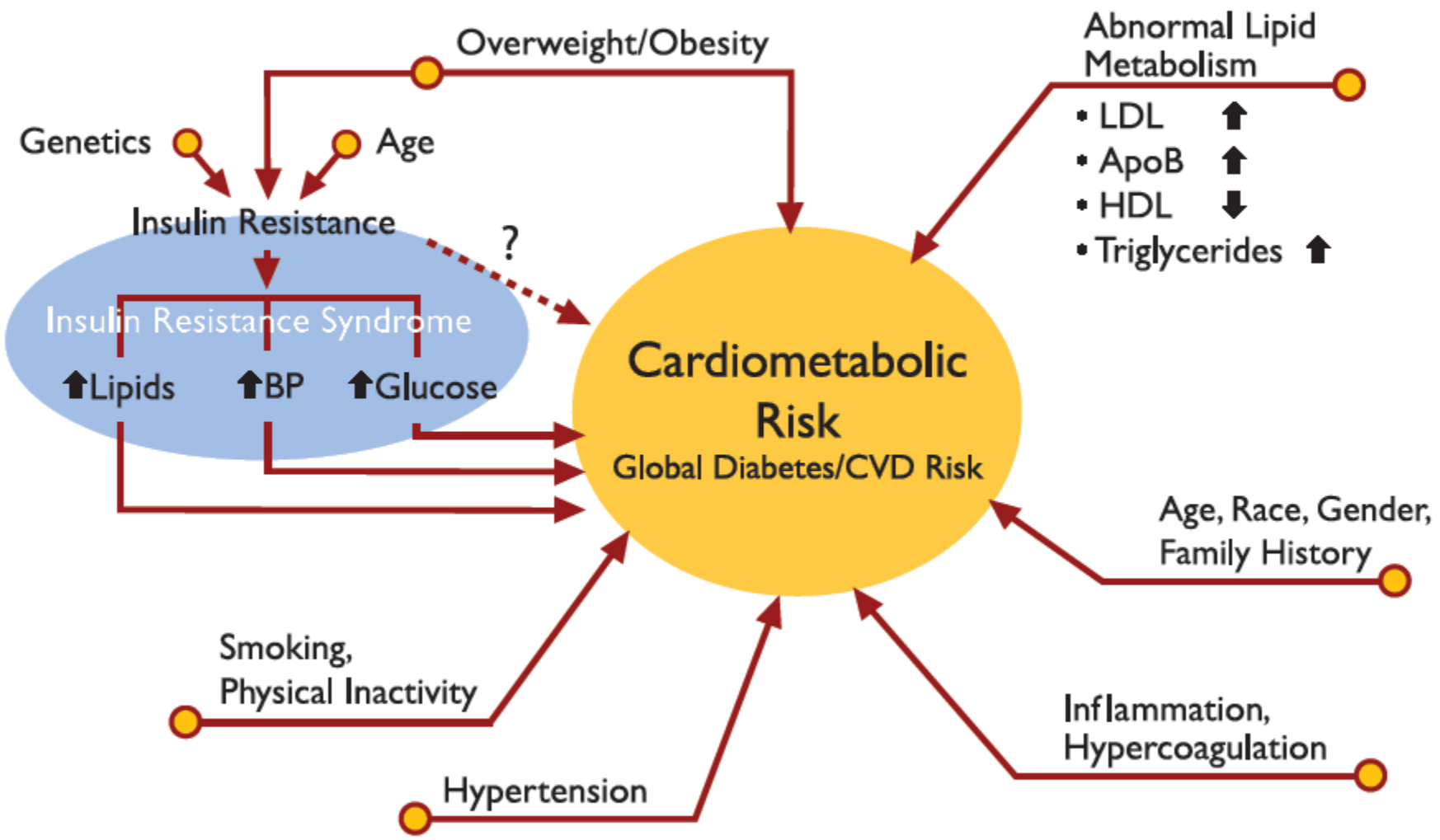
Mar 5, 2021

THURSDAY, March 4, 2021 (HealthDay News) — In a finding that suggests overweight people should be prioritized for COVID-19 vaccines, a new report released Thursday shows the risk for death from COVID-19 infection is about 10 times higher in countries where most of the population is overweight.

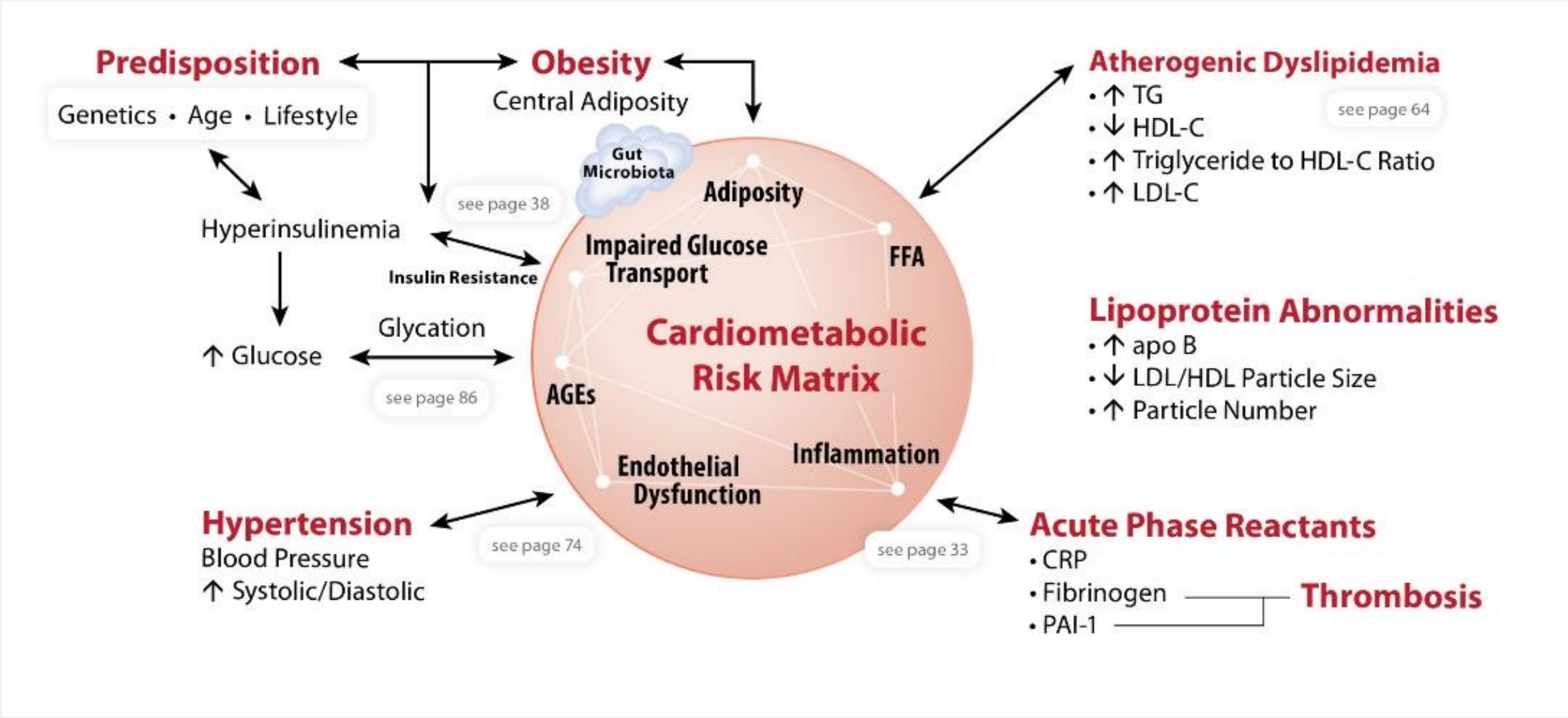
The World Obesity Federation report revealed that 88 percent of deaths due to COVID-19 in the first year of the pandemic were in countries where more than half of the population is classified as overweight. Among the nations with overweight populations above the 50 percent threshold were also those with some of the largest proportions of

Factors Contributing to Cardiometabolic Risk

American Diabetes Association.
Cure • Care • Commitment

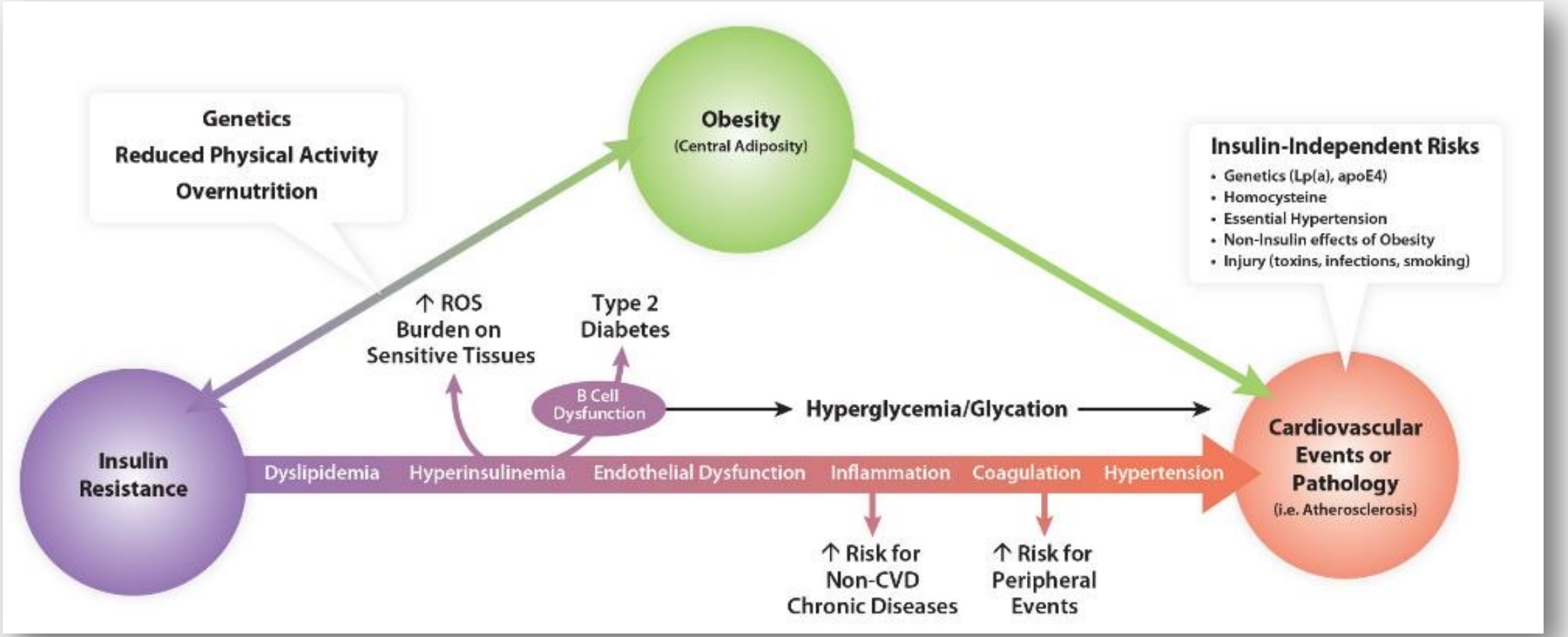


RISK IS NOT A NUMBER, BUT A PROCESS!

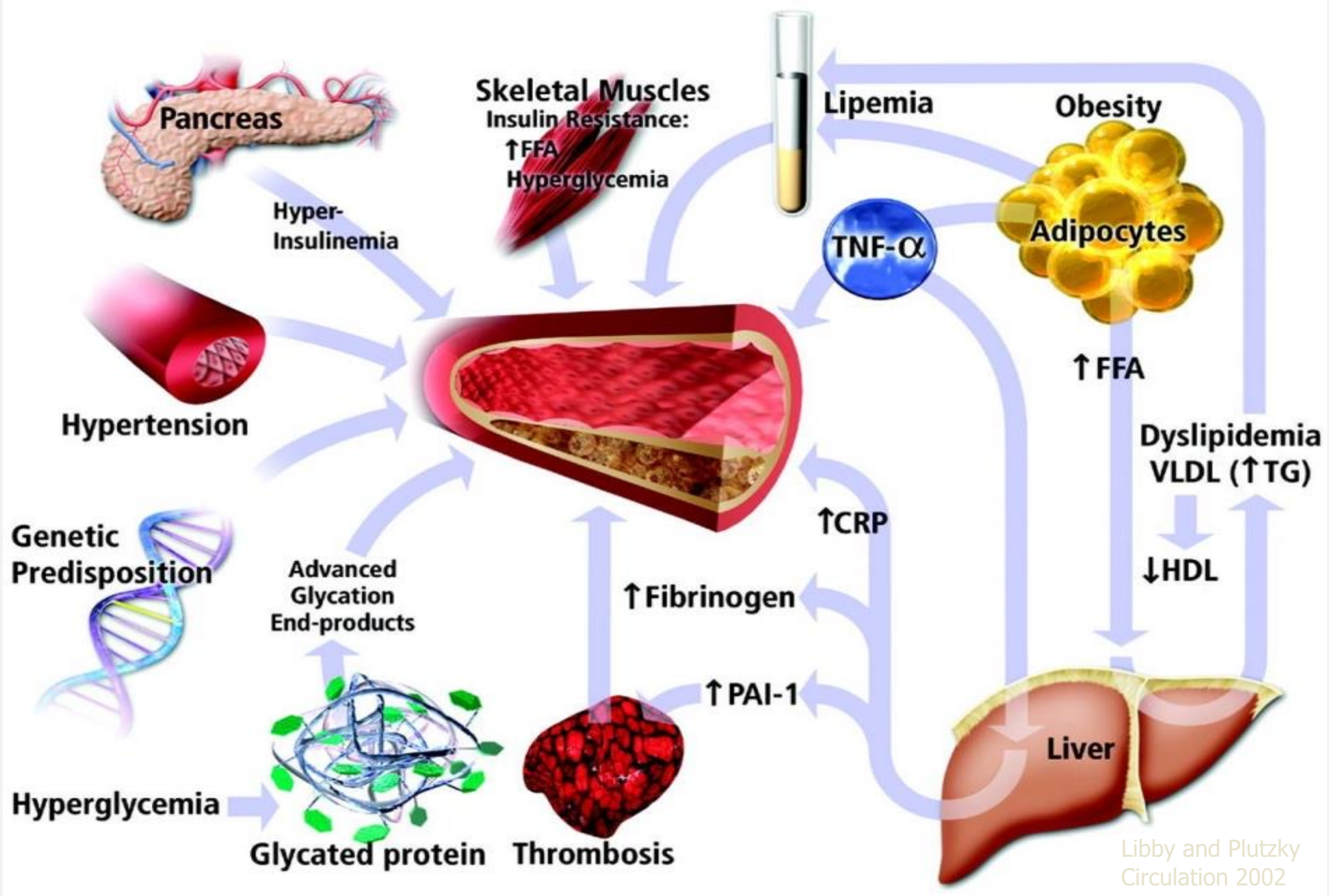


Guilliams. Cardiometabolic Risk Management: A Functional and Lifestyle Approach- 2018

CARDIOVASCULAR TO CARDIOMETABOLIC



Guilliams. Cardiometabolic Risk Management: A Functional and Lifestyle Approach- 2018


Pancreas
Skeletal Muscles
Insulin Resistance:
↑FFA
Hyperglycemia
Lipemia
Obesity
Hyper-
Insulinemia
TNF-α
Adipocytes
Hypertension
↑FFA
Dyslipidemia
VLDL (↑TG)
↑CRP
Genetic
Predisposition
Advanced
Glycation
End-products
↑Fibrinogen
↓HDL
↑PAI-1
Liver
Hyperglycemia
Glycated protein
Thrombosis
Libby and Plutzky
Circulation 2002

Glycation (Receptor-Independent Pathway)

Protein, lipid, nucleic acid + reducing sugar

Glycated Hemoglobin (HbA1c)

- Marker of glycation

Glycated apoB-100 on LDL

- Decreased binding affinity for LDLR
- Increased binding affinity for scavenger receptors
- Increased susceptibility for LDL oxidation
- Associated with decreased expression of eNos
- May modify platelet properties
- Small dense LDL may have more lysine residues available for glycation

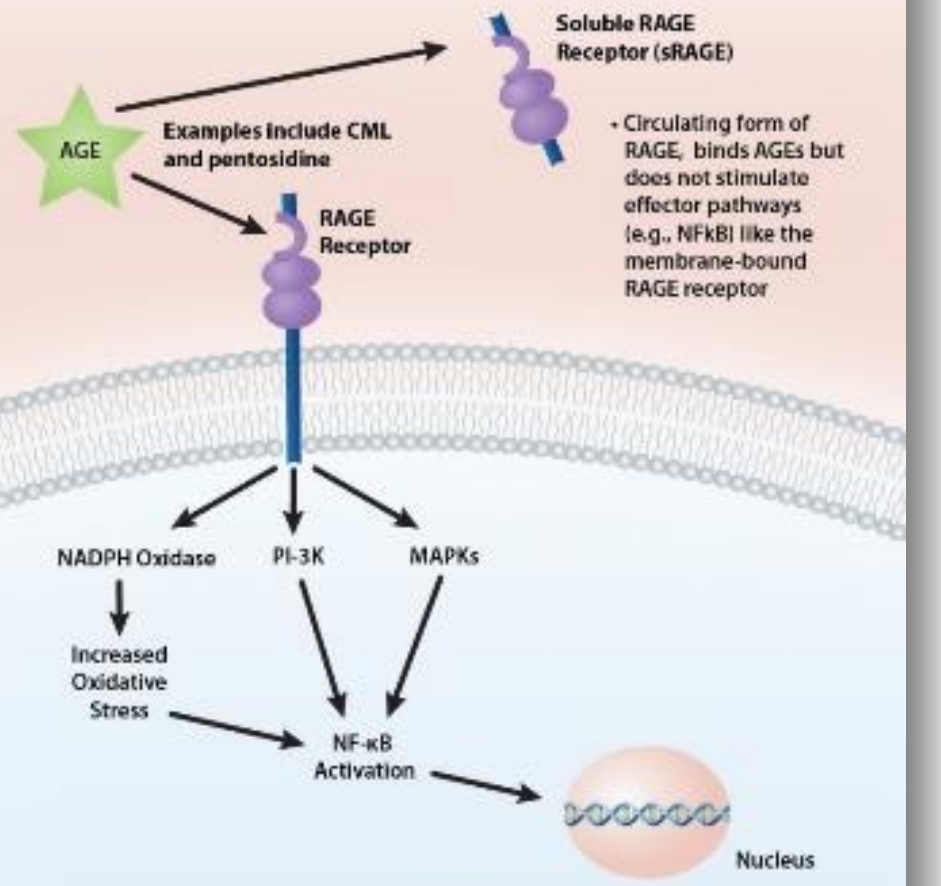
Glycated HDL

- Decreased activity of antioxidant enzyme paraoxonase
- Impaired inhibitory activity on monocyte adhesion to aortic endothelial cells in response to oxidized LDL
- Impairment in reverse cholesterol transport
- Increased intracelullar lipid accumulation

Glycated Collagen

- Since collagen is a long-lived protein, it may progress to an AGE via crosslinking
- Glycated and cross-linked collagen is associated with increased vascular stiffness

AGE (Receptor-Mediated Pathway)



Consequences of NF-κB Activation by AGE/RAGE

- Increased inflammatory markers (e.g., TNF-α, IL-6, VCAM-1)
- Increased transcription of RAGE
- Decreased endothelial barrier function
- Suppression of ABCA1 and ABCG1 transcription affecting reverse cholesterol transport
- Increased platelet activation
- Increased production of ADMA and suppression of ADMA breakdown

Signals that drive metabolic risk

- Sense of belonging
- Group dynamics
- Life purpose

- Insulin Response to Food
- Meal Timing & Energy
- Phytonutrients-genomics

- Addictive foods
- Alcohol/Drugs
- Poor oral hygiene

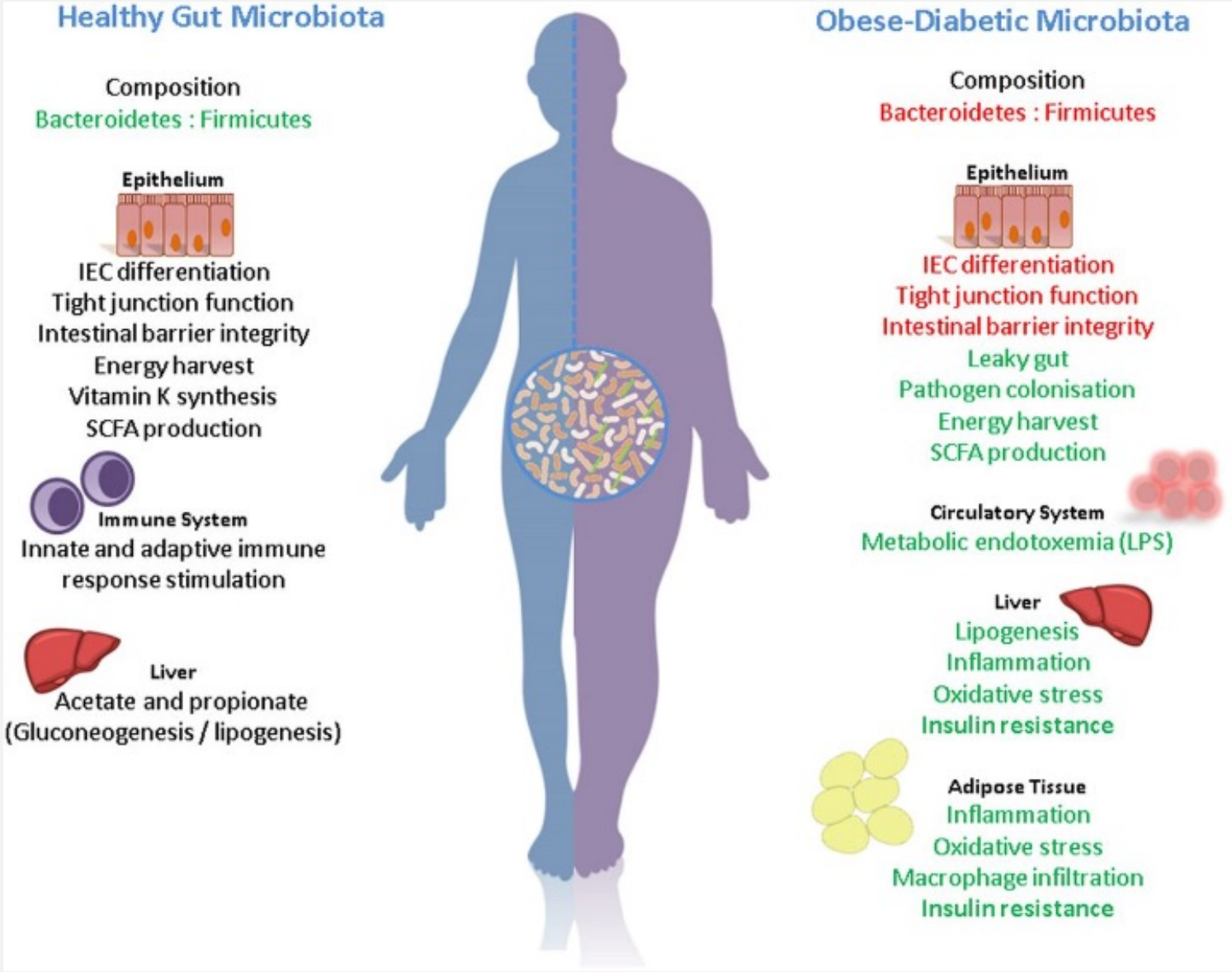
- Sedentary Time
- Energy Expenditure
- Exercise signals

- Stress-induced eating
- Cortisol – Stress hormone powerful metabolic signal

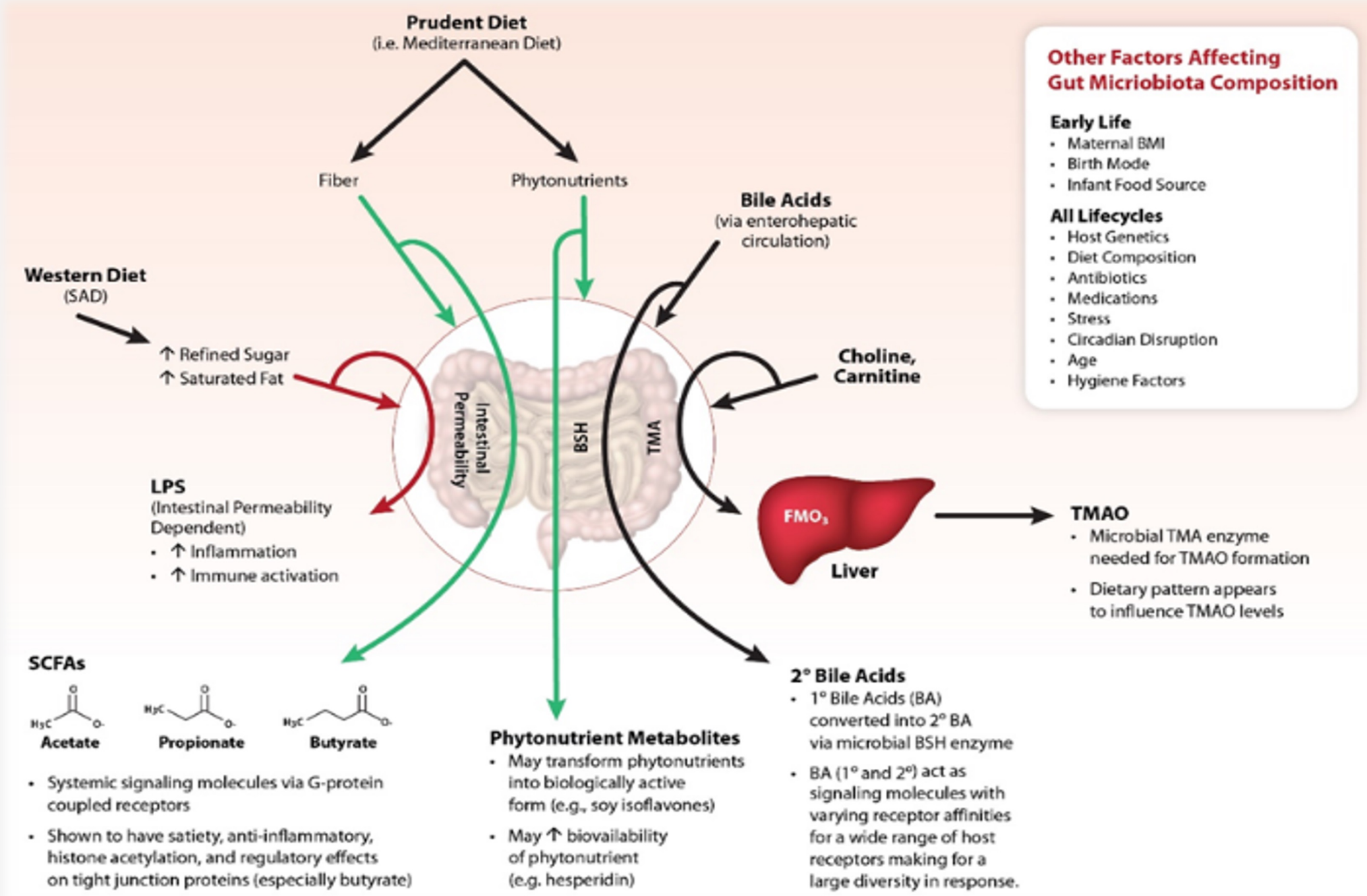
- "Obesogenic" Toxins (BPA)
- Sunlight-Vit D
- Microflora Gut Bacteria

- Sleep time & patterns
- Seasonal changes
- Phase-shifters

IS THERE AN OBESE MICROBIOME?



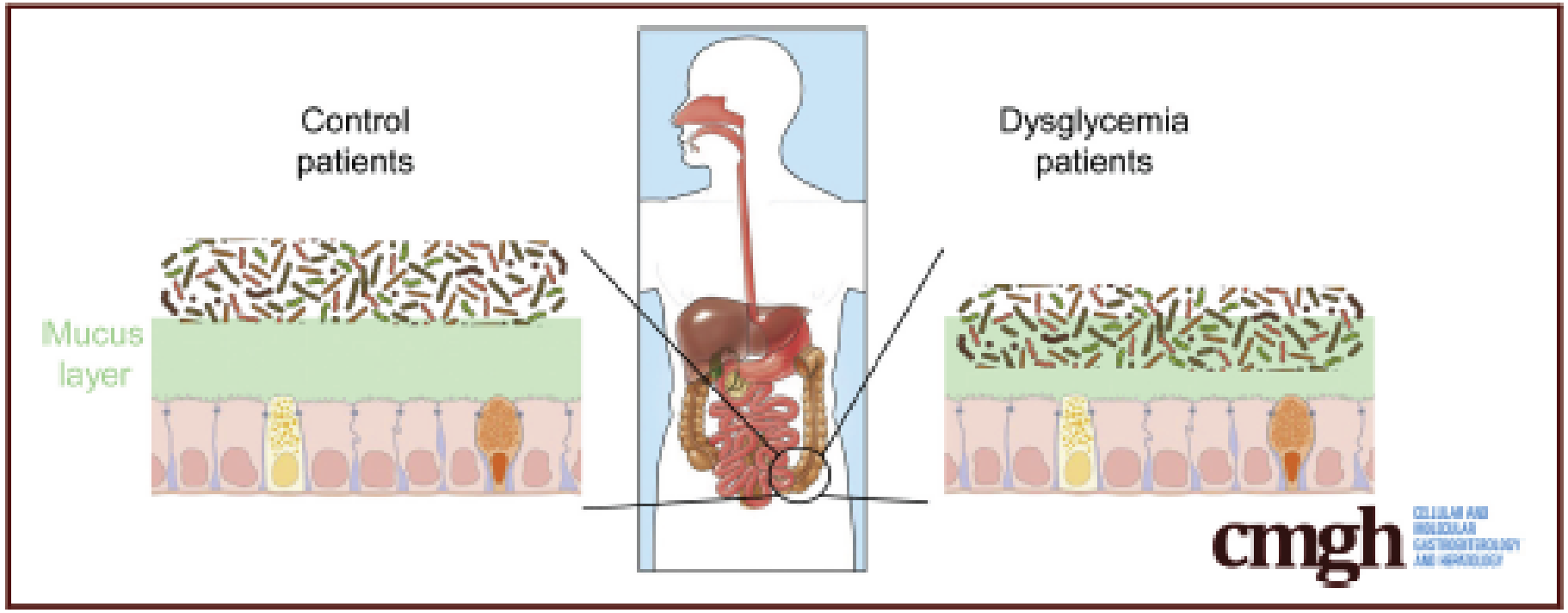
doi: 10.1136/postgradmedj-2015-133285


Prudent Diet
(i.e. Mediterranean Diet)
Fiber
Phytonutrients
Bile Acids
(via enterohepatic circulation)
Western Diet
(SAD)
↑ Refined Sugar
↑ Saturated Fat
Choline, Carnitine
Intestinal Permeability
BSH
TMA
LPS
(Intestinal Permeability Dependent)
• ↑ Inflammation
• ↑ Immune activation
FMO3
Liver
TMAO
• Microbial TMA enzyme needed for TMAO formation
• Dietary pattern appears to influence TMAO levels
Other Factors Affecting Gut Micriobiota Composition
Early Life
• Maternal BMI
• Birth Mode
• Infant Food Source
All Lifecycles
• Host Genetics
• Diet Composition
• Antibiotics
• Medications
• Stress
• Circadian Disruption
• Age
• Hygiene Factors
SCFAs
Acetate
Propionate
Butyrate
• Systemic signaling molecules via G-protein coupled receptors
• Shown to have satiety, anti-inflammatory, histone acetylation, and regulatory effects on tight junction proteins (especially butyrate)
Phytonutrient Metabolites
• May transform phytonutrients into biologically active form (e.g., soy isoflavones)
• May ↑ biovailability of phytonutrient (e.g. hesperidin)
2° Bile Acids
• 1° Bile Acids (BA) converted into 2° BA via microbial BSH enzyme
• BA (1° and 2°) act as signaling molecules with varying receptor affinities for a wide range of host receptors making for a large diversity in response.

Colonic Microbiota Encroachment Correlates With Dysglycemia in Humans

Benoit Chassaing,[1] Shreya M. Raja,[2,3] James D. Lewis,[4] Shanthi Srinivasan,[2,3] and Andrew T. Gewirtz[1,2]

[1]Center for Inflammation, Immunity and Infection, Institute for Biomedical Sciences, Georgia State University, Atlanta, Georgia; [2]Digestive Diseases Division, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia; [3]Atlanta VA Medical Center, Decatur, Georgia; [4]Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania



Cell Mol Gastroenterol Hepatol. 2017 Apr 13;4(2):205-221.

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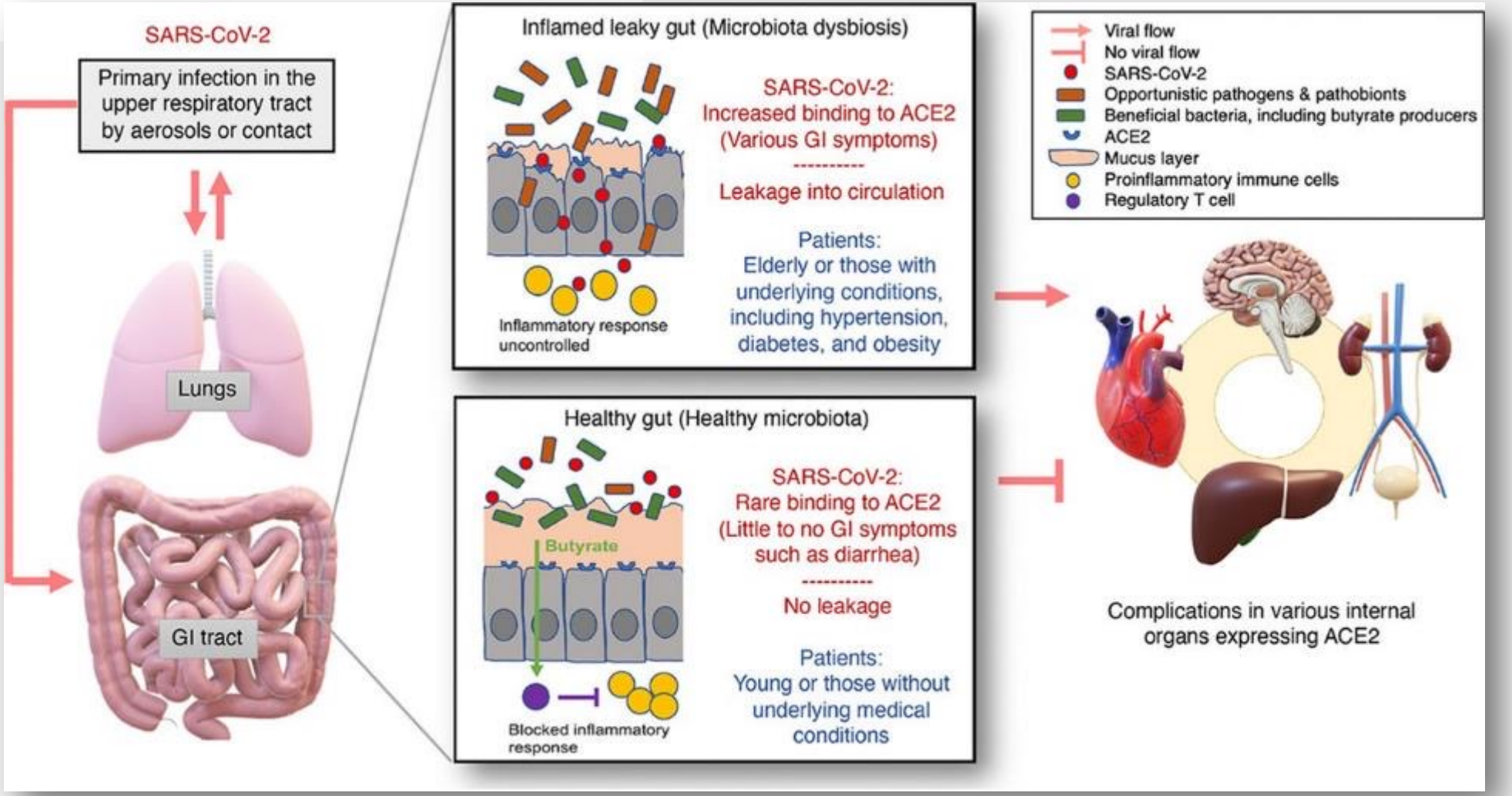
PERSPECTIVE
Clinical Science and Epidemiology

Do an Altered Gut Microbiota and an Associated Leaky Gut Affect COVID-19 Severity?

Heenam Stanley Kim[a]

mBio Jan 2021, 12 (1) e03022-20; DOI: 10.1128/mBio.03022-20



Contents lists available at ScienceDirect

Trends in Food Science & Technology

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

Review article: Probiotics, prebiotics and dietary approaches during COVID-19 pandemic

Jielun Hu [a,b,c,1], Lin Zhang [a,b,1], Winnie Lin [a,b,d], Whitney Tang [a,b], Francis K.L. Chan [a,b,d], Siew C. Ng [a,b,d,*]

[a] Center for Gut Microbiota Research, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, China
[b] Institute of Digestive Disease, State Key Laboratory of Digestive Disease, LKS Institute of Health Science, The Chinese University of Hong Kong, Hong Kong, China
[c] State Key Laboratory of Food Science and Technology, China-Canada Joint Lab of Food Science and Technology (Nanchang), Nanchang University, Nanchang, China
[d] Microbiota I-Center (MagIC) Limited, The Chinese University of Hong Kong, Hong Kong, China

ARTICLE INFO

Keywords:
SARS-CoV-2
Probiotics
Prebiotics
Diet
Nutrition

ABSTRACT

Background: Patients with COVID-19 caused by SARS-CoV-2 exhibit diverse clinical manifestations and severity including enteric involvement. Commensal gut bacteria can contribute to defense against potential pathogens by promoting beneficial immune interactions. Interventions targeting the gut microbiome may have systemic anti-viral effects in SARS-CoV-2 infection.

Scope and approach: To summarise alterations of gut microbiota in patients with COVID-19 including impact of specific bacteria on disease severity, discuss current knowledge on the role of probiotics, prebiotics and dietary approaches including vitamin D in preventing and reducing disease susceptibility and review clinical studies using probiotics to target coronavirus. A literature review on SARS-CoV-2, COVID-19, gut microbiome and immunity was undertaken and relevant literature was summarised and critically examined.

Key findings and conclusions: Integrity of gut microbiome was perturbed in SARS-CoV-2 infections and associated with disease severity. Poor prognosis in SARS-CoV-2 infection was observed in subjects with underlying co-morbidities who had increased gut permeability and reduced gut microbiome diversity. Dietary microbes, including probiotics or selected prebiotics of Chinese origin, had anti-viral effects against other forms of coronavirus, and could positively impact host immune functions during SARS-CoV-2 infection. Numerous studies are investigating the role of probiotics in preventing and reducing susceptibility to SARS-CoV-2 infection in healthcare workers, household contacts and affected patients. An approach to strengthen intestinal barrier and lower pro-inflammatory states by adopting a more diversified diet during COVID-19 pandemic.

SARS-CoV-2 infection is associated with immune dysfunction and gut microbiota alterations. Delineating mechanisms of probiotics, prebiotics and diet with anti-SARS-CoV-2 immunity present opportunities for discovery of microbial therapeutics to prevent and treat COVID-19.

1. Introduction

In December 2019, the Coronavirus disease 2019 (COVID-19), caused by a novel coronavirus SARS-CoV-2, emerged in Wuhan, Hubei province, China (Li, Fan, et al., 2020) and soon spread rapidly across the world (Li, Guan, et al., 2020). To date, more than 9.2 million people have contracted COVID-19 infection with over 470,000 deaths worldwide. Therapeutic options are limited and clinically proven vaccine are lacking. In particular, there is a need for safe and effective interventions to prevent, reduce susceptibility and lessen the severity of COVID-19 (Amanat & Krammer, 2020). A striking observation during the pandemic is the heterogenous presentation and clinical outcomes of infected subjects across different geographic locations. Elderly individuals, along with those with pre-existing conditions, such as diabetes mellitus, hypertension, cardiovascular diseases and cancer have a demonstrated higher risk for developing more severe disease as well as suffering a higher risk of mortality, suggesting that the immune system may play a crucial role (Wang, Hu, et al., 2020). Patients with severe

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E-mail address: siewchicng@cuhk.edu.hk (S.C. Ng).
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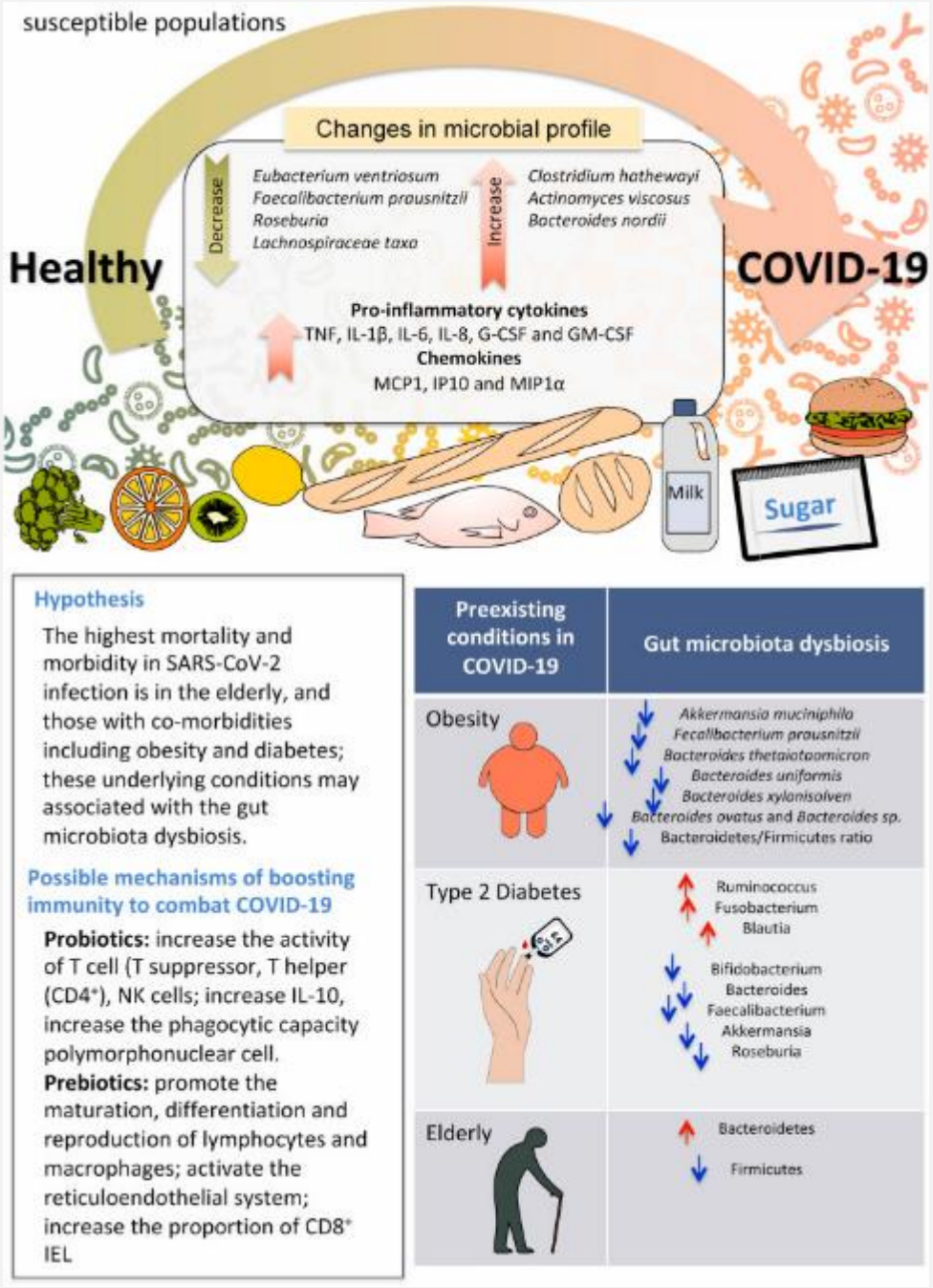
Received 16 July 2020; Received in revised form 11 November 2020; Accepted 10 December 2020
Available online 14 December 2020



Signals that drive metabolic risk

- Sense of belonging
- Group dynamics
- Life purpose

- Insulin Response to Food
- Meal Timing & Energy
- Phytonutrients-genomics

- Sedentary Time
- Energy Expenditure
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- "Obesogenic" Toxins (BPA)
- Sunlight-Vit D
- Microflora Gut Bacteria

- Addictive foods
- Alcohol/Drugs
- Poor oral hygiene

Science of the Total Environment 470–471 (2014) 726–732

Contents lists available at ScienceDirect

Science of the Total Environment

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

Bisphenol A and cardiometabolic risk factors in obese c

Naila Khalil [a,*,1], James R. Ebert [b,1], Lei Wang [c], Scott Belcher [d], Miryou
Stefan A. Czerwinski [f], Kurunthachalam Kannan [c]

HIGHLIGHTS

- Cross sectional study of 39 obese and overweight children aged 3–8 years.
- Urinary BPA (u-BPA) measured by liquid chromatography-tandem mass spectrometry
- Association between u-BPA and obesity analyzed by linear regression, spline analyses
- U-BPA concentration in male obese children was associated with adverse liver and metabolic effects

ARTICLE INFO

Article history:
Received 11 July 2013
Received in revised form 26 September 2013
Accepted 26 September 2013
Available online xxxx

Editor: Frank Kiger

Keywords:
Bisphenol A
Endocrine disruptor
Non-monotonic dose response
Childhood obesity
Nonalcoholic fatty liver disease
Spline analysis

ABSTRACT

Background and objective: Bisphenol-A (BPA) is an en
and metabolic changes in liver in humans. Non-al
children in the United States. Association of BPA wi
if BPA might play a role.
Methods: In a cross sectional study of 39 obese a
Children Medical Center of Dayton, Ohio, anthropom
were conducted. Urinary BPA was measured by liqui
and was adjusted for urinary creatinine BPA (creati
Results: Higher urinary BPA (creatinine) concentratio
creasing free thyroxine. In male children BPA (creati
liver enzyme aspartate aminotransferase and dia
persisted even after adjusting for age and ethnicity.
was significantly associated with serum fasting insul
(HOMA-IR) showing non-monotonic exposure–resp
Conclusion: Urinary BPA in obese children, at least in
and high diastolic blood pressure.

1. Introduction

Obesity in children is a major public health concern. Early life obesity not only tracks to adulthood, increasing the risk of metabolic and cardiovascular disease (CVD) but also is associated with liver abnormalities

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E-mail addresses: naila.khalil@wright.edu (N. Khalil), james.ebert@wright.edu (J.R. Ebert), Scott.Belcher@ac.edu (S. Belcher), miryoung.lee@wright.edu (M. Lee), stefan.czerwinski@wright.edu (S.A. Czerwinski), kkannan@wadsworth.org (K. Kannan).
1 Both authors contributed equally to the manuscript.

http://dx.doi.org/10.1016/j.scitotenv.2013.09.088

Journal of *Clinical Medicine*

MDPI

Review

Is There a Link between Bisphenol A (BPA), a Key Endocrine Disruptor, and the Risk for SARS-CoV-2 Infection and Severe COVID-19?

Aeman Zahra [1], Cristina Sisu [1], Elisabete Silva [1], Sophie-Christine De Aguiar Greca [1], Harpal S. Randeva [2,3,4], Kamaljit Chatha [4,5], Ioannis Kyrou [2,3,4,†] and Emmanouil Karteris [1,*,†]

1 Biosciences, College of Health, Medicine and Life Sciences, Brunel University London, Uxbridge UB8 3PH, UK; aeman.zahra@brunel.ac.uk (A.Z.); cristina.sisu@brunel.ac.uk (C.S.); elisabete.silva@brunel.ac.uk (E.S.); sophieja3@gmail.com (S.-C.D.A.G.)
2 Warwickshire Institute for the Study of Diabetes, Endocrinology and Metabolism (WISDEM), University Hospitals Coventry and Warwickshire NHS Trust, Coventry CV2 2DX, UK; harpal.randeva@uhcw.nhs.uk (H.S.R.); i.kyrou@aston.ac.uk (I.K.)
3 Aston Medical Research Institute, Aston Medical School, Aston University, Birmingham B4 7ET, UK
4 Warwick Medical School, University of Warwick, Coventry CV4 7AL, UK; kamaljit.chatha@uhcw.nhs.uk
5 Department of Biochemistry and Immunology, University Hospitals Coventry and Warwickshire NHS Trust, Coventry CV2 2DX, UK
* Correspondence: emmanouil.karteris@brunel.ac.uk
† Ioannis Kyrou and Emmanouil Karteris are joint senior co-authors.

Received: 27 August 2020; Accepted: 7 October 2020; Published: 14 October 2020

check for updates

Abstract: Infection by the severe acute respiratory syndrome (SARS) coronavirus-2 (SARS-CoV-2) is the causative agent of a new disease (COVID-19). The risk of severe COVID-19 is increased by certain underlying comorbidities, including asthma, cancer, cardiovascular disease, hypertension, diabetes, and obesity. Notably, exposure to hormonally active chemicals called endocrine-disrupting chemicals (EDCs) can promote such cardio-metabolic diseases, endocrine-related cancers, and immune system dysregulation and thus, may also be linked to higher risk of severe COVID-19. Bisphenol A (BPA) is among the most common EDCs and exerts its effects via receptors which are widely distributed in human tissues, including nuclear oestrogen receptors (ERα and ERβ), membrane-bound oestrogen receptor (G protein-coupled receptor 30; GPR30), and human nuclear receptor oestrogen-related receptor gamma. As such, this paper focuses on the potential role of BPA in promoting comorbidities associated with severe COVID-19, as well as on potential BPA-induced effects on key SARS-CoV-2 infection mediators, such as angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2). Interestingly, GPR30 appears to exhibit greater co-localisation with TMPRSS2 in key tissues like lung and prostate, suggesting that BPA exposure may impact on the local expression of these SARS-CoV-2 infection mediators. Overall, the potential role of BPA on the risk and severity of COVID-19 merits further investigation.

higher risk

Check for updates

Science of the Total Environment 763 (2021) 142941

Contents lists available at ScienceDirect

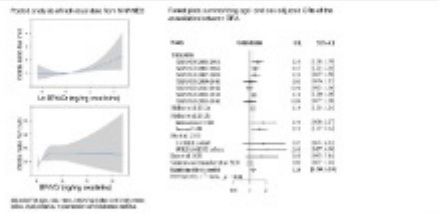
Science of the Total Environment

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

bisphenol A on cardiovascular disease: An epidemiological
ng National Health and Nutrition Examination Survey
16 and meta-analysis

[a], Sung Hoon Yu [b], Chang Beom Lee [b], Young Joo Park [c], Hyung Joon Yoo [a,d], Dong Sun Kim [b,*]

GRAPHICAL ABSTRACT



ABSTRACT

As the most widely consumed endocrine-disrupting chemical, bisphenol A (BPA) has been linked to reproductive dysfunction, diabetes mellitus, and obesity. However, the evidence for an association between BPA and cardiovascular disease (CVD) remains insufficient. In the present study, we aimed to identify the association between BPA and CVD, using data from the 2003–2016 National Health and Nutrition Examination Surveys (NHANES). We estimated urine BPA concentration after adjustments for creatinine (ng/mg) and normalized the asymmetrical distribution using natural logarithmic transformation (ln-BPA/Cr). A multivariate logistic regression was performed to evaluate the odds ratio (OR) and 95% confidence interval (CI) for CVD, with ln-BPA/Cr concentration as predictor. We then performed a Mantel–Haenszel meta-analysis with five eligible studies and NHANES 2003–2016 data. Our subjects were 11,857 adults from the NHANES data. After adjusting for age, sex, race/ethnicity, body mass index (BMI), cigarette smoking, diabetes status, hypertension, and dyslipidemia, OR between ln-BPA/Cr and CVD was 1.13 [95% CI: 1.02–1.24]. After propensity-score-matching with age, sex, race/ethnicity, BMI, cigarette smoking, diabetes, hypertension, and dyslipidemia, OR continued to be significant for the association between ln-BPA/Cr and CVD (OR: 1.38, 95% CI: 1.04–1.33). A restricted cubic spline plot of this relationship revealed a dose-dependent increase in OR. However, untransformed BPA had a linear relationship with CVD only at low concentrations, whereas the OR of BPA plateaued at high concentrations. In a meta-analysis with 22,878

Original Research

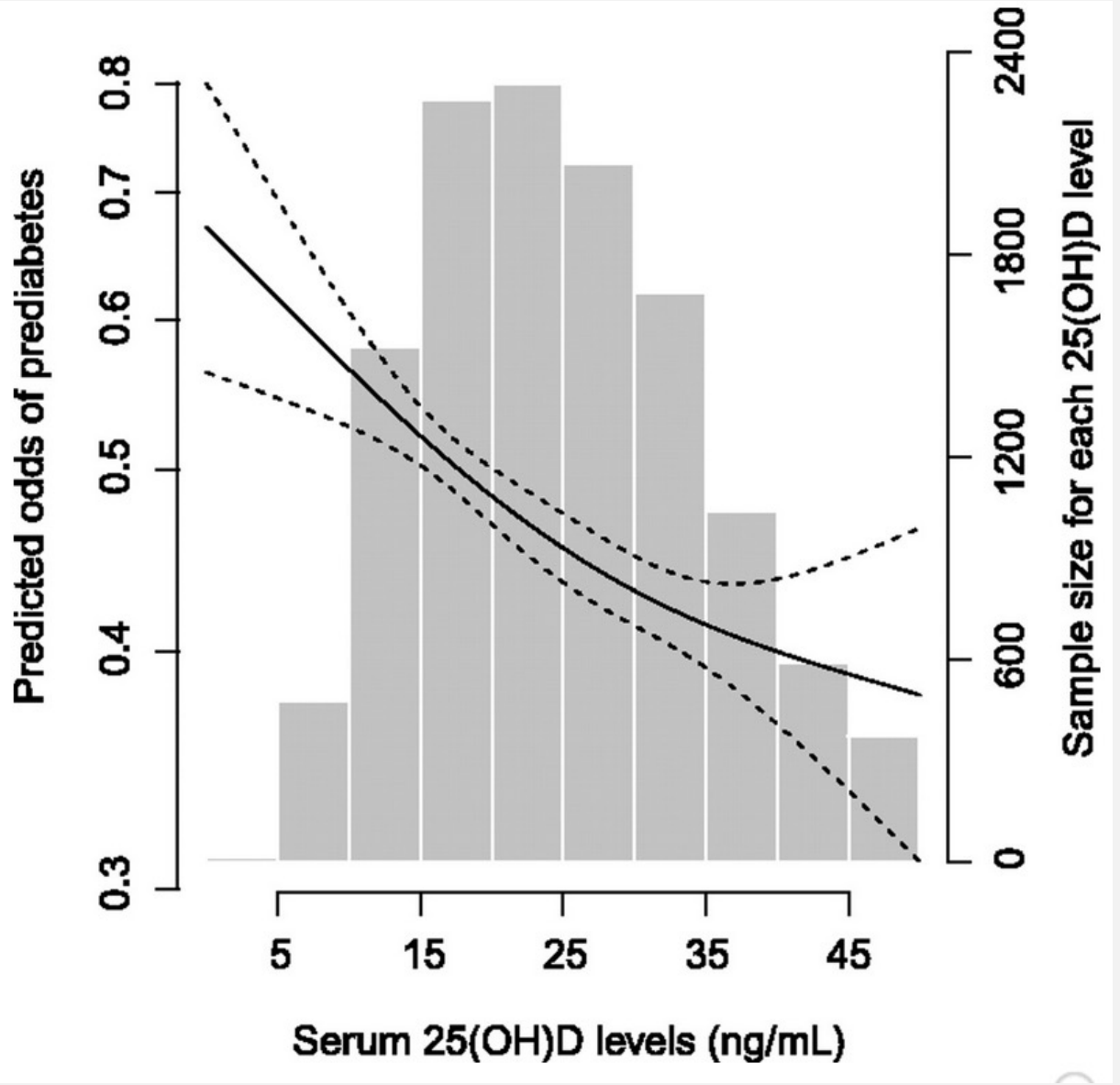
Serum 25-Hydroxyvitamin D Levels and Prediabetes Among Subjects Free of Diabetes

Anoop Shankar, MD, PHD[1], Charumathi Sabanayagam, MD, PHD[1] **and** Sita Kalidindi, MS[1,2]

Author Affiliations

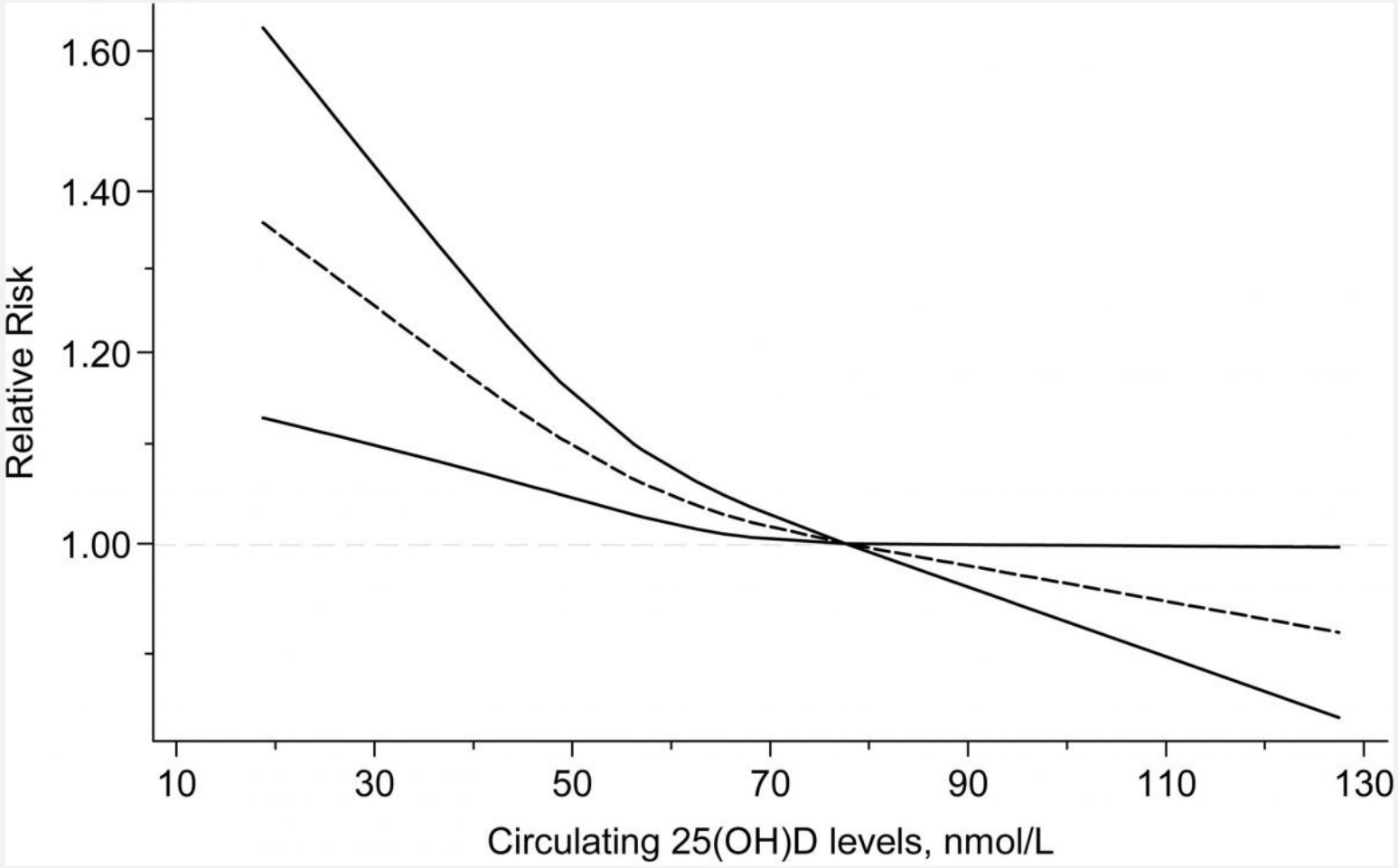
Corresponding author: Anoop Shankar, ashankar@hsc.wvu.edu.

Diabetes Care 2011 May; 34(5): 1114-1119.
https://doi.org/10.2337/dc10-1203

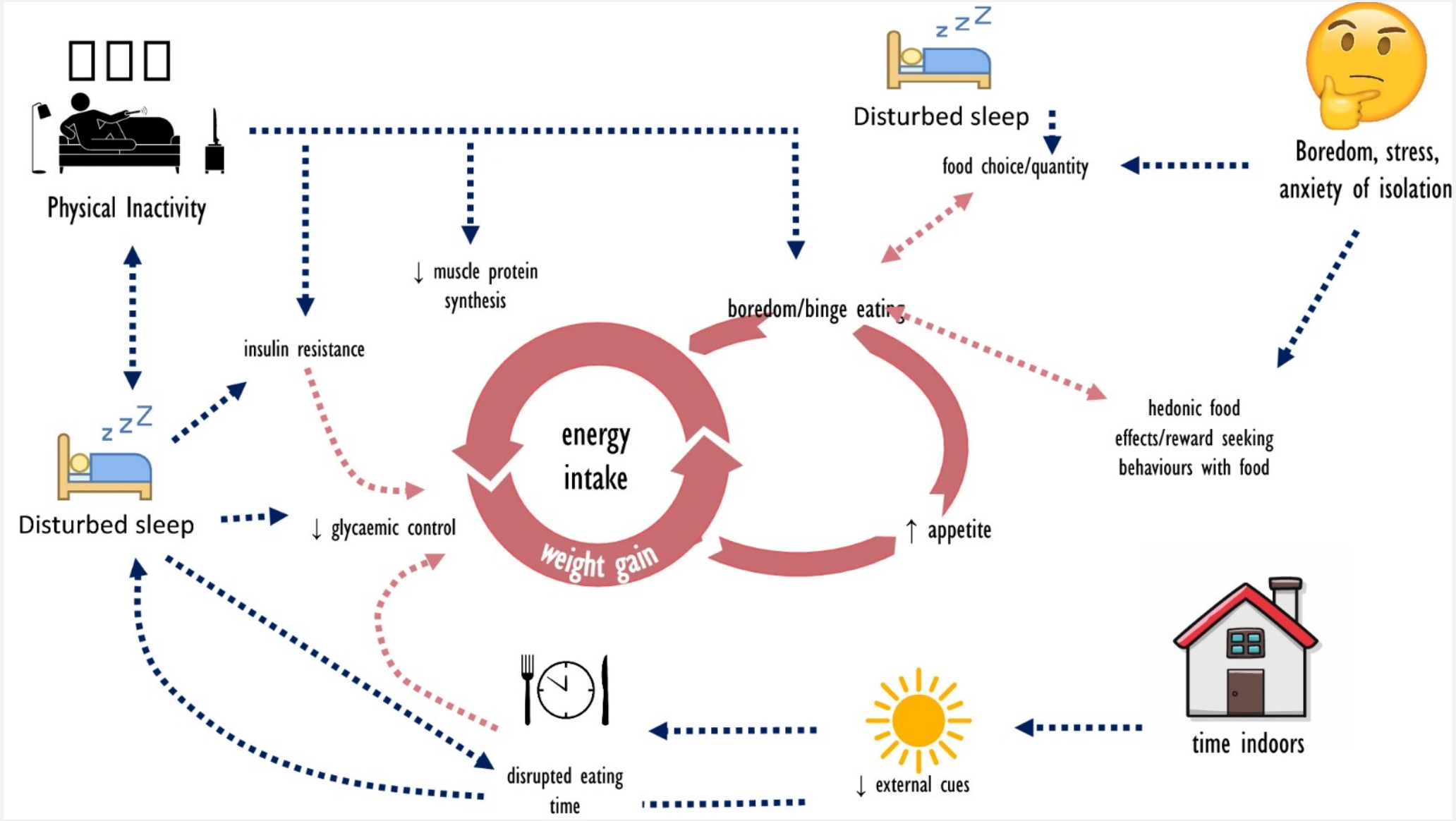


Effect of Vitamin D on Blood Pressure and Hypertension in the General Population: An Update Meta-Analysis of Cohort Studies and Randomized Controlled Trials

Suggested citation for this article: Zhang D, Cheng C, Wang Y, Sun H, Yu S, Xue Y, et al. Effect of Vitamin D on Blood Pressure and Hypertension in the General Population: An Update Meta-Analysis of Cohort Studies and Randomized Controlled Trials. Prev Chronic Dis 2020;17:190307. DOI: http://dx.doi.org/10.5888/pcd17.190307 .



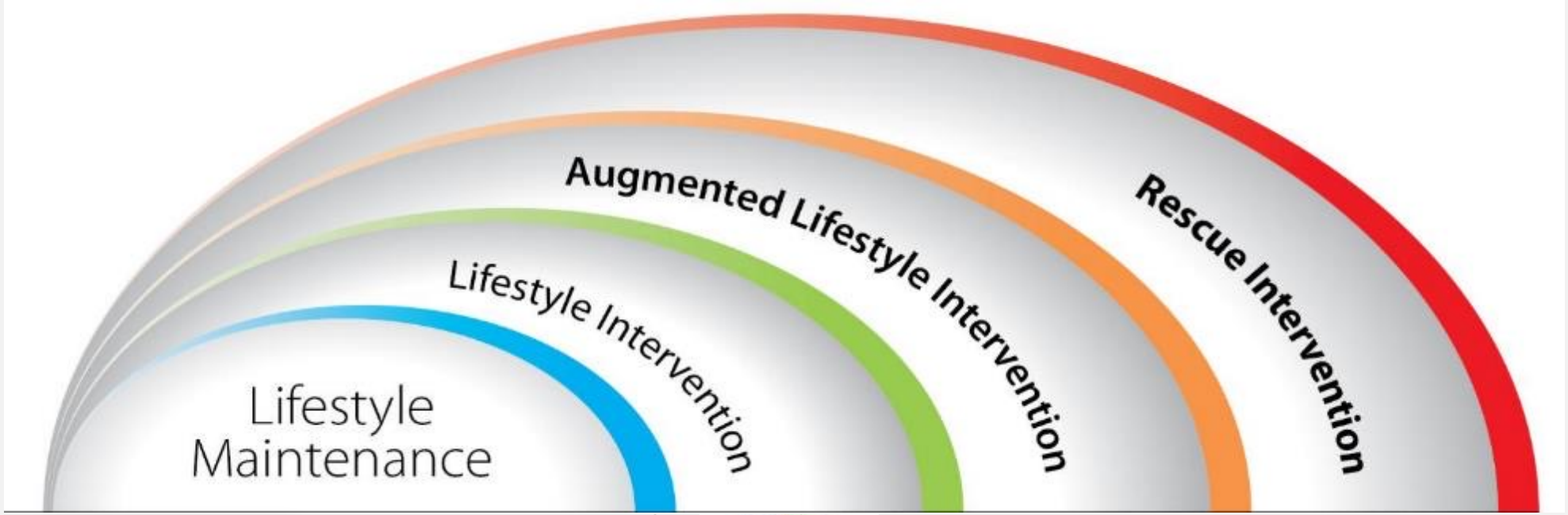
THE CHALLENGE OF MAINTAINING METABOLIC HEALTH DURING A GLOBAL PANDEMIC



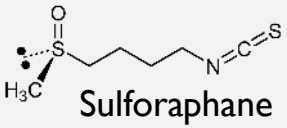
Sports Medicine **volume 50**, pages 1233–1241 (2020)

LIFESTYLE AND FUNCTIONAL APPROACH

- Understanding a patient's risk potential, is not the same thing as understanding *How* and *Why* the patient is at risk!
  - i.e., Predicting Risk using algorithms is not the same as understanding the drivers or root causes of risk.
- If a patient is at-risk because of low vitamin K2, low CoQ10 and a low omega-3 index; a statin drug will not address these vulnerabilities.
- CVD Risk must be place in the larger context of a patient's chronic [And Acute] disease vulnerability.
- Simple Lifestyle Behaviors can have profound preventative and therapeutic effects related to Cardiometabolic risk and outcomes

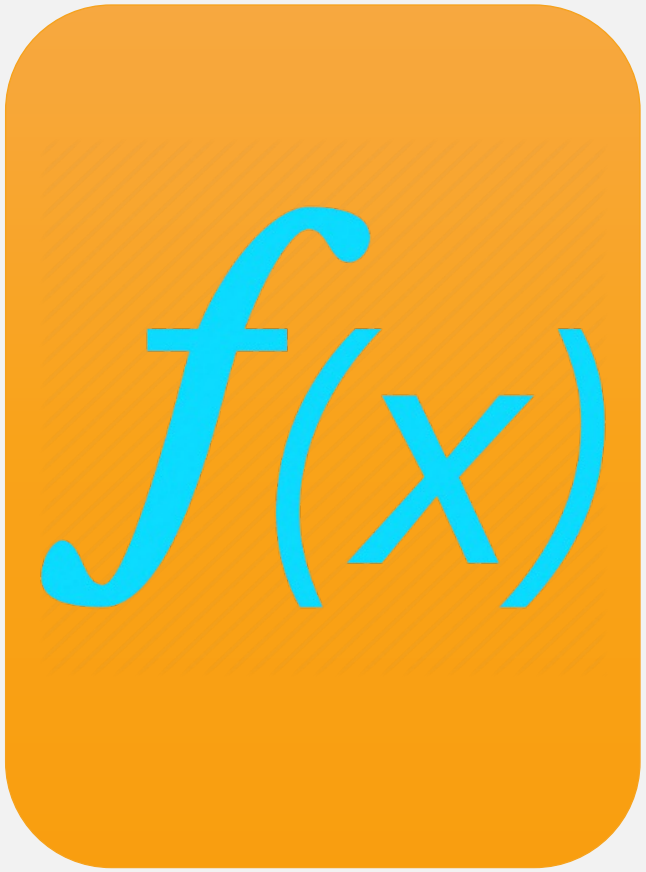

Lifestyle Maintenance
Lifestyle Intervention
Augmented Lifestyle Intervention
Rescue Intervention


BALANCED DIET


Sulforaphane


B12
Vitamin

WHAT STANDS BETWEEN FUNCTION AND DYSFUNCTION?



Resiliency

The ability to withstand a metabolic challenge and be ready for the next.

Reserve

Stored capacity to buffer sustained metabolic challenges while rebuilding resiliency

THERAPEUTIC TARGETS FOR CARDIOMETABOLIC RESILIENCE

A Functional Approach to Cardiometabolic Risk

For many healthcare providers that are learning or implementing a functional or integrative medicine approach for cardiometabolic risk, the debate about whether these metabolic abnormalities should be defined as a syndrome, what term should be used to define that syndrome, and which specific cluster of measurable biomarkers are more important than others, may appear to be of little clinical value. Furthermore, many argue that such debates about semantics are fruitless since they may cause the clinician to forget that most of the risk in such patients is rooted in poor lifestyle behaviors. While we find these arguments compelling, we believe that all clinicians should understand that while cardiometabolic pathologies are chronic and progressive, they can also result in acute life-threatening events with little warning. Therefore, while is important to understand that lifestyle-based interventions should always be the foundation of therapies designed to improve cardiometabolic health, clinicians must also be cognizant that a patient's near-term risk for an event should often dictate additional (non-lifestyle) interventions. Please review our Prevention-to-Intervention Hierarchy (page 15) for a discussion of this philosophy.

Therefore, when it comes to managing cardiometabolic risk, a functional and integrative medicine professional must have an appreciation for the progressive continuum of pathophysiological changes that are involved in precipitating cardiometabolic outcomes and how to assess an individual's place along that continuum. The use of biomarker clusters, such as the metabolic syndrome or advanced lipoprotein analysis, can be helpful in recognizing different patterns of underlying pathophysiology to help choose appropriate therapies (e.g., those rooted in progressive insulin resistance as opposed to genetic dyslipidemia) or simply to gauge their risk for a CVD event. It is well established that simply using the basic measures that define the metabolic syndrome (at least 3 of 5 components) identifies subjects who are twice as likely to experience an MI or sudden cardiac death, five times more likely to progress to type 2 diabetes, and 50% more likely to die of any cause than those without this diagnosis.[1,2,3,4]

The Metabolic Continuum

In many ways, the process that results in cardiometabolic outcomes is the best example of a progressive chronic disease that slowly depletes a patient's physiological resilience and metabolic reserve (see page 12 for discussion of these concepts). While the CDC tells us that heart disease is the single greatest cause of death, the ultimate causes of death are lifestyle related: dietary choices, sedentary behavior, and smoking.[5] Each lifestyle decision adds, in some small way, to the eventual metabolic outcome, either building or depleting a small amount of our resilience and reserve. This progression is often referred to as the metabolic continuum or metabolic drift as a way to explain the slow progression that takes an insulin-responsive teen with a BMI of 21 and clear arteries to an obese 50-year-old with hypertension, dyslipidemia, impaired fasting insulin, and progressing atherosclerosis.

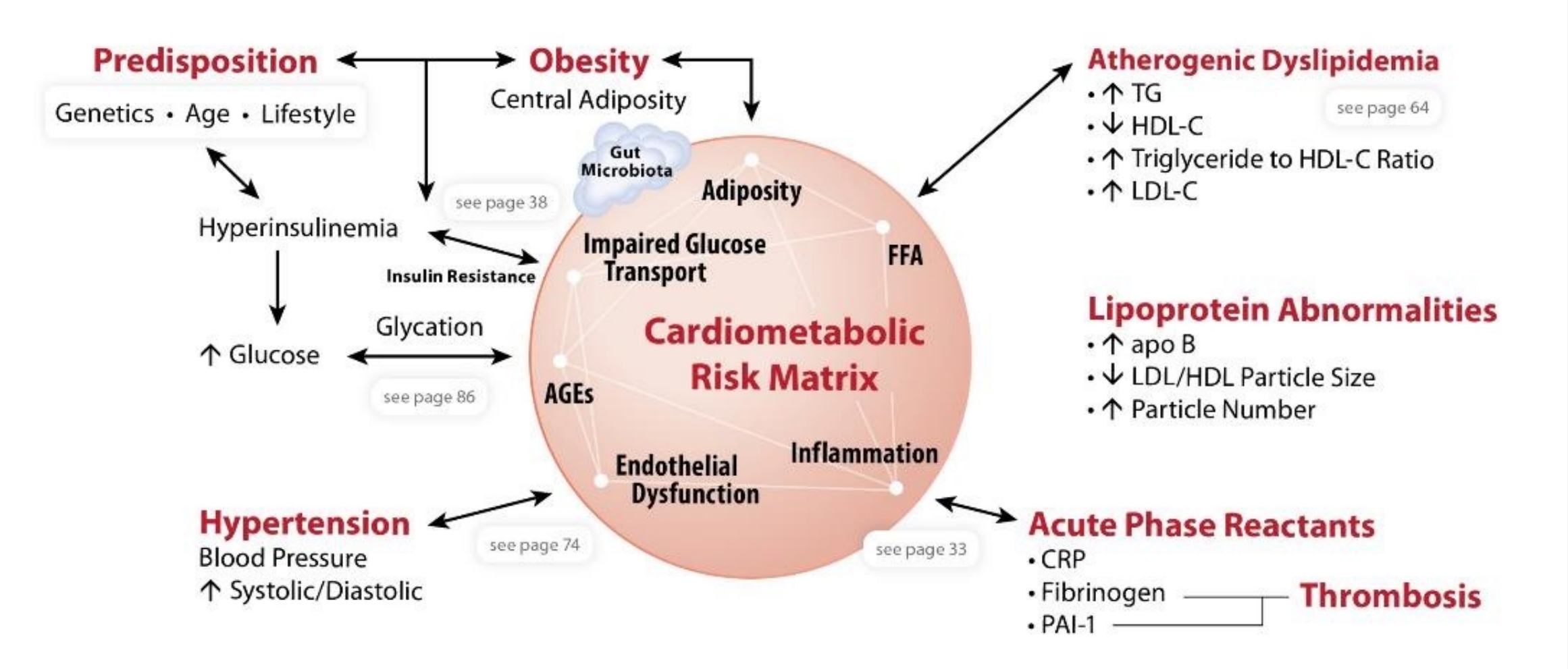
The importance of using the metabolic continuum paradigm is best illustrated in the progression toward type 2 diabetes, where the diagnostic definition is not an end-point per se, but a point along a continuum of metabolic dysfunction. Predicting which pre-diabetic, insulin-resistant patient has a higher and more immediate risk to cross over the diagnostic threshold defined as "diabetes" is critical, since these patients are most at risk for cardiovascular events and microvascular complications.

Essentially, this means predicting which patients will have adequate pancreatic β-cell function to produce enough insulin to properly dispose of glucose (allowing them to maintain normal fasting glucose levels). While these patients still retain the risk for macrovascular

Functional Strategies for Improving Cardiometabolic Resilience

- Decrease Central Adiposity
- Improve Peripheral Insulin Sensitivity
- Reduce Inflammatory Signaling
- Protect/Improve Pancreatic Beta Cell Function
- Reduce Post-Prandial Hyperinsulinemia (i.e., Reduce Meal Glycemic Impact)
- Reduce Lipoprotein Atherogenicity
- Improve Endothelial Function
- Reduce Glycation and the Formation and Accumulation of AGEs
- Modulate/Balance Coagulation Capacity
- Improve Mitochondrial Efficiency
- Reduce Oxidative Burden (i.e., Restore Antioxidant Reserve)
- Restore Metabolically-Favorable Gut Microbiota
- Reduce Circulating Free Fatty Acids
- Improve Appropriate Incretin Signaling
- Modulate Inappropriate HPA-axis Regulation and Cortisol Burden
- Maintain/Improve Kidney Metabolic Capacity
- Maintain Circadian Alignment

BIOMARKERS OF PHYSIOLOGICAL CHANGES



Guilliams: *Cardiometabolic Risk Management: A Functional and Lifestyle Approach* (Point Institute- 2018)

PRIORITIZING INSULIN RESISTANCE

Suggested Insulin Resistance Score (IRS) Categories

Our suggested approach is to prioritize a patient's support protocol only after determining the patient's need for comprehensive insulin sensitizing therapeutic strategies. This can be accomplished by placing each patient into one of three risk categories (low, moderate, high) based on one or more of the following criteria, including determine metabolic syndrome status.

Does patient have metabolic syndrome?	Check all that apply:
Fasting blood glucose _____	☐ >100 mg/dL
Waist circumference _____	☐ Women > 88 cm, Men > 102 cm (see Table pg 22)
Fasting triglycerides _____	☐ >150 mg/dL
HDL-Cholesterol _____	☐ Men < 40 mg/dL, Women < 50 mg/dL
Blood pressure _____	☐ Systolic > 130 mmHg, diastolic > 85 mmHg

1	2	3	4	5
NO		YES		YES-HIGH RISK

Insulin Resistance Scoring

Risk Category		LOW		MODERATE				HIGH		
Metabolic Syndrome	0	1	2	3		4		5		
HbA1c	≤5.5	5.6	5.7	5.8	5.9	6.0	6.2	6.3	6.4	≥6.5
TG:HDL Ratio	F	<3.0		3.0–4.5				>4.5		
	M	<3.5		3.5–5				>5		
Fasting Insulin		Normal Range		High–Normal/High				Above Reference Range		
Type 2 Diabetes		No		No				YES		
Conclusion		☐ LOW		☐ MEDIUM				☐ HIGH		

Additional (non-insulin) Risk Markers

	LOW	MODERATE	HIGH
CRP/hsCRP mg/L	<1	1.0–3.0	>3
Homocysteine µmol/L	<7.0	7.0–13	>13
Lp(a) mg/dL	<30	30–40	>40
apoB mg/dL	<80	80–115	>115
Omega 3-Index	>8%	4–8%	<4%
Blood Pressure mmHg	<120/80	120–139/80–89	140/90

Moderate Insulin Resistance Score

Overall Cardiometabolic Goals: This patient is at moderate risk for adverse cardiometabolic-related outcomes and is likely to have impaired glucose tolerance and be pre-diabetic. The goal in such patients is to strengthen their metabolic reserve by using a comprehensive insulin sensitizing protocol first, while identifying any cardiovascular risk(s) that are unrelated to insulin resistance. With the exception of elevated and uncontrolled blood pressure, targeted therapies for these (other) risks should be commenced after assessing the results of this comprehensive insulin sensitizing protocol (minimum 3-6 months).

Dietary Recommendation: Our recommendation for all chronic disease prevention is rooted in the principles of the **Mediterranean Diet** with an emphasis on **reducing carbohydrate consumption to 40%** of caloric intake. Special instructions should be given to emphasize low glycemic index foods, increase soluble fiber intake, and avoid skipping breakfast (shifting calories toward morning and away from evenings). These subjects may particularly benefit from daily use of ready-to-mix protein-based "meal replacements" that are specifically designed to improve glycemic control, improve satiety, and control caloric intake. See diet section on pages 118—126.

Weight-Loss Recommendations: If patient's BMI is greater than 28.5 or exceeds waist circumference reference ranges for metabolic syndrome (see table on page 22), **a weight loss goal of at least 7% body weight** should be set (over 6-12 months if possible).

Physical Activity Recommendations: 150 minutes per week of walking (or an equivalent activity) and resistance exercises. Additional activities can be recommended to meet specific fitness or body composition goals. See recommendations on page 138.

Stress Management Suggestions: Based on clinical observation, patient history, signs, and symptoms, clinicians may choose to evaluate a patient's perceived stress (through questionnaires) and/or HPA axis hormonal output to determine the need for HPA axis/Stress modulation. See our Road map—*The Role of Stress and the HPA Axis in Chronic Disease Management* (Point Institute, 2015) for more details.

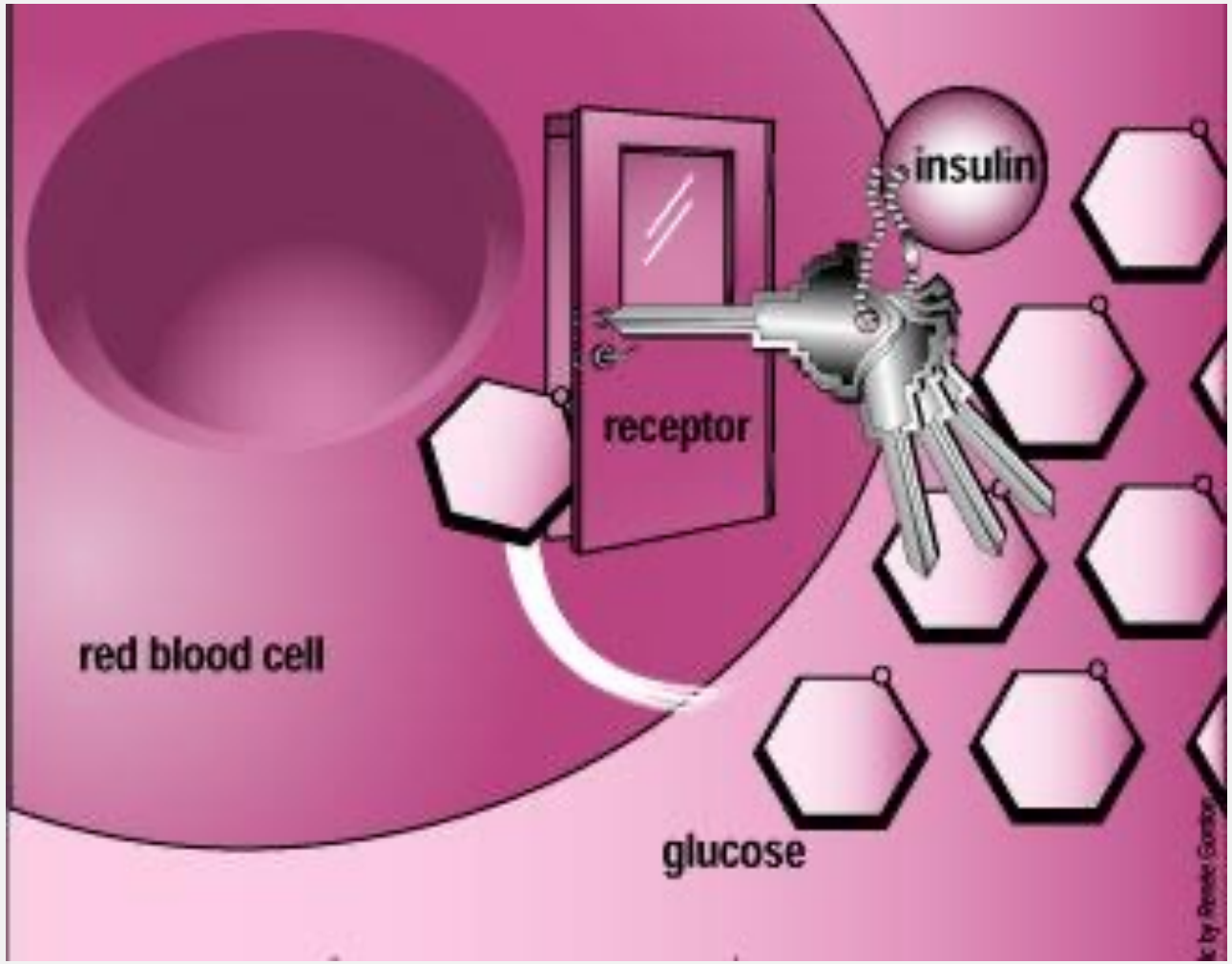
Dietary Supplement Support Suggestions:

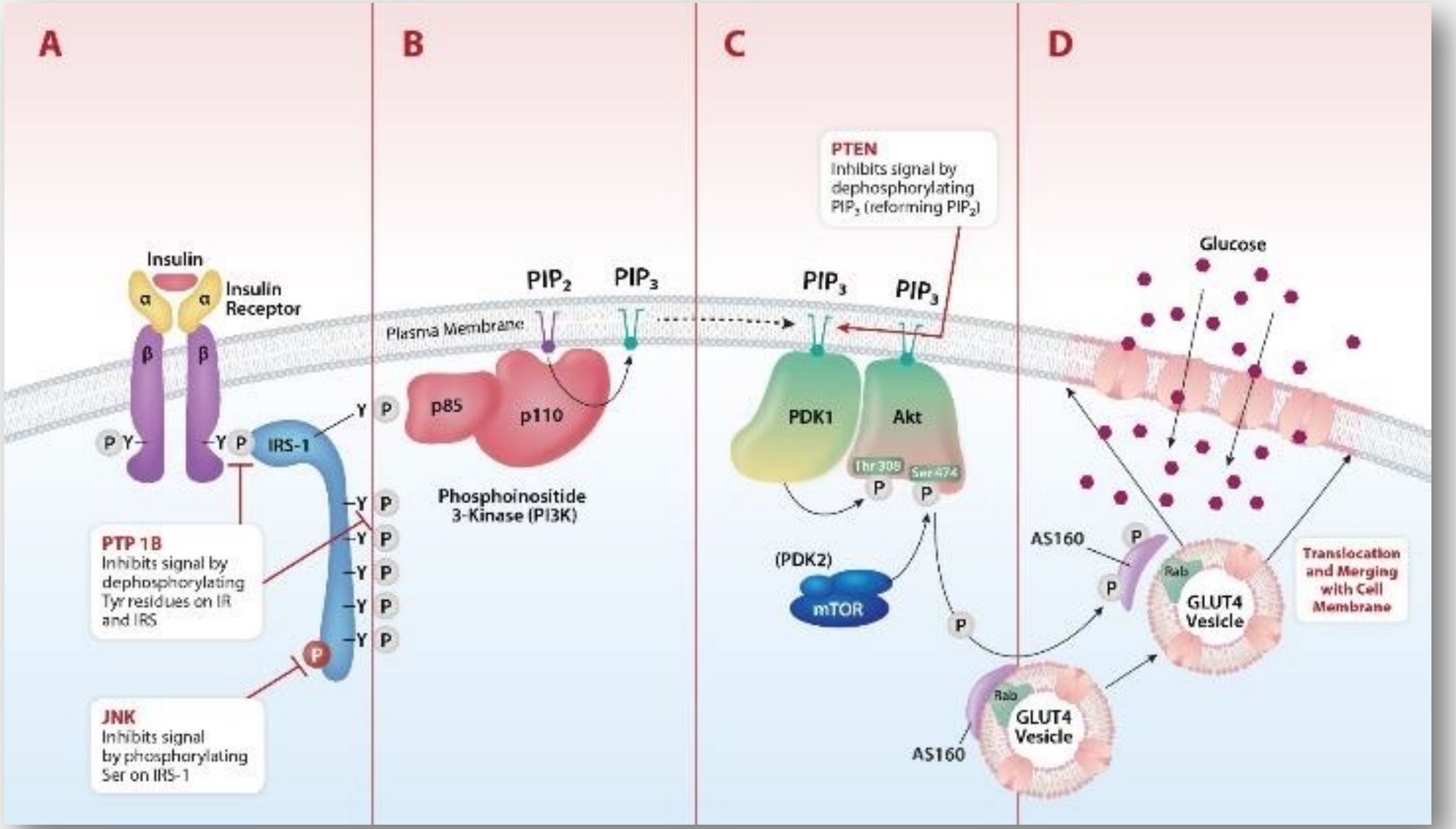
- **Multivitamin/Mineral:** Consider based on diet diary/food frequency questionnaire and other health conditions.
- **Omega-3 (EPA + DHA):** Consider daily supplementation to reach and maintain omega-3 index of 8% or greater (see monograph page 269).
- **Vitamin D3:** Consider daily (or weekly) supplementation to reach or maintain 25(OH)D levels of 30 ng/mL (see monograph page 312).
- **Probiotic:** Consider daily supplementation (especially in subjects with GI-related symptoms). Multi-strain product containing 20-40 billion CFU (see monograph page 291).
- **Insulin Sensitizing Nutrients:** Consider some of the following:
  - **Berberine HCl** (500-1,000 mg/day—see monograph page 175)
  - **Lipoic Acid** (300-600 mg/day—see monograph page 245)
  - **Chromium** (800-1,000 mcg/day—see monograph page 189)
  - **Vanadium** (50-150 mg/day vanadyl sulfate—see monograph page 308)
  - **Cinnamon Extracts** (variable doses—see monograph page 196)

Additional Support Suggestions: Clinicians may want to consider additional support for patients including products containing CoQ10 (see monograph page 203), magnesium (see monograph page 254), resveratrol, quercetin, green tea, or similar phytonutrients to increase cardiometabolic resilience.

HOW DOES INSULIN WORK?

The simple explanation



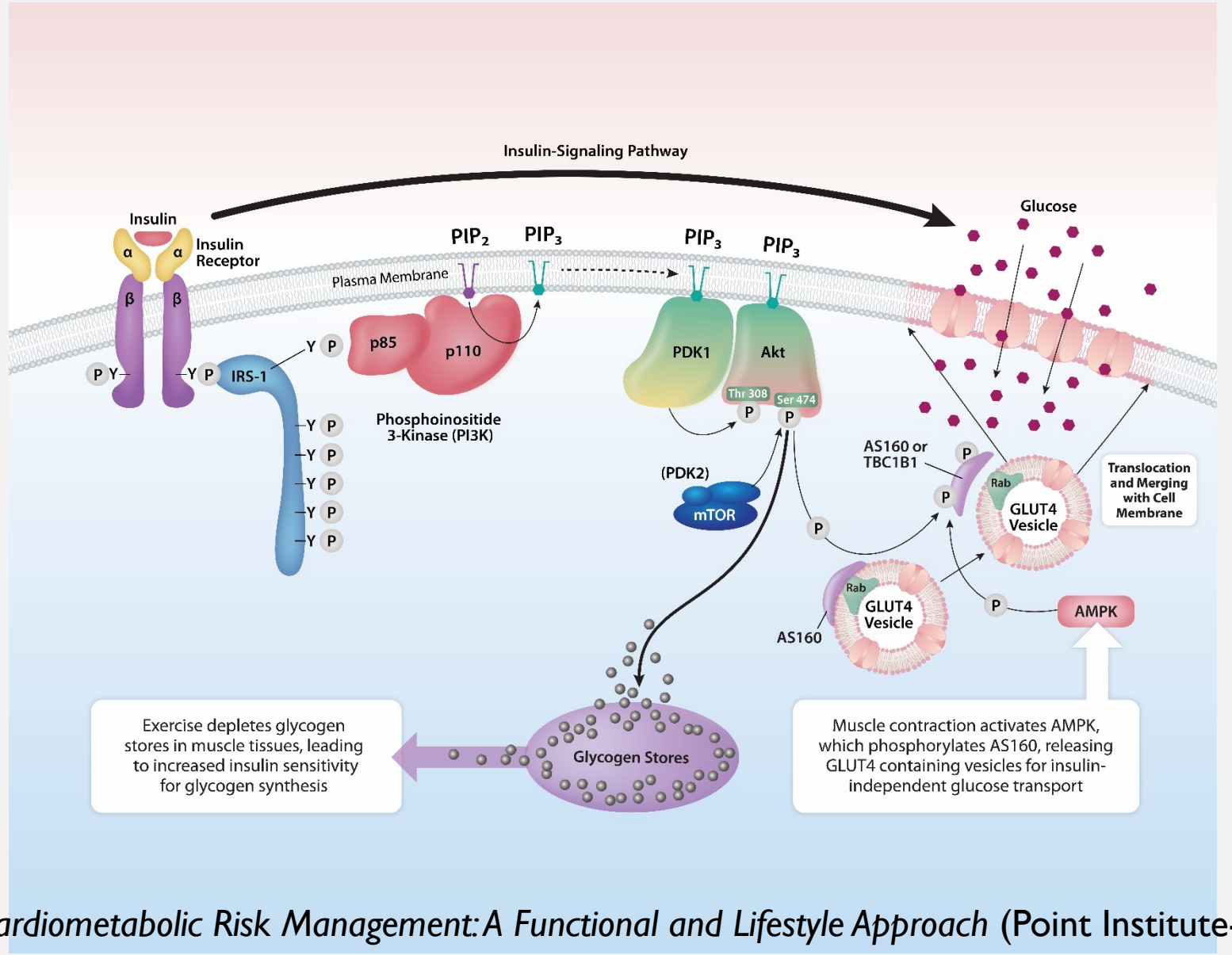


Guilliams: *Cardiometabolic Risk Management: A Functional and Lifestyle Approach* (Point Institute- 2018)

IMPROVING INSULIN RESISTANCE

- Dietary: Low Glycemic Impact, Diverse Insulin sensitizing botanicals and nutrients
- Physical Activity- Moderate, Consistent, range of intensities
- Lipoic Acid (a.k.a. thioctic acid)
- Berberine (HCL/Sulfate)
- Chromium/Vanadium
- Spices (cinnamon)
- Botanicals

EXERCISE INDUCED GLUCOSE DISPOSAL



Guilliams: *Cardiometabolic Risk Management: A Functional and Lifestyle Approach* (Point Institute- 2018)

QUARANTINE AND EXERCISE

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VIEWPOINT

Quarantine during COVID-19 outbreak: Changes in diet and physical activity increase the risk of cardiovascular disease

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KEYWORDS
Quarantine;
COVID-19;
Stress;
Lifestyle;
Gender;
Physical activity;
Vitamin D

Abstract *Aims:* CoV-19/SARS-CoV-2 is a highly pathogenic virus that is causing a global pandemic with a high number of deaths and infected people. To contain the diffusion of infection, several governments have enforced restrictions on outdoor activities or even collective quarantine on the population. The present commentary briefly analyzes the effects of quarantine on lifestyle, including nutrition and physical activity and the impact of new technologies in dealing with this situation.
Data synthesis: Quarantine is associated with stress and depression leading to unhealthy diet and reduced physical activity. A diet poor in fruit and vegetables is frequent during isolation, with a consequent low intake of antioxidants and vitamins. However, vitamins have recently been identified as a principal weapon in the fight against the Cov-19 virus. Some reports suggest that Vitamin D could exert a protective effect on such infection. During quarantine, strategies to further increase home-based physical activity and to encourage adherence to a healthy diet should be implemented. The WHO has just released guidance for people in self-quarantine, those without any symptoms or diagnosis of acute respiratory illness, which provides practical advice on how to stay active and reduce sedentary behavior while at home.
Conclusion: Quarantine carries some long-term effects on cardiovascular disease, mainly related to unhealthy lifestyle and anxiety. Following quarantine, a global action supporting healthy diet and physical activity is mandatory to encourage people to return to a good lifestyle routine.

The emergence of novel coronavirus, officially known as Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2), has presented an important challenge for healthcare systems across the world. Rapid transmission is due to

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nutrients

MDPI

Review

Metabolic Impacts of Confinement during the COVID-19 Pandemic Due to Modified Diet and Physical Activity Habits

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check for updates

Abstract: While the detrimental effects of a chronic positive energy balance due to a sedentary lifestyle have been well established, the impacts of a short period of abruptly reduced physical activity and overeating arising from strict confinement due to the COVID-19 pandemic will soon start to emerge. To reasonably anticipate major consequences according to the available evidence, we hereby review the literature for studies that have explored the health impacts of several weeks of a reduction in physical activity and daily step-count combined with modified eating habits. These studies identify as main metabolic consequences increases in insulin resistance, total body fat, abdominal fat and inflammatory cytokines. All these factors have been strongly associated with the development of metabolic syndrome, which in turn increases the risk of multiple chronic diseases. A plausible mechanism involved in these impacts could be a positive energy balance promoted by maintaining usual dietary intake while reducing energy expenditure. This means that just as calorie intake restriction could help mitigate the deleterious impacts of a bout of physical inactivity, overeating under conditions of home confinement is very likely to exacerbate these consequences. Moreover, hypertension, diabetes, and cardiovascular disease have been identified as potential risk factors for more severely ill patients with COVID-19. Thus, adequate control of metabolic disorders could be important to reduce the risk of severe COVID-19.

Keywords: COVID-19; acute sedentary lifestyle; step reduction; positive energy balance; metabolic consequences; insulin resistance; metabolic syndrome; sarcopenia

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PERSPECTIVES | *Integrative Cardiovascular Physiology and Pathophysiology*

Social isolation during the COVID-19 pandemic can increase physical inactivity and the global burden of cardiovascular disease

Tiago Peçanha,[1]* Karla Fabiana Goessler,[1,2]* Hamilton Roschel,[1,2] and Bruno Gualano[1,2,3]

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Peçanha T, Goessler KF, Roschel H, Gualano B. Social isolation during the COVID-19 pandemic can increase physical inactivity and the global burden of cardiovascular disease. *Am J Physiol Heart Circ Physiol* 318: H1441–H1446, 2020. First published May 15, 2020; doi:10.1152/ajpheart.00268.2020.—Emerging data indicate a substantial decrease in global physical activity levels during the period of social isolation adopted worldwide to contain the spread of the coronavirus disease 2019 (COVID-19). Confinement-induced decreases in physical activity levels and increases in sedentary behavior may provoke a rapid deterioration of cardiovascular health and premature deaths among populations with increased cardiovascular risk. Even short-term (1–4 wk) inactivity has been linked with detrimental effects in cardiovascular function and structure and increased cardiovascular risk factors. In this unprecedented and critical scenario, home-based physical activity programs arise as a clinically relevant intervention to promote health benefits to cardiac patients. Many studies have demonstrated the feasibility, safety, and efficacy of different models of home-based exercise programs in the primary and secondary prevention of cardiovascular diseases and major cardiovascular events among different populations. This body of knowledge can inform evidence-based policies to be urgently implemented to counteract the impact of increased physical inactivity and sedentary behavior during the COVID-19 outbreak, thereby alleviating the global burden of cardiovascular disease.

cardiac diseases; coronavirus; exercise; sedentary behavior

Coronavirus disease 2019 (COVID-19) is an infectious disease of pandemic proportions, with more than 4,000,000 cases and approximately 278,000 deaths reported worldwide as of May 12, 2020 (50). COVID-19 is a public health emergency of international concern (51), and as such, it requires coordinated, protective responses from national and supranational entities around the world. The absence of specific preventive or therapeutic medical interventions for COVID-19 infection, alongside its rapid transmission rate and apparently substantial undocumented contamination and transmission numbers, has led to the scientifically sound recommendation that individuals must stay home to avoid social interactions and restrain the disease spread, thereby reducing pressure on health systems worldwide. Despite being effective for infection control, this strategy has potential behavioral and clinical repercussions.

Home isolation is likely to result in a profound decrease in moderate-to-vigorous physical activity levels and increase in sedentary behavior, e.g., "any waking behavior characterized by an energy expenditure of ≤1.5 MET while in a sitting or reclining posture" (48). Although the actual impact of worldwide isolation on physical activity levels remains to be shown, Fitbit, Inc., an American company that develops wearable devices that track an individual's physical activity level, has recently shared physical activity data from 30 million users that demonstrates a substantial reduction (ranging from 7% to 38%) in average step counts in almost all countries during the week ending March 22, 2020, as compared with the same period last year (20). This preliminary evidence suggests that quarantine may provoke a substantial decline in physical activity levels, similar to that which is observed in other confined conditions, such as spaceflight exploration and incarceration (1, 5). Several levels of evidence, from epidemiology to molecular sciences, suggest that the potential increase in physical inactivity induced by the pandemic may have substantial repercussions for cardiovascular health.

The seminal study by Morris et al. (35) showing increased cardiovascular mortality in bus drivers (inactive) compared with bus conductors (active) from the London double-decker buses encouraged a number of epidemiological studies that demonstrated the links between physical inactivity and cardiovascular risk. Of interest is that the adjusted relative risks of coronary heart disease and overall mortality associated with physical inactivity are 1.16 (1.04–1.30) and 1.28 (1.21–1.36), respectively (32). More recently, evidence from clinical trials and mechanistic studies have demonstrated that physical inactivity can lead to cardiovascular abnormalities as well as their molecular mechanisms. Data from bed rest studies, a model of muscle unloading and inactivity, have demonstrated that a few weeks of immobilization promote cardiac atrophy and dysfunction (41), luminal narrowing of peripheral vessels (38), arterial stiffening (36), and impairment of endothelium-dependent function in the macro- (36, 44) and microcirculation (11). Even less severe models of physical inactivity have shown similar outcomes. For instance, Teixeira et al. (45) observed a large reduction in popliteal artery flow-mediated dilation (~56% decline) after 1 wk of reduced daily physical activity (from >10,000 to <5,000 steps/wk). Using a similar step reduction model, Boyle et al. (8) observed a reduction in the brachial artery diameter and an increase in markers of vascular apoptosis and activation within 3–5 days of inactivity. There is

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May omega-3 fatty acid dietary supplementation help reduce severe complications in Covid-19 patients?

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ABSTRACT

In around 10% of SARS-CoV-2 infected patients, coronavirus disease-2019 (Covid-19) symptoms are complicated with a severe lung damage called Acute Respiratory Distress Syndrome (ARDS), which is often lethal. ARDS is mainly associated with an uncontrolled overproduction of immune cells and cytokines, called "cytokine storm syndrome"; it appears 7–15 days following the onset of symptoms, leading to systemic inflammation and multiple organ failure. Because they are well-known metabolic precursors of specialized pro-resolving lipid mediators (SPMs), omega-3 long-chain polyunsaturated fatty acids (omega-3 LC-PUFAs) could help improve the resolution of the inflammatory balance, limiting therefore the level and duration of the critical inflammatory period. Omega-3 LC-PUFAs may also interact at different stages of the viral infection, notably on the virus entry and replication. In the absence of demonstrated treatment and while waiting for vaccine possibility, the use of omega-3 LC-PUFAs deserve therefore to be considered, based on previous clinical studies suggesting that omega-3 supplementation could improve clinical outcomes of critically ill patients at the acute phase of ARDS. In this context, it is crucial to remind that the omega-3 PUFA dietary intake levels in Western countries remains largely below the current recommendations, considering both the omega-3 precursor α-linolenic acid (ALA) and long chain derivatives such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). An optimized omega-3 PUFAs status could be helpful to prevent infectious diseases, including Covid-19.

1. Introduction

The viral epidemic caused by the new Coronavirus SARS-CoV-2 is responsible for the Coronavirus-2019 disease (Covid-19). Upon binding via its Spike (S) protein, SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) as an entry receptor in several cell types, including lung alveolar epithelial cells (type 1 and type 2 pneumocytes). This receptor-mediated endocytosis is followed by the activation of the S protein in the viral envelope by the transmembrane serine protease 2 (TMPRSS2), a membrane-bound enzyme localized near the ACE2 receptor [1]. Alternatively, direct proteolytic cleavage of the viral S protein by TMPRSS2 on the surface of host cells has been described to induce the fusion of the viral and plasma membranes, leading to the release of the viral single stranded-RNA into the cytoplasm [2]. Once in endosomes or cytoplasm, the viral RNA

Abbreviations: ALA, α-linolenic acid; ARA, arachidonic acid; ARDS, Acute Respiratory Distress Syndrome; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; LC-PUFA, long-chain polyunsaturated fatty acid; SPM, specialized pro-resolving lipid mediators; SREBP, Sterol Regulatory Element Binding Protein.

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Review Article

Check for updates

Omega 3 Fatty Acids and COVID-19: A Comprehensive Review

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ABSTRACT

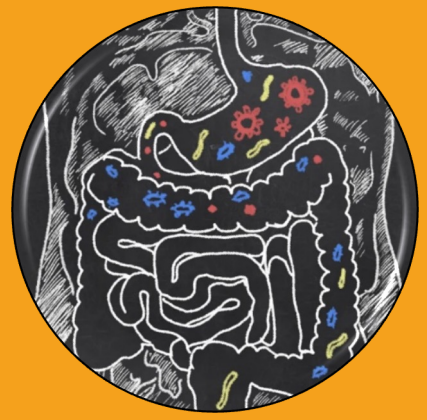
The rapid international spread of severe acute respiratory syndrome coronavirus 2 responsible for coronavirus disease 2019 (COVID-19) has posed a global health emergency in 2020. It has affected over 52 million people and led to over 1.29 million deaths worldwide, as of November 13th, 2020. Patients diagnosed with COVID-19 present with symptoms ranging from none to severe and include fever, shortness of breath, dry cough, anosmia, and gastrointestinal abnormalities. Severe complications are largely due to overdrive of the host immune system leading to "cytokine storm". This results in disseminated intravascular coagulation, acute respiratory distress syndrome, multiple organ dysfunction syndrome, and death. Due to its highly infectious nature and concerning mortality rate, every effort has been focused on prevention and creating new medications or repurposing old treatment options to ameliorate the suffering of COVID-19 patients including the immune dysregulation. Omega-3 fatty acids are known to be incorporated throughout the body into the bi-phospholipid layer of the cell membrane leading to the production of less pro-inflammatory mediators compared to other fatty acids that are more prevalent in the Western diet. In this article, the benefits of omega-3 fatty acids, especially eicosapentaenoic acid and docosahexaenoic acid, including their anti-inflammatory, immunomodulating, and possible antiviral effects have been discussed.

Keywords: SARS-CoV-2; Omega-3 fatty acids; Eicosapentaenoic acid; Docosahexaenoic acid; COVID-19

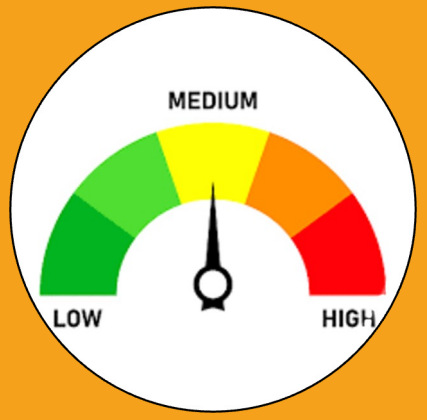
INTRODUCTION

The coronavirus disease 2019 (COVID-19), now known the world over, is an emerging respiratory disease that was first identified in December 2019, in Wuhan, the capital of China's Hubei province. It has since spread globally, resulting in the ongoing COVID-19 pandemic [1, 2]. In December 2019, this world-changing phenomenon began with an outbreak of pneumonia due to an unknown cause in Wuhan, with an epidemiological link to the Huanan Seafood Wholesale Market Place. The World Health Organization (WHO) was notified on December 31, 2019, by the Chinese Health Authorities [1]. The Chinese Center for Disease Control and Prevention identified a novel coronavirus on January 7, 2020, from the throat swab of a patient, which the WHO subsequently named 2019-nCoV [3]. This

Nutrient Intake



Factors that influence the absorption, transport, incorporation or use of O-3 fatty acids



Nutrient Status

Nutrient Intake Estimates are Often Disconnected with Nutrient Status Measurements

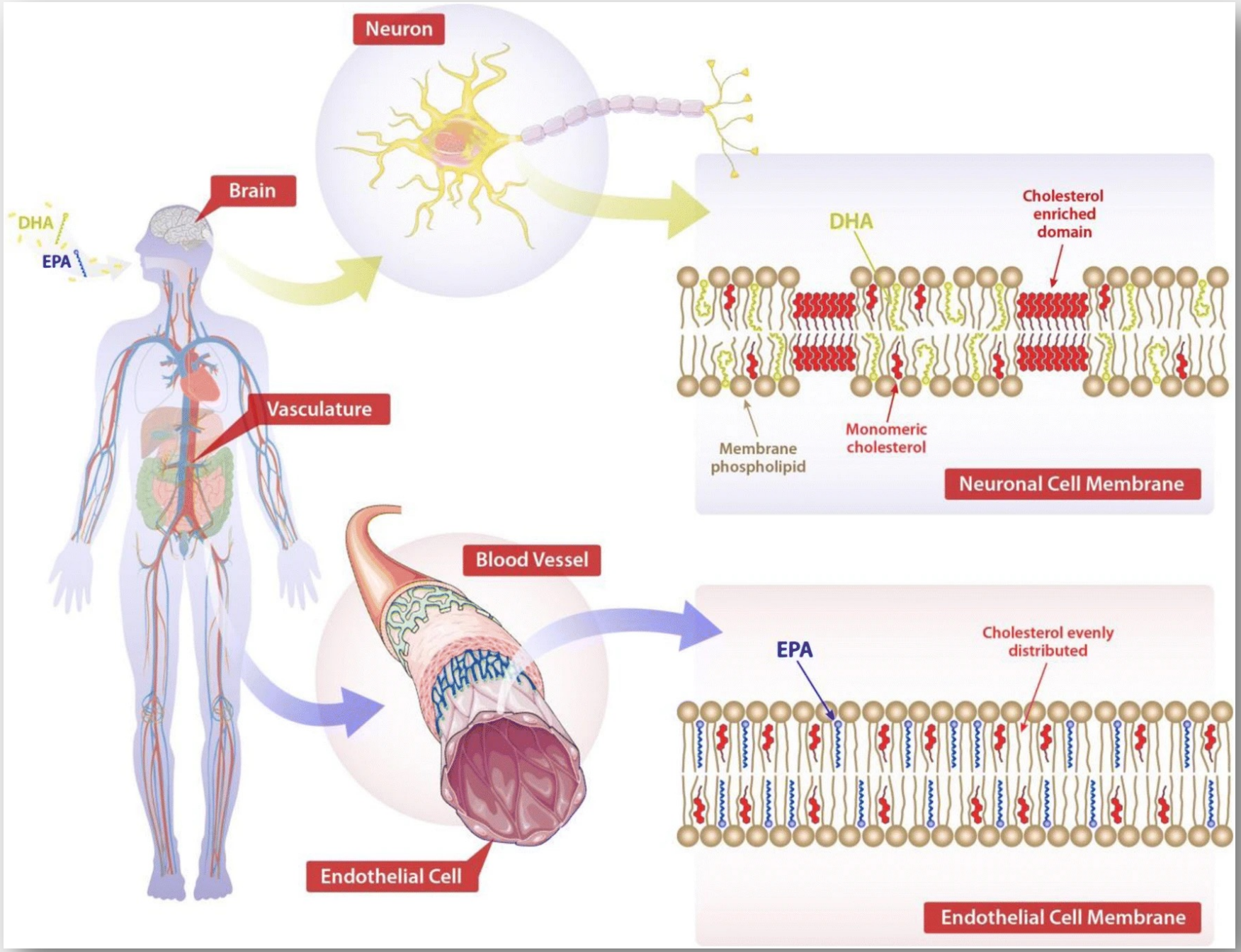
CLINICAL GAP BETWEEN NUTRIENT INTAKE AND STATUS

Utilization of O-3 Fats can be limited by:

- Reduced Bile Production/Secretion
- Reduced Pancreatic Lipase Production
- Fast Bowel Transit Time
- Chemistry of the fatty acid itself (i.e., EE vs TG forms in supplements)
- Content of Meal (are there other fats?)
- High intake of O-6 Fatty acids
- Obesity (BMI, but mostly Fat Mass)
- Drugs that Block Fat Absorption

MEASURING OMEGA-3 NUTRIENT RESERVE/STATUS

- As with many other nutrients, serum/plasma levels of fatty acids are greatly influenced by recent ingestion/absorption from meals or supplementation- not consistent enough to represent reserve/status
- LCPUFA are regularly incorporated into cell membranes
  - Influence membrane fluidity and function



Preston Mason R. New Insights into Mechanisms of Action for Omega-3 Fatty Acids in Atherothrombotic Cardiovascular Disease. Curr Atheroscler Rep. 2019 Jan 12;21(1):2.

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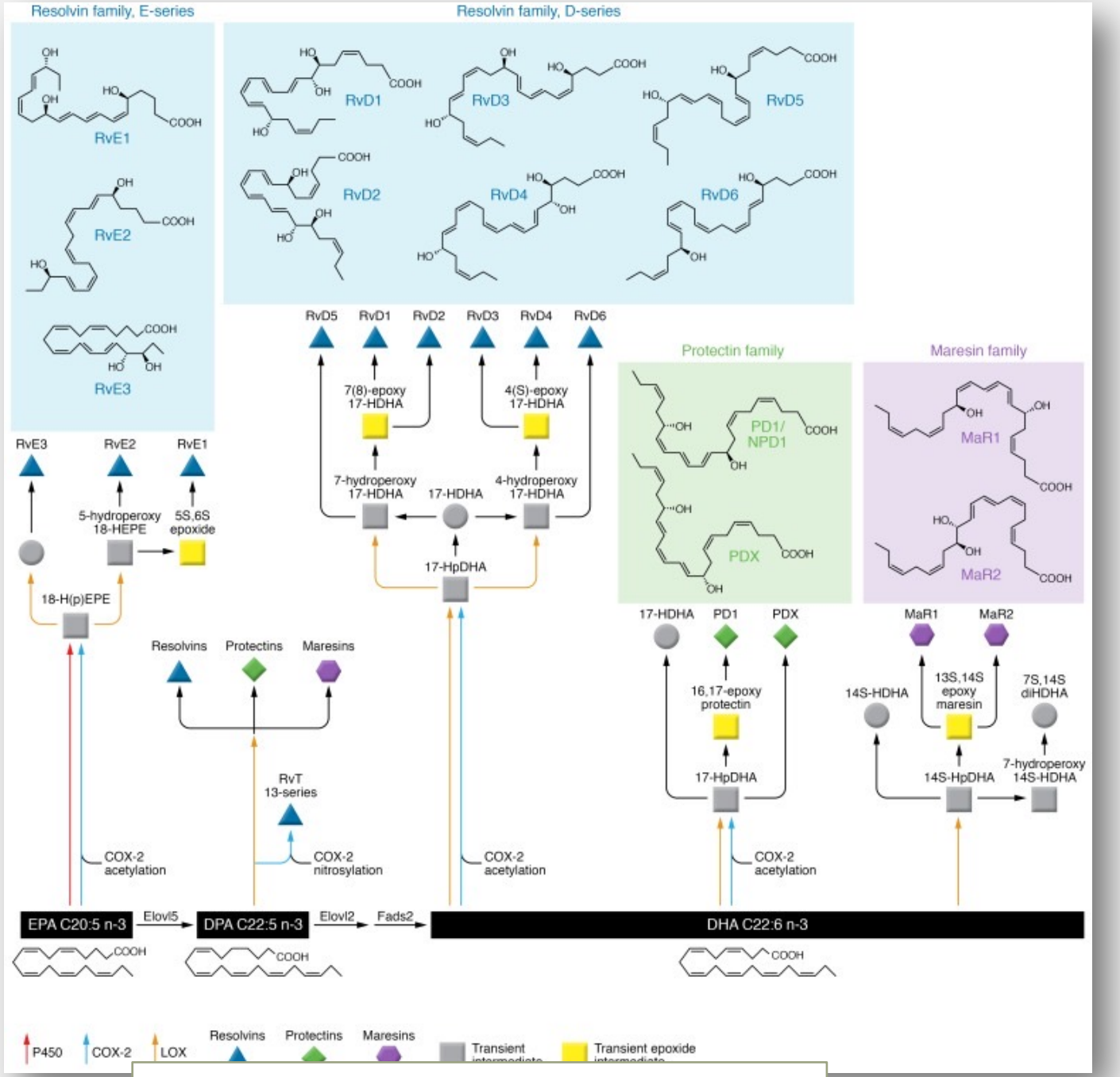
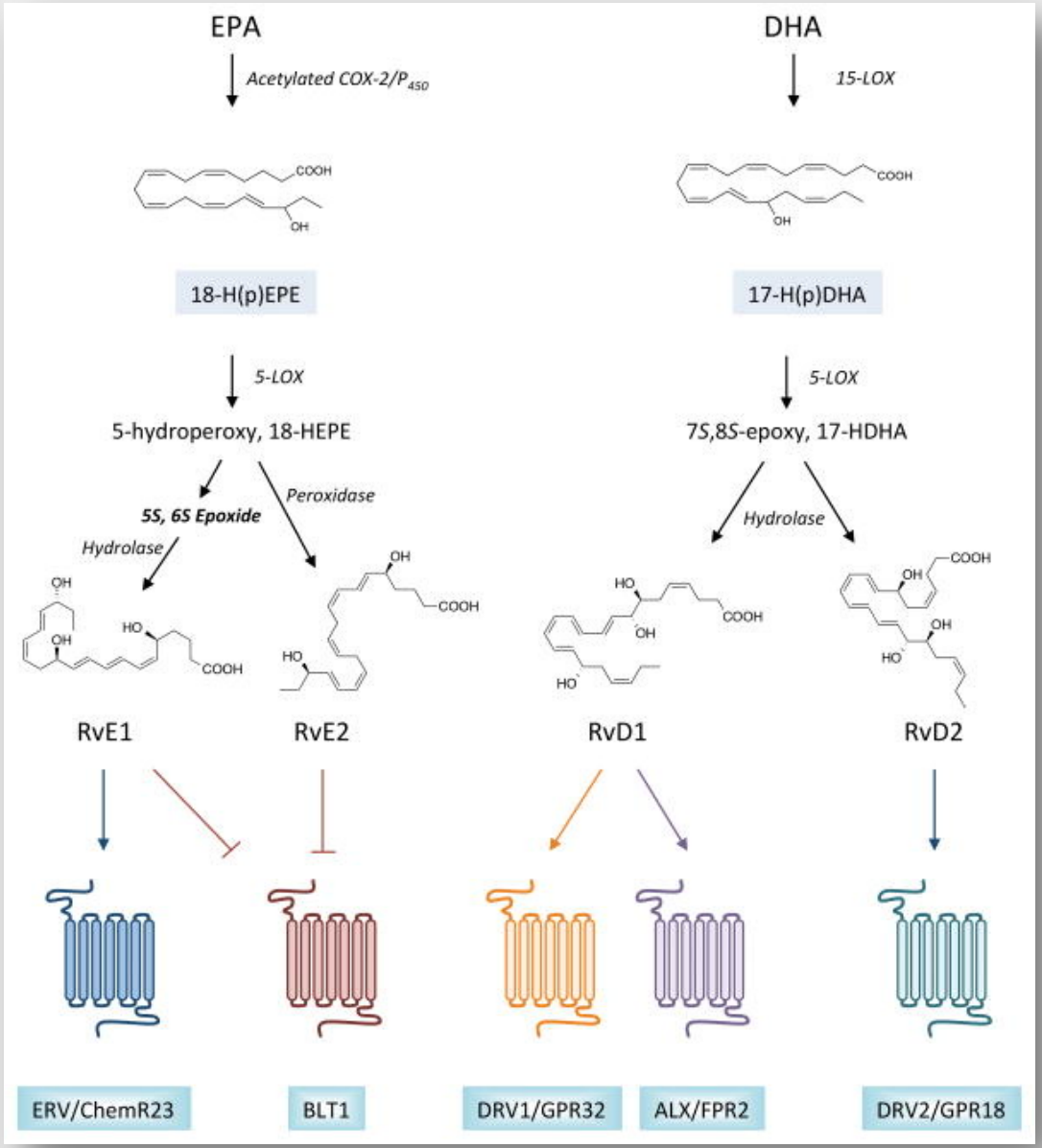


J Clin Invest. 2018 Jul 2;128(7):2657-2669.

Circulation Research, 01 Jun 2016, 119(1):113-130



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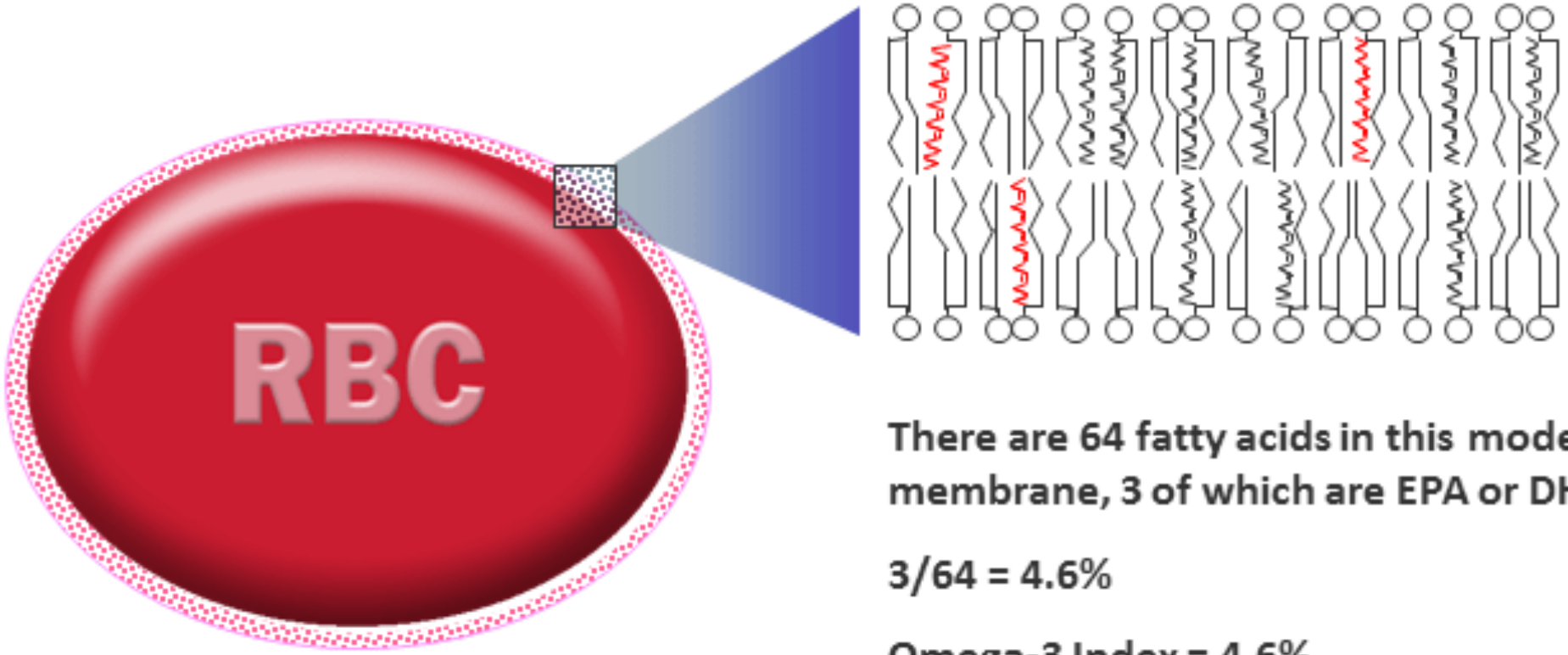
- LCPUFA are regularly incorporated into cell membranes
  - Influence membrane fluidity and function
  - Available precursors for important lipid mediators
- Measuring the level (by percent) of LCPUFA in membranes of cells that are readily accessible -with a known turnover- is a better way to measure the bodies reserve capacity (nutrient status) for these fatty acids.
  - Red Blood Cell (RBC) membranes are a perfect candidate for such a measure
- This measure can then act as a surrogate measure for other membranes and tissues which cannot be readily assessed in most subjects (heart, brain, etc.)

A measure of the amount of EPA+DHA in red blood cell membrane phospholipids expressed as the percent of total fatty acids



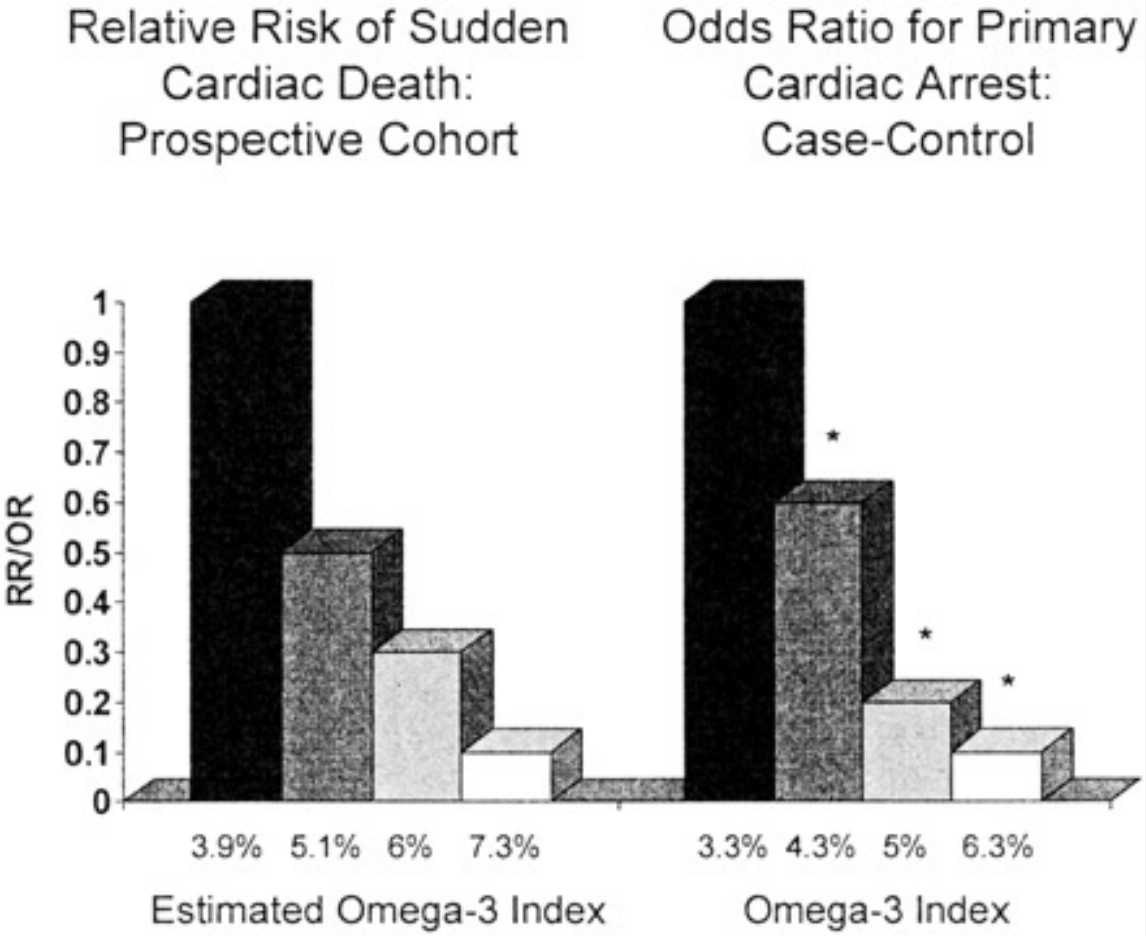
There are 64 fatty acids in this model membrane, 3 of which are EPA or DHA

3/64 = 4.6%

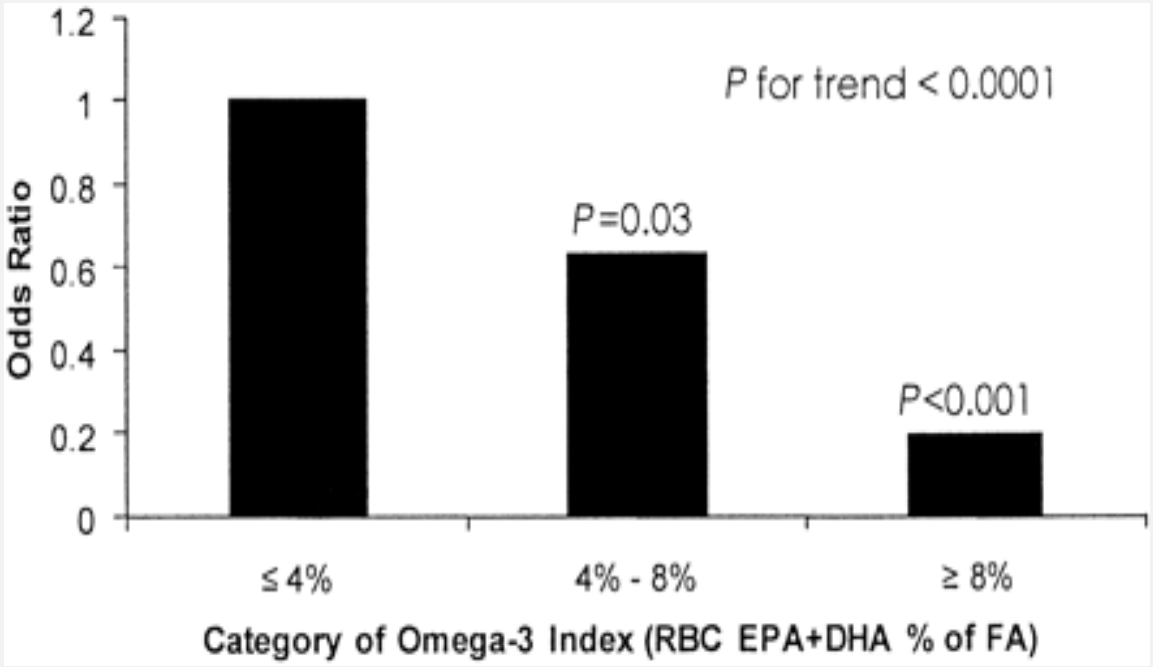
Omega-3 Index = 4.6%

Harris WS and von Schacky C. *Prev Med* 2004;39:212-220.

EPA/DHA STATUS (IN RBC) MEASURES RISK!

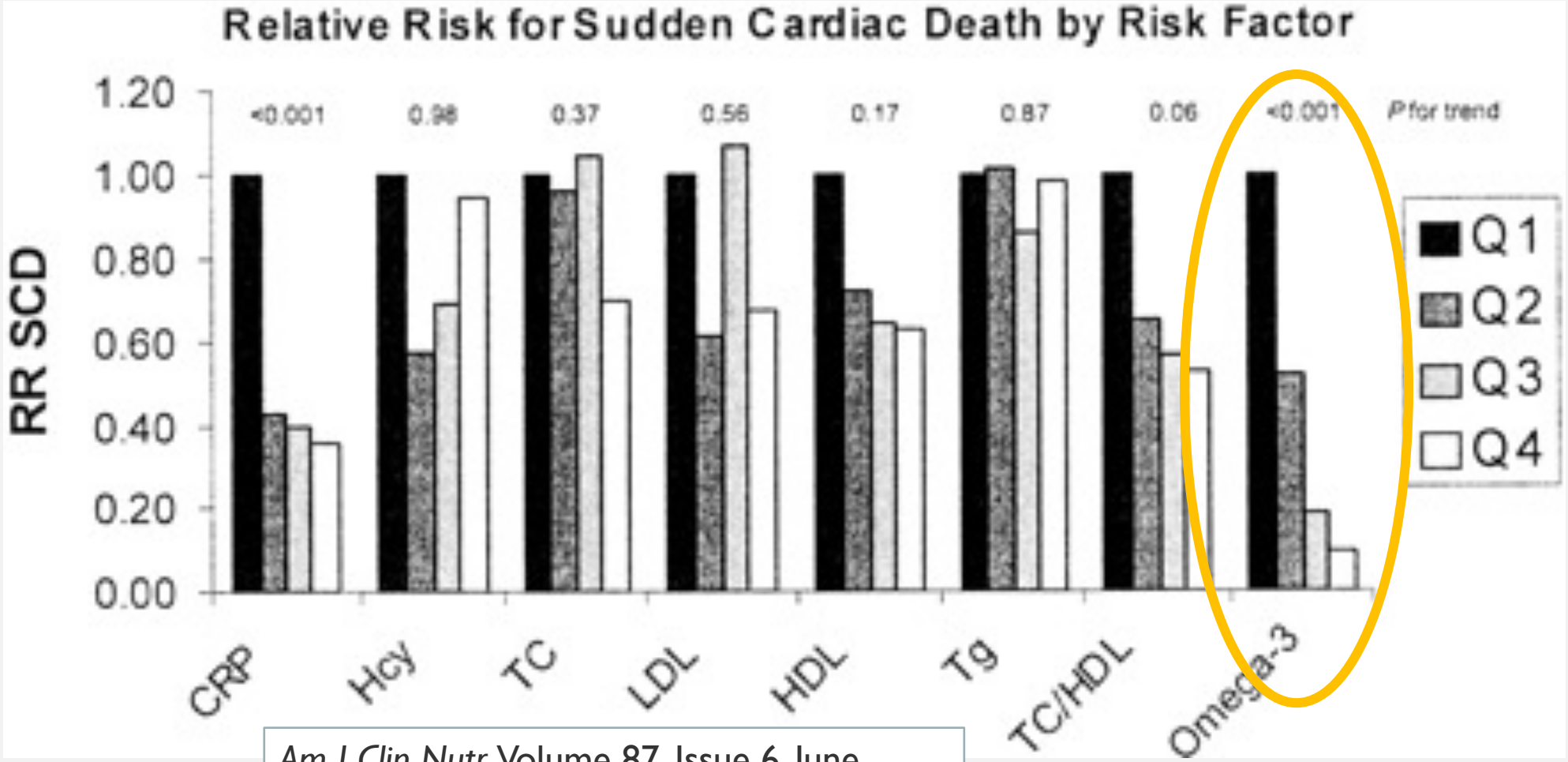


Odds ratios for acute coronary syndrome



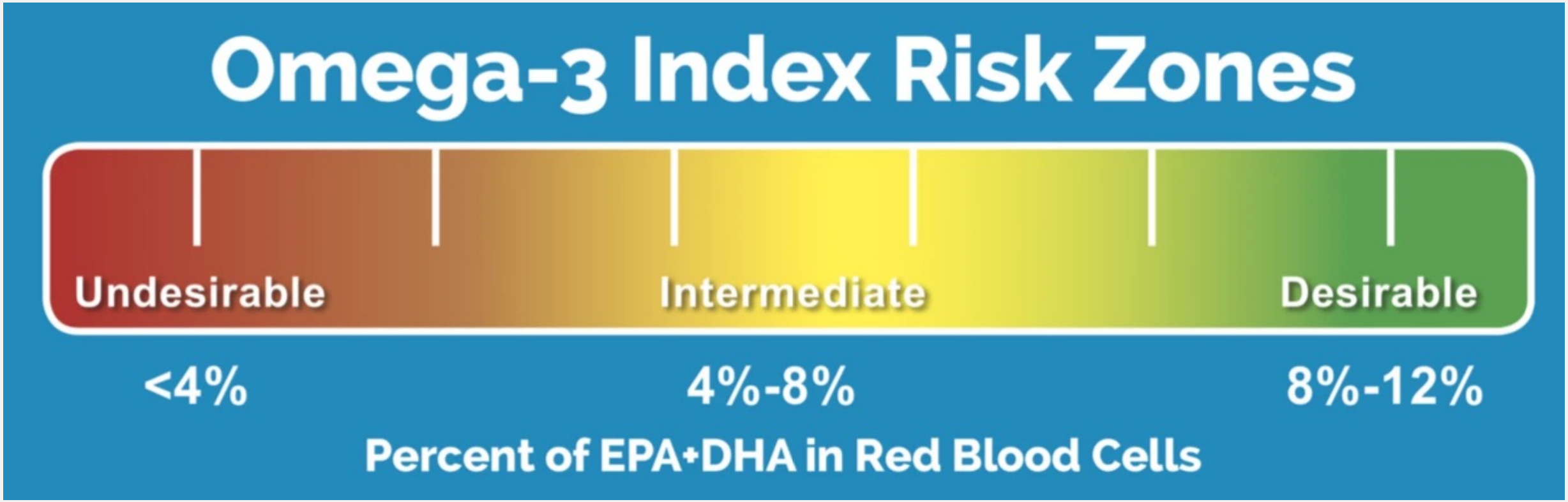
Am J Clin Nutr, Volume 87, Issue 6, June 2008, Pages 1997S–2002S

MORE PREDICTIVE FOR EACH QUARTILE OF MEASURE

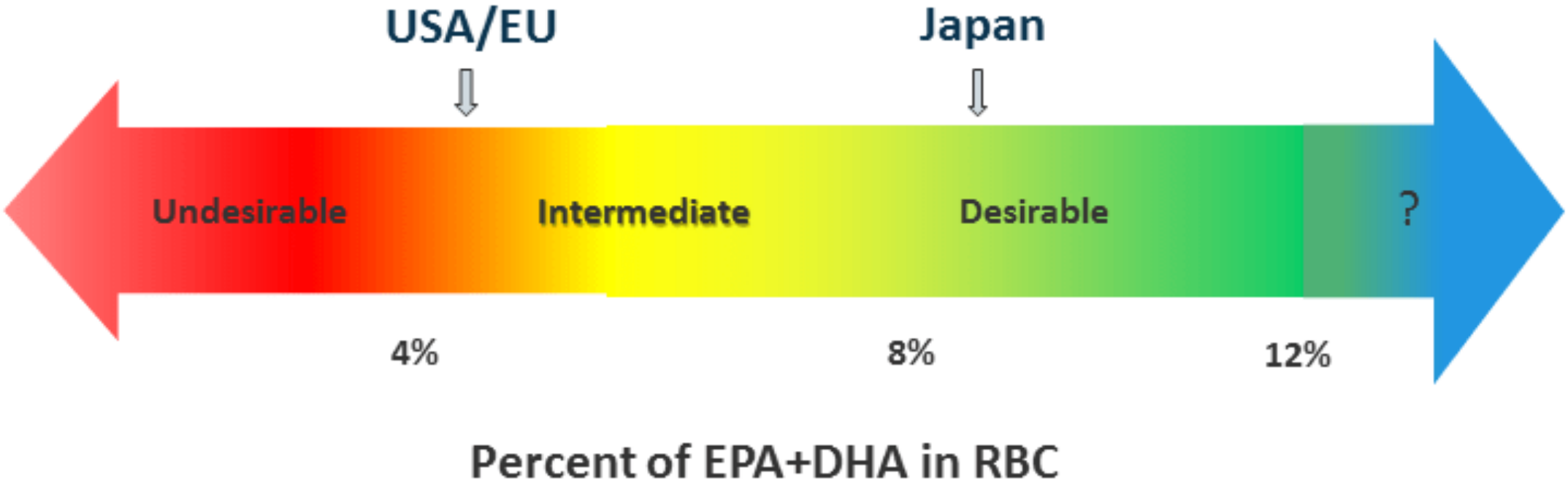


Am J Clin Nutr, Volume 87, Issue 6, June 2008, Pages 1997S–2002S

A SIMPLE MEASURE OF RISK FOR CVD AND BEYOND

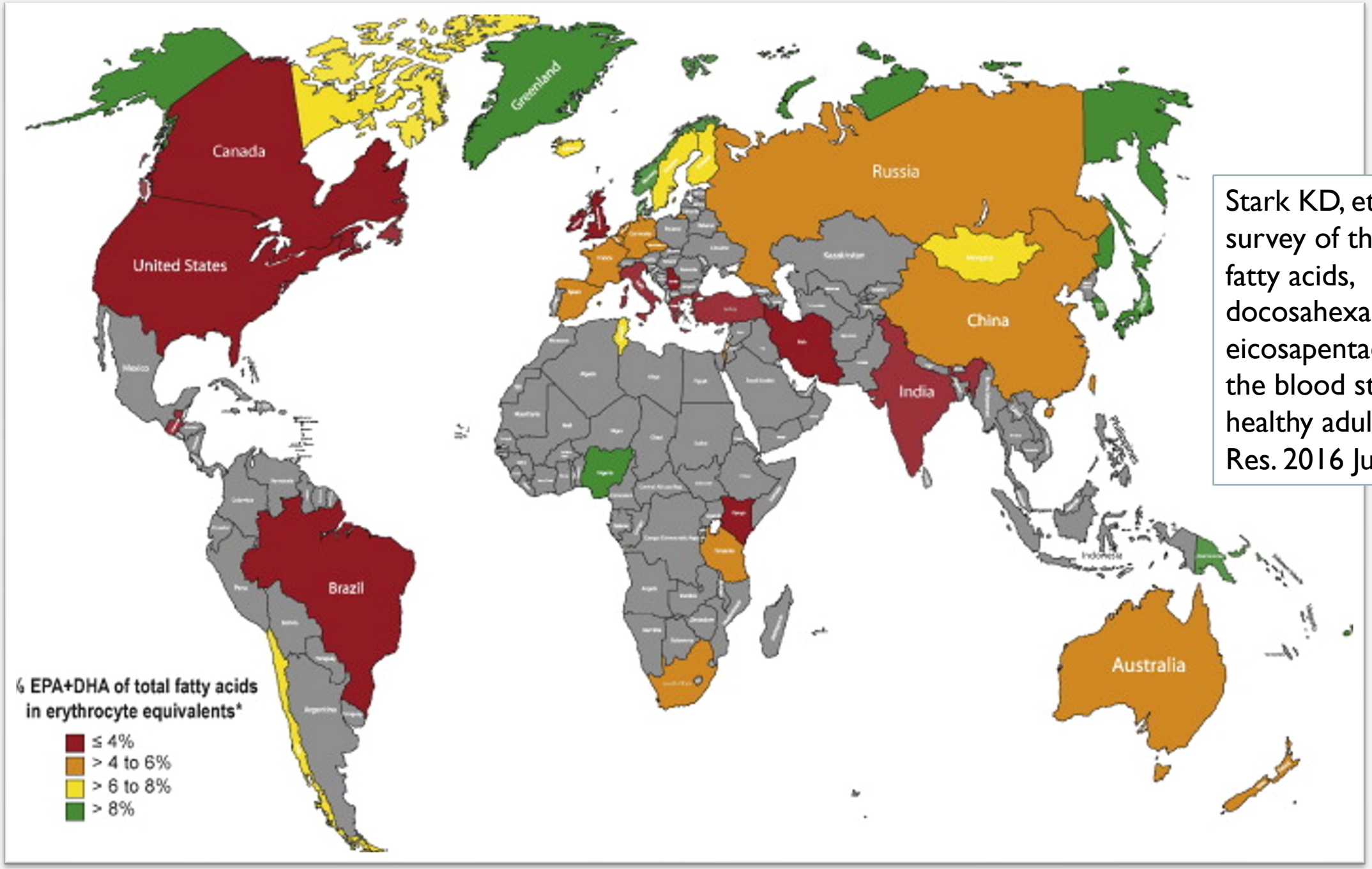


COULD RBC OMEGA-3 LEVELS EXPLAIN THIS?



Itomura, *in vivo* 2008;22:131-136.

Harris and von Schacky. *Prev Med* 2004;39:212-220.



Stark KD, et. al. Global survey of the omega-3 fatty acids, docosahexaenoic acid and eicosapentaenoic acid in the blood stream of healthy adults. Prog Lipid Res. 2016 Jul;63:132-52.

Measures of EPA, DPA, DHA (but not ALA) significantly linked to reduced mortality

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-021-22370-2 OPEN

Blood n-3 fatty acid levels and total and cause-specific mortality from 17 prospective studies

William S. Harris[1,2✉], Nathan L. Tintle[2,3], Fumiaki Imamura[4], Frank Qian[5,6], Andres V. Ardisson Korat[6], Matti Marklund[7,8], Luc Djoussé[6], Julie K. Bassett[9], Pierre-Hugues Carmichael[10], Yun-Yu Chen[11], Yoichiro Hirakawa[12], Leanne K. Küpers[13], Federica Laguzzi[14], Maria Lankinen[15], Rachel A. Murphy[16], Cécilia Samieri[17], Mackenzie K. Senn[18], Peilin Shi[19], Jyrki K. Virtanen[15], Ingeborg A. Brouwer[20], Kuo-Liong Chien[21,22], Gudny Eiriksdottir[23], Nita G. Forouhi[4], Johanna M. Geleijnse[13], Graham G. Giles[2], Vilmundur Gudnason[23,25], Catherine Helmer[17], Allison Hodge[24], Rebecca Jackson[26], Kay-Tee Khaw[4], Markku Laakso[27], Heidi Lai[19,28], Danielle Laurin[10,29], Karin Leander[14], Joan Lindsay[30], Renata Micha[19], Jaako Mursu[15], Toshiharu Ninomiya[31], Wendy Post[9], Bruce M. Psaty[32], Ulf Risérus[33], Jennifer G. Robinson[34,3], Aladdin H. Shadyab[36], Linda Snetselaar[35], Aleix Sala-Vila[2,37], Yangbo Sun[35,38], Lyn M. Steffen[39], Michael Y. Tsai[40], Nicholas J. Wareham[4], Alexis C. Wood[18], Jason H. Y. Wu[7], Frank Hu[5,6], Qi Sun[5,6], David S. Siscovick[41], Rozenn N. Lemaitre[32], Dariush Mozaffarian[19] & The Fatty Acids and Outcomes Research Consortium (FORCE)*

The health effects of omega-3 fatty acids have been controversial. Here we report the results of a de novo pooled analysis conducted with data from 17 prospective cohort studies examining the associations between blood omega-3 fatty acid levels and risk for all-cause mortality. Over a median of 16 years of follow-up, 15,720 deaths occurred among 42,466 individuals. We found that, after multivariable adjustment for relevant risk factors, risk for death from all causes was significantly lower (by 15–18%, at least $p < 0.003$) in the highest vs the lowest quintile for circulating long chain (20–22 carbon) omega-3 fatty acids (eicosapentaenoic, docosapentaenoic, and docosahexaenoic acids). Similar relationships were seen for death from cardiovascular disease, cancer and other causes. No associations were seen with the 18-carbon omega-3, alpha-linolenic acid. These findings suggest that higher circulating levels of marine n-3 PUFA are associated with a lower risk of premature death.

Nat Commun. 2021 Apr 22;12(1):2329.

A full list of author affiliations appears at the end of the paper.

Table 3 Meta-analysis of circulating n-3 PUFA biomarkers with mortality types by cohort-specific quintiles (hazard ratios and 95% CIs[a]): Fatty Acids and Outcomes Research Consortium.

Fatty acid	Quintiles	All-cause mortality (17 cohorts)	CVD mortality (15 cohorts)	Cancer mortality (15 cohorts)	Other mortality (14 cohorts)
ALA	Q1	1	1	1	1
	Q2	0.95 (0.87-1.04)	0.95 (0.87-1.04)	0.98 (0.89-1.08)	0.94 (0.87-1.01)
	Q3	0.94 (0.89-0.99)	1.00 (0.91-1.10)	0.96 (0.87-1.05)	0.93 (0.86-1.00)
	Q4	0.95 (0.90-1.01)	0.99 (0.91-1.09)	0.99 (0.90-1.09)	0.95 (0.88-1.03)
	Q5	0.94 (0.89-0.99)	0.98 (0.89-1.08)	0.88 (0.80-0.98)	0.93 (0.86-1.01)
	P for Trend[b]	0.13	0.96	0.14	0.32
EPA	Q1	1	1	1	1
	Q2	0.92 (0.87-0.97)	0.98 (0.90-1.07)	0.90 (0.82-0.99)	0.91 (0.84-0.98)
	Q3	0.88 (0.83-0.92)	0.98 (0.90-1.07)	0.86 (0.78-0.95)	0.86 (0.79-0.93)
	Q4	0.85 (0.81-0.90)	0.89 (0.81-0.98)	0.87 (0.78-0.96)	0.83 (0.77-0.90)
	Q5	0.82 (0.78-0.87)	0.85 (0.77-0.94)	0.82 (0.74-0.91)	0.78 (0.72-0.85)
	P for Trend	<0.0001	0.006	0.008	<0.0001
DPA	Q1	1	1	1	1
	Q2	0.95 (0.90-1.01)	0.96 (0.87-1.07)	0.96 (0.86-1.07)	0.94 (0.86-1.02)
	Q3	0.92 (0.87-0.98)	0.99 (0.89-1.09)	0.98 (0.88-1.10)	0.91 (0.84-0.99)
	Q4	0.90 (0.85-0.96)	0.98 (0.88-1.09)	0.92 (0.82-1.03)	0.88 (0.80-0.96)
	Q5	0.84 (0.79-0.90)	0.87 (0.78-0.98)	0.79 (0.70-0.90)	0.85 (0.78-0.93)
	P for Trend	0.0001	0.16	0.008	0.007
DHA	Q1	1	1	1	1
	Q2	0.95 (0.90-1.00)	0.96 (0.88-1.05)	0.91 (0.83-1.00)	0.96 (0.89-1.04)
	Q3	0.92 (0.88-0.97)	0.87 (0.80-0.95)	0.88 (0.80-0.97)	0.97 (0.89-1.05)
	Q4	0.97 (0.94-1.01)	0.92 (0.84-1.01)	0.91 (0.83-1.00)	0.90 (0.83-0.97)
	Q5	0.85 (0.81-0.90)	0.79 (0.72-0.88)	0.86 (0.78-0.95)	0.87 (0.80-0.94)
	P for Trend	0.01	0.002	0.06	0.008
EPA + DHA	Q1	1	1	1	1
	Q2	0.94 (0.89,0.99)	0.96 (0.88,1.04)	0.93 (0.85-1.03)	0.93 (0.86-1.00)
	Q3	0.92 (0.88,0.97)	0.91 (0.83,1.00)	0.90 (0.82-0.99)	0.94 (0.87-1.02)
	Q4	0.89 (0.84,0.93)	0.86 (0.79,0.95)	0.92 (0.83-1.02)	0.89 (0.82-0.96)
	Q5	0.84 (0.79,0.89)	0.80 (0.73,0.88)	0.87 (0.78-0.96)	0.82 (0.75-0.89)
	P for Trend	<0.0001	0.0004	0.06	0.0008

SUPPLEMENTING THE OMEGA-3 RISK GAP

Does it work, How much is Needed?

PLOS ONE

RESEARCH ARTICLE

Dietary and Biological Assessment of the Omega-3 Status of Collegiate Athletes: A Cross-Sectional Analysis

Peter P. Ritz[1], Mark B. Rogers[1,2], Jennifer S. Zabinsky[1,3], Valisa E. Hedrick[3], John A. Rockwell[4], Ernest G. Rimer[5,6], Samantha B. Kostelnik[3], Matthew W. Hulver[3,7,8], Michelle S. Rockwell[3,7]*

1 Athletics Department, Virginia Tech, Blacksburg, VA, United States of America, 2 Edward Via College of Osteopathic Medicine, Blacksburg, VA, United States of America, 3 Department of Human Nutrition, Foods and Exercise, Virginia Tech, Blacksburg, VA, United States of America, 4 Department of Medicine, Carilion Clinic, Roanoke, VA, United States of America, 5 Department of Exercise & Sport Science, College of Health, University of Utah, Salt Lake City, UT, United States of America, 6 Athletics Department, University of Utah, Salt Lake City, UT, United States of America, 7 Center for Transformative Research on Health Behaviors, Fralin Biomedical Research Institute Roanoke, Roanoke, VA, United States of America, 8 Fralin Life Sciences Institute, Virginia Tech, Blacksburg, VA, United States of America

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OPEN ACCESS

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Data Availability Statement: All relevant data are within the paper.

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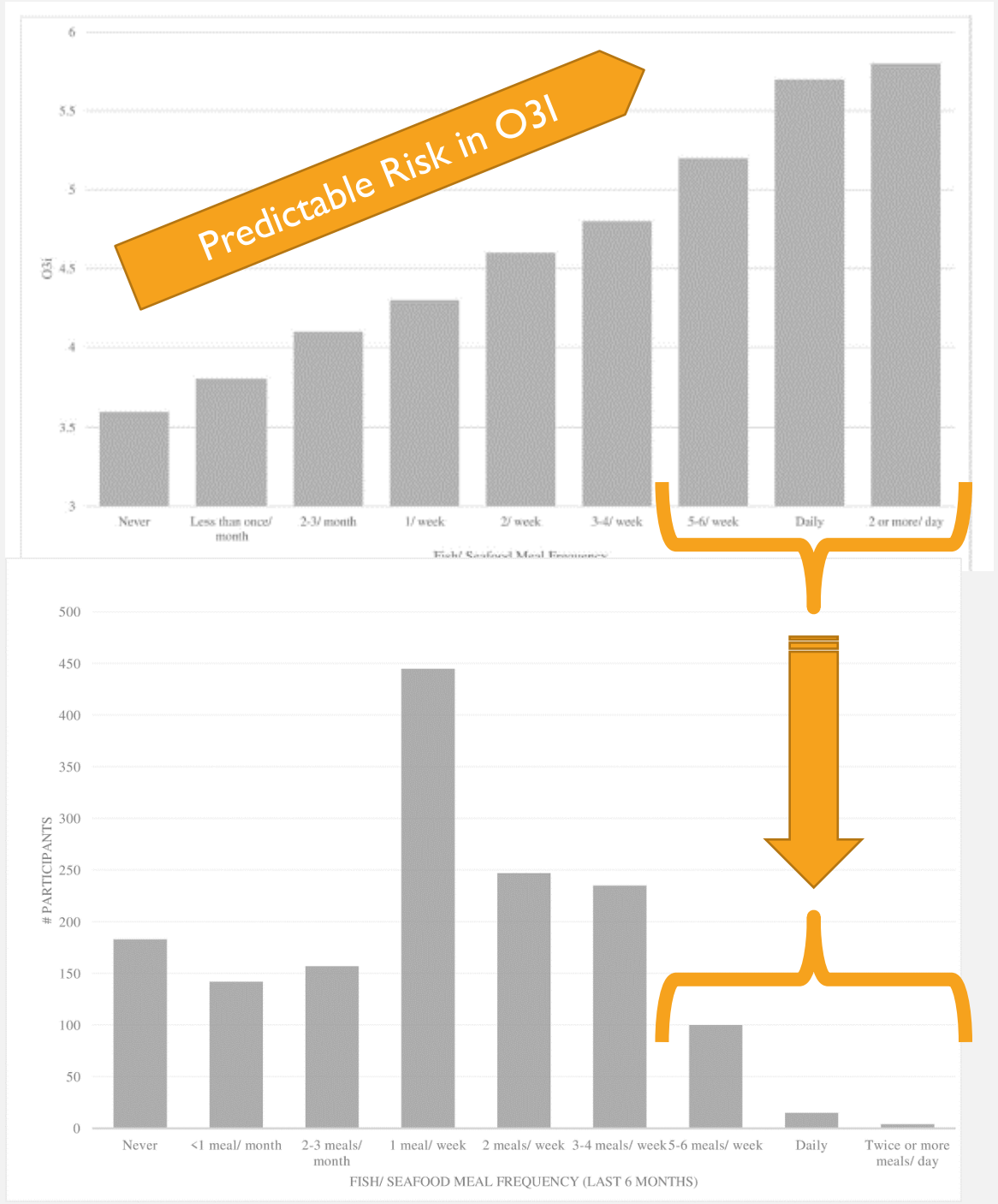
Abstract

Omega-3 fatty acids (ω-3 FA) are associated with cardiovascular health, brain function, reduction of inflammation, and several other physiological roles of importance to competitive athletes. The ω-3 FA status of National Collegiate Athletic Association (NCAA) Division I athletes has not been well-described. The purpose of this study was to evaluate the ω-3 FA status of NCAA Division I athletes using dietary and biological assessment methodology. Athletes from nine NCAA Division I institutions from throughout the U.S. (n = 1,528, 51% male, 34 sports represented, 19.9 ± 1.4 years of age) completed a food frequency questionnaire (FFQ) to assess ω-3 FA from diet and supplements. Omega-3 Index (O3i) was evaluated in a sub-set of these participants (n = 298, 55% male, 21 sports represented, 20.0 ± 1.3 years of age) using dried blood spot sampling. Only 6% (n = 93) of athletes achieved the Academy of Nutrition & Dietetics' recommendation to consume 500 mg DHA+EPA per day. Use of ω-3 FA supplements was reported by 15% (n = 229) of participants. O3i was 4.33 ± 0.81%, with no participants meeting the O3i benchmark of 8% associated with the lowest risk of cardiovascular disease. Every additional weekly serving of fish or seafood was associated with an absolute O3i increase of 0.27%. Overall, sub-optimal ω-3 FA status was observed among a large, geographically diverse group of male and female NCAA Division I athletes. These findings may inform interventions aimed at improving ω-3 FA status of collegiate athletes. Further research on athlete-specific ω-3 FA requirements is needed.

Introduction

Omega-3 polyunsaturated fatty acids (ω-3 FA), namely long-chain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), serve as structural components within phospholipid



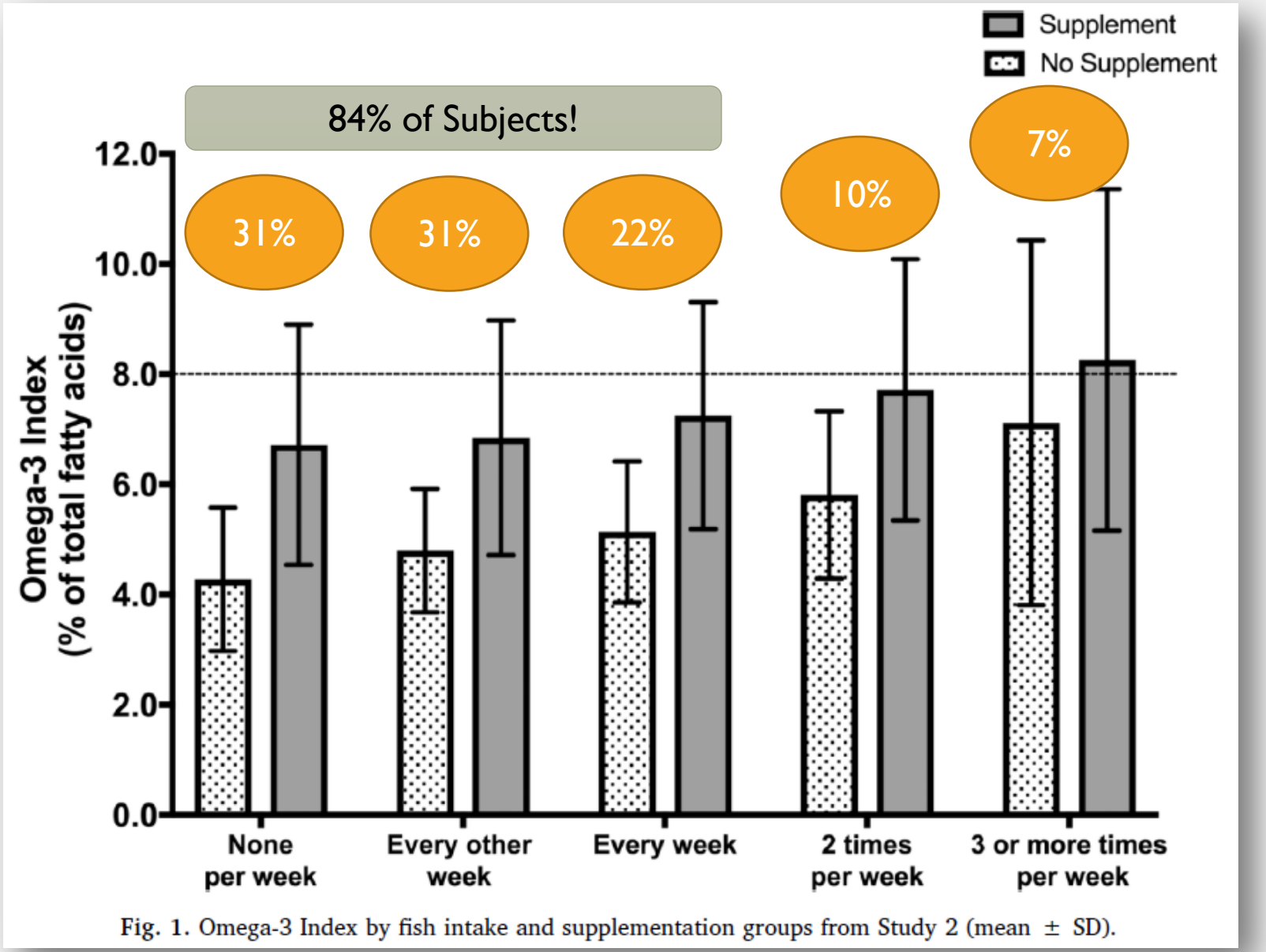


Fig. 1. Omega-3 Index by fish intake and supplementation groups from Study 2 (mean ± SD).

Omega-3 Index measures of 3458 subjects (mean 51 yo, 60% female)

Answering these questions:

"How often do you eat tuna or other non-fried fish?"

"Do you take an omega-3 supplement?"

Association of reported fish intake and supplementation status with the omega-3 index. *Prostaglandins Leukot Essent Fatty Acids*. 2019 Mar;142:4-10.

HOW MUCH EPA/DHA DOES IT TAKE?

ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Determinants of Erythrocyte Omega-3 Fatty Acid Content in Response to Fish Oil Supplementation: A Dose–Response Randomized Controlled Trial

Michael R. Flock, BS; Ann C. Skulas Ray, PhD; William S. Harris, PhD; Terry D. Etherton, PhD; Jennifer A. Fleming, MS, RD; Penny M. Kris Etherton, PhD, RD

Background—The erythrocyte membrane content of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which constitutes the omega-3 index (O3I), predicts cardiovascular disease mortality. The amount of EPA+DHA needed to achieve a target O3I is poorly defined, as are the determinants of the O3I response to a change in EPA+DHA intake. The objective of this study was to develop a predictive model of the O3I response to EPA+DHA supplementation in healthy adults, specifically identifying factors that determine the response.

Methods and Results—A randomized, placebo-controlled, double-blind, parallel-group study was conducted in 115 healthy men and women. One of 5 doses (0, 300, 600, 900, 1800 mg) of EPA+DHA was given daily as placebo or fish oil supplements for ≈5 months. The O3I was measured at baseline and at the end of the study. There were no significant differences in the clinical characteristics between the groups at baseline. The O3I increased in a dose-dependent manner ($P<0.0001$), with the dose of EPA+DHA alone accounting for 68% (quadratic, $P<0.0001$) of the variability in the O3I response. Dose adjusted per unit body weight (g/kg) accounted for 70% (linear, $P<0.0001$). Additional factors that improved prediction of treatment response were baseline O3I, age, sex, and physical activity. Collectively, these explained 78% of the response variability ($P<0.0001$).

Conclusions—Our findings validate the O3I as a biomarker of EPA+DHA consumption and identify additional factors, particularly body weight, that can be used to tailor EPA+DHA recommendations to achieve a target O3I. (***J Am Heart Assoc.* 2013;2:e000513 doi: 10.1161/JAHA.113.000513**)

Key Words: blood cell • fatty acids • fish oil • metabolism • nutrition

The marine-derived omega-3 (n-3) fatty acids (FAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are recommended for reducing the risk of cardiovascular disease (CVD), especially sudden cardiac death.[1–4] However, a dietary reference intake for EPA+DHA has not been established.[5] Use of biomarker-based approaches has made it possible to study the association of different blood or tissues levels of EPA+DHA on important health benefits or outcomes, such as risk of CVD events. The omega-3 index (O3I), which is the sum of EPA+DHA content in red blood cell (RBC) membranes, is a biomarker of n-3 FA status[6,7] that is highly correlated with myocardial EPA+DHA content.[8,9] An O3I of ≥8% has been recommended as a cardioprotective level[7] on the basis of associations with reduced risk of primary cardiac arrest,[10] sudden cardiac death,[11] coronary atherosclerosis,[12] and acute coronary syndrome.[13,14] In studies of Americans not taking n-3 FA supplements, mean O3I values range from 4% to 5%.[15–18] In 2 larger observational studies of US adults that did not exclude supplement users, O3I values were somewhat higher, averaging 5.3%[19] and 5.6%.[20]

Because of limitations in the current evidence, dietary recommendations for achieving a target O3I cannot be made. Observational studies have confirmed that dietary or supplemental intake of EPA+DHA is associated with higher levels of the O3I,[13,15,21,22] and additional factors such as body weight and health status modify this relationship.[13,15,20–23] However, these studies lack precision and accuracy because of use of food frequency questionnaires and other dietary recall methods.[24]

From the Departments of Nutritional Sciences (M.R.F., A.C.S.-R., J.A.F., P.M.K.-E.) and Animal Science (T.D.E.), Penn State University, University Park, PA; Health Diagnostic Laboratory, Inc, Richmond VA (W.S.H.).

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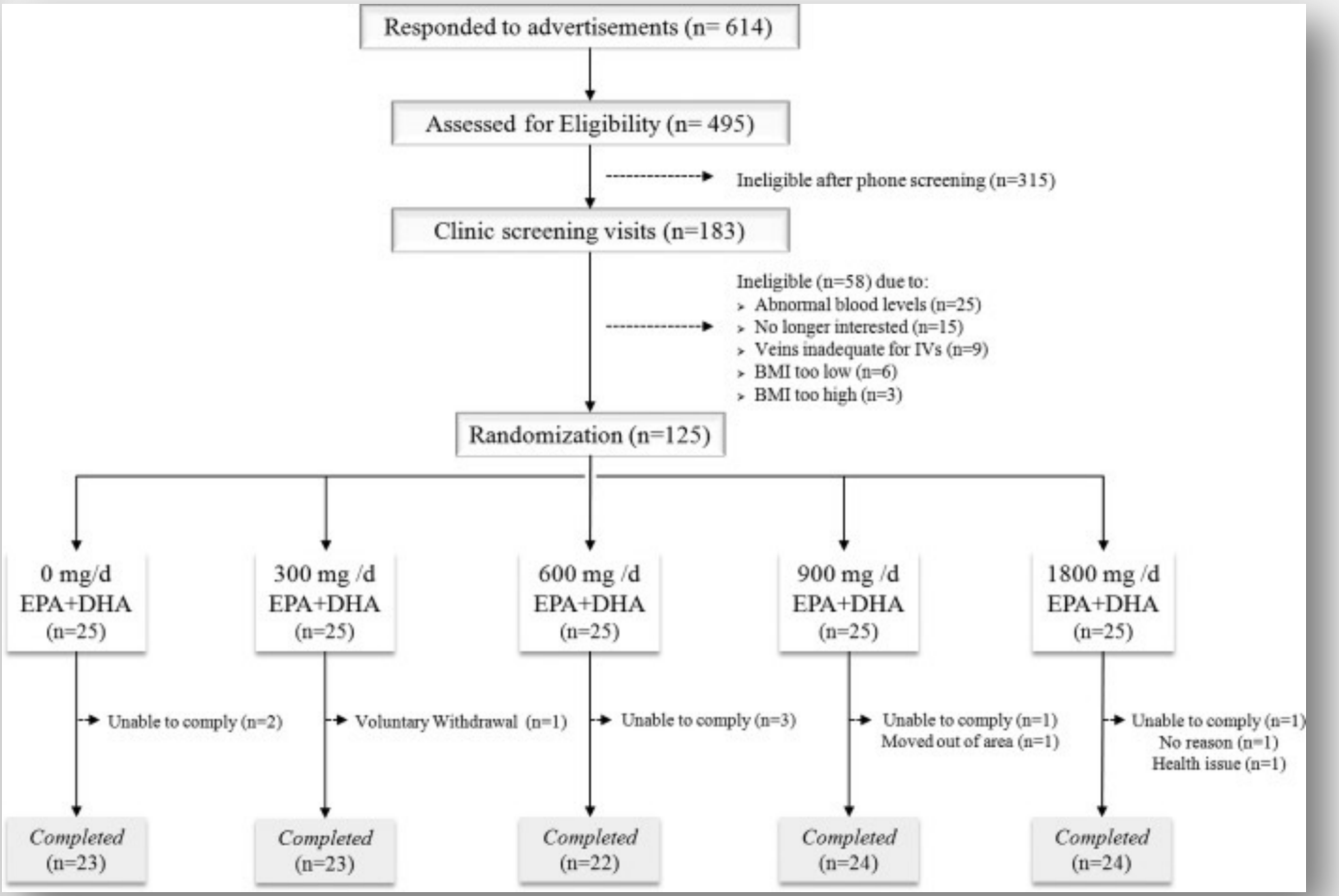
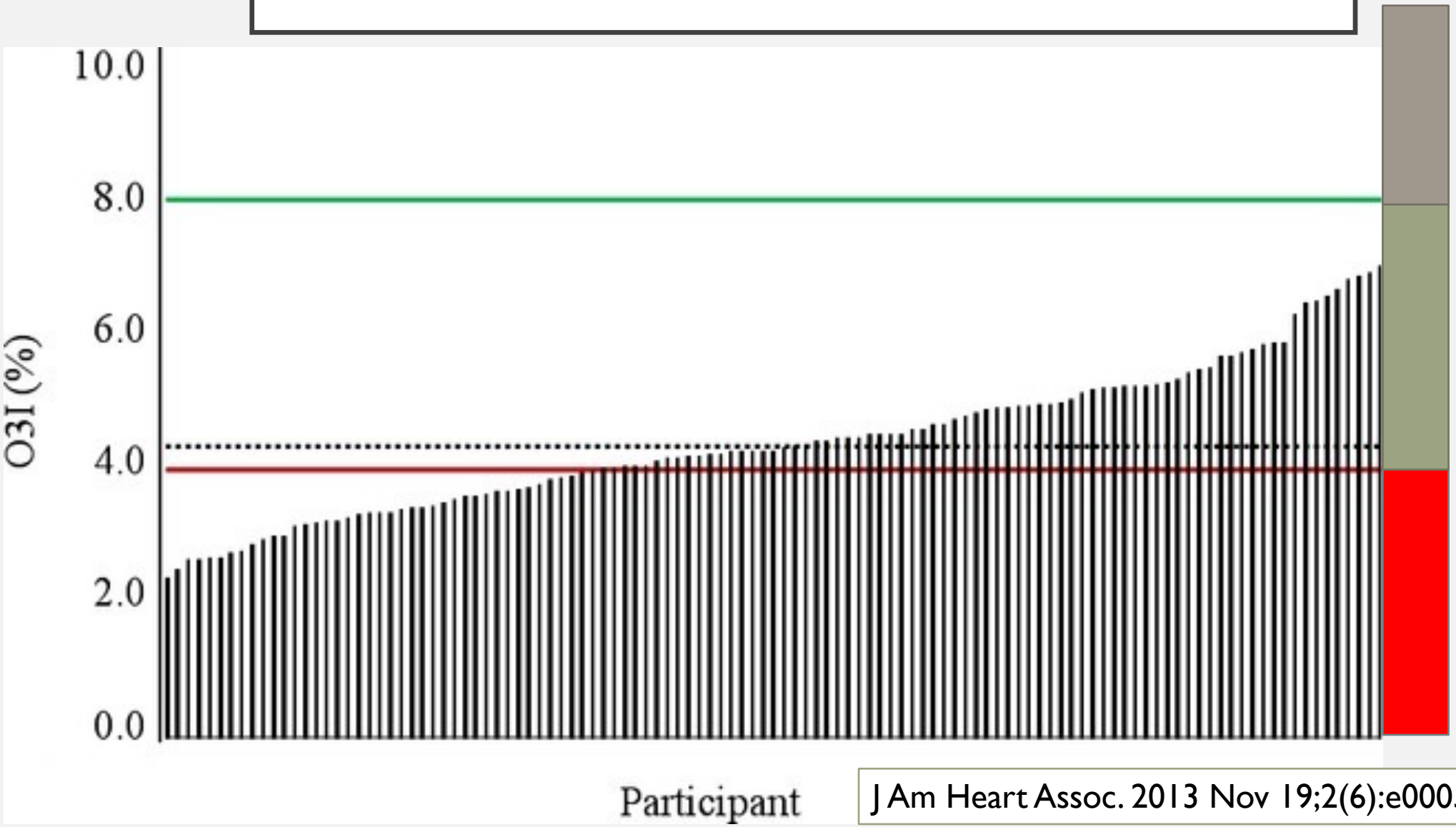


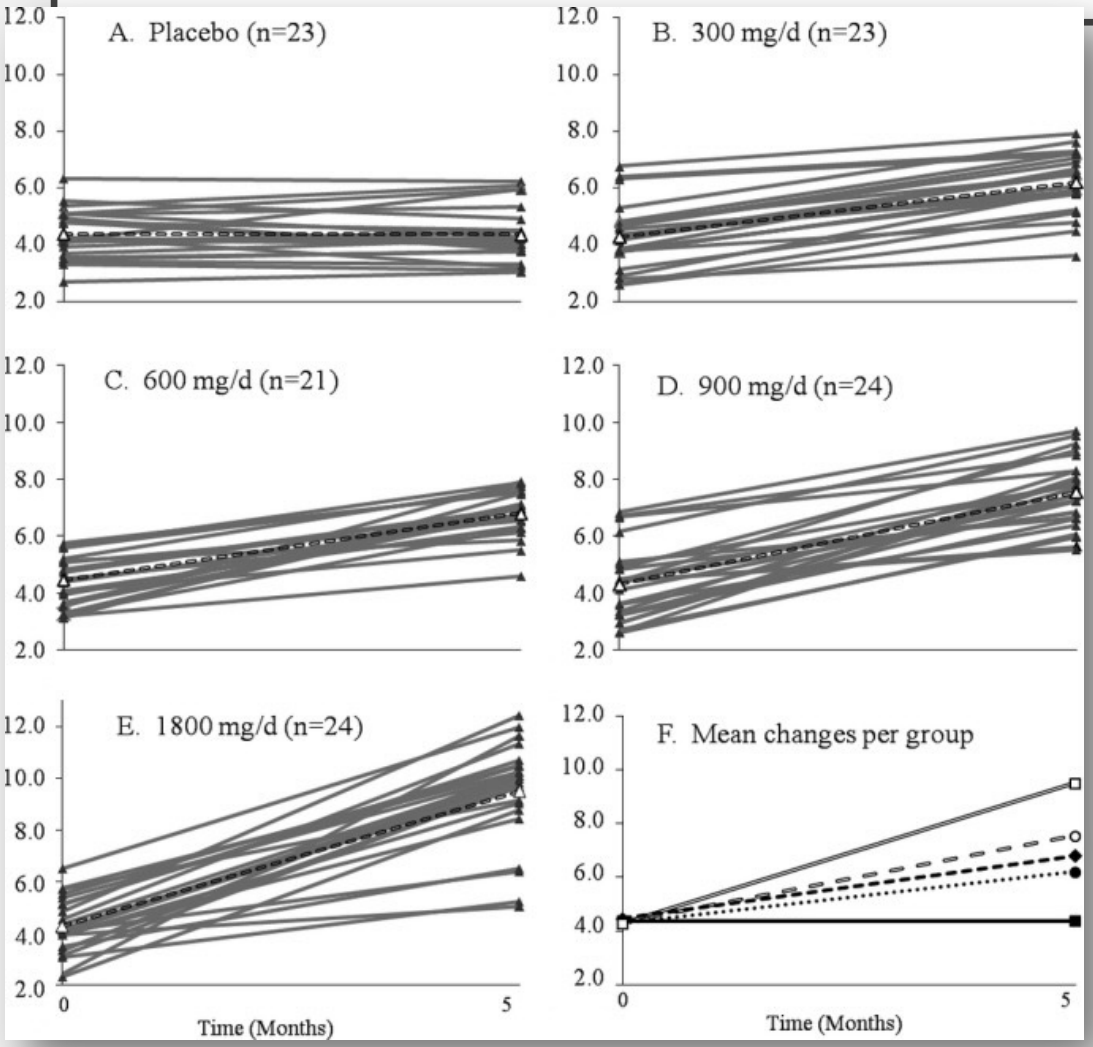
J Am Heart Assoc. 2013 Nov 19;2(6):e000513.

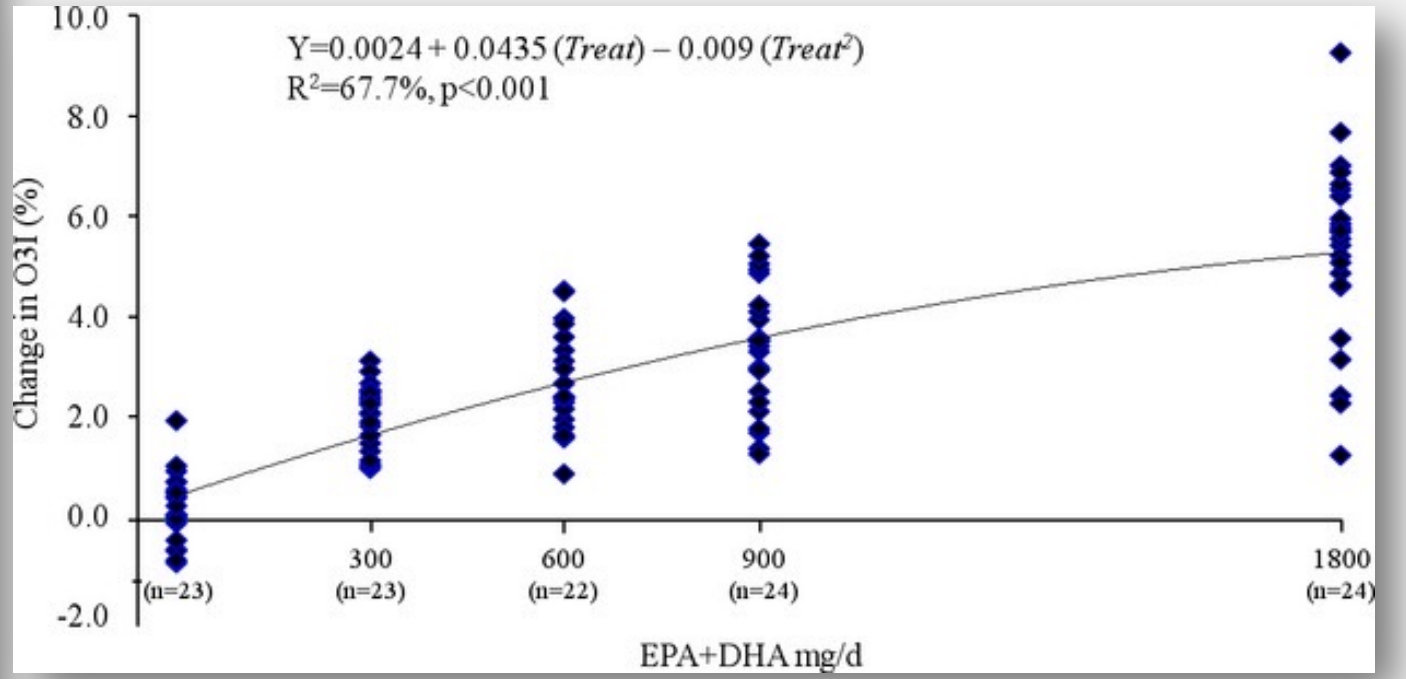
BASELINE RBC OMEGA-3 LEVELS



J Am Heart Assoc. 2013 Nov 19;2(6):e000513.

DOSE HAD THE GREATEST IMPACT IN RAISING RBC O-3





From our findings, we estimate that an average healthy adult with a low O3I (ie, 4.3%) would require at least 1 g/day of EPA+DHA for 5 months to achieve an O3I of 8%

OTHER IMPORTANT VARIABLES FOR INCORPORATION

- Body Mass Index (and Fat Mass) was one of the greatest predictors in the change in O3-I by dose. Suggesting that dose needs to be indexed (increased) for individuals with higher BMI
- Having a lower baseline RBC O3 level resulted in a greater increase after supplementation suggesting a dynamic absorption/incorporation curve that begins to saturate as O3 levels risk to optimal levels.
- Older individuals experienced a greater increase in O3I after supplementation which might reflect their lower baseline levels or some other, undiscovered, reason.

INTERVENTION STUDIES- IS MORE BETTER?

nutrients

MDPI

Review

An Update on Omega-3 Polyunsaturated Fatty Acids and Cardiovascular Health

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Abstract: Interest in the potential cardiovascular (CV) benefits of omega-3 polyunsaturated fatty acids (Ω-3) began in the 1940s and was amplified by a subsequent landmark trial showing reduced CV disease (CVD) risk following acute myocardial infarction. Since that time, however, much controversy has circulated due to discordant results among several studies and even meta-analyses. Then, in 2018, three more large, randomized trials were released—these too with discordant findings regarding the overall benefits of Ω-3 therapy. Interestingly, the trial that used a higher dose (4 g/day highly purified eicosapentaenoic acid (EPA)) found a remarkable, statistically significant reduction in CVD events. It was proposed that insufficient Ω-3 dosing (<1 g/day EPA and docosahexaenoic acid (DHA)), as well as patients aggressively treated with multiple other effective medical therapies, may explain the conflicting results of Ω-3 therapy in controlled trials. We have thus reviewed the current evidence regarding Ω-3 and CV health, put forth potential reasoning for discrepant results in the literature, highlighted critical concepts such as measuring blood levels of Ω-3 with a dedicated Ω-3 index and addressed current recommendations as suggested by health care professional societies and recent significant scientific data.

Keywords: omega 3 polyunsaturated fatty acid; omega 3 index; cardiovascular disease

check for updates

Citation: Elagizi, A.; Lavie, C.J.; O'Keefe, E.; Marshall, K.; O'Keefe, J.H.; Milani, R.V. An Update on Omega-3 Polyunsaturated Fatty Acids and Cardiovascular Health. *Nutrients* **2021**, *13*, 204. https://doi.org/10.3390/nu13010204

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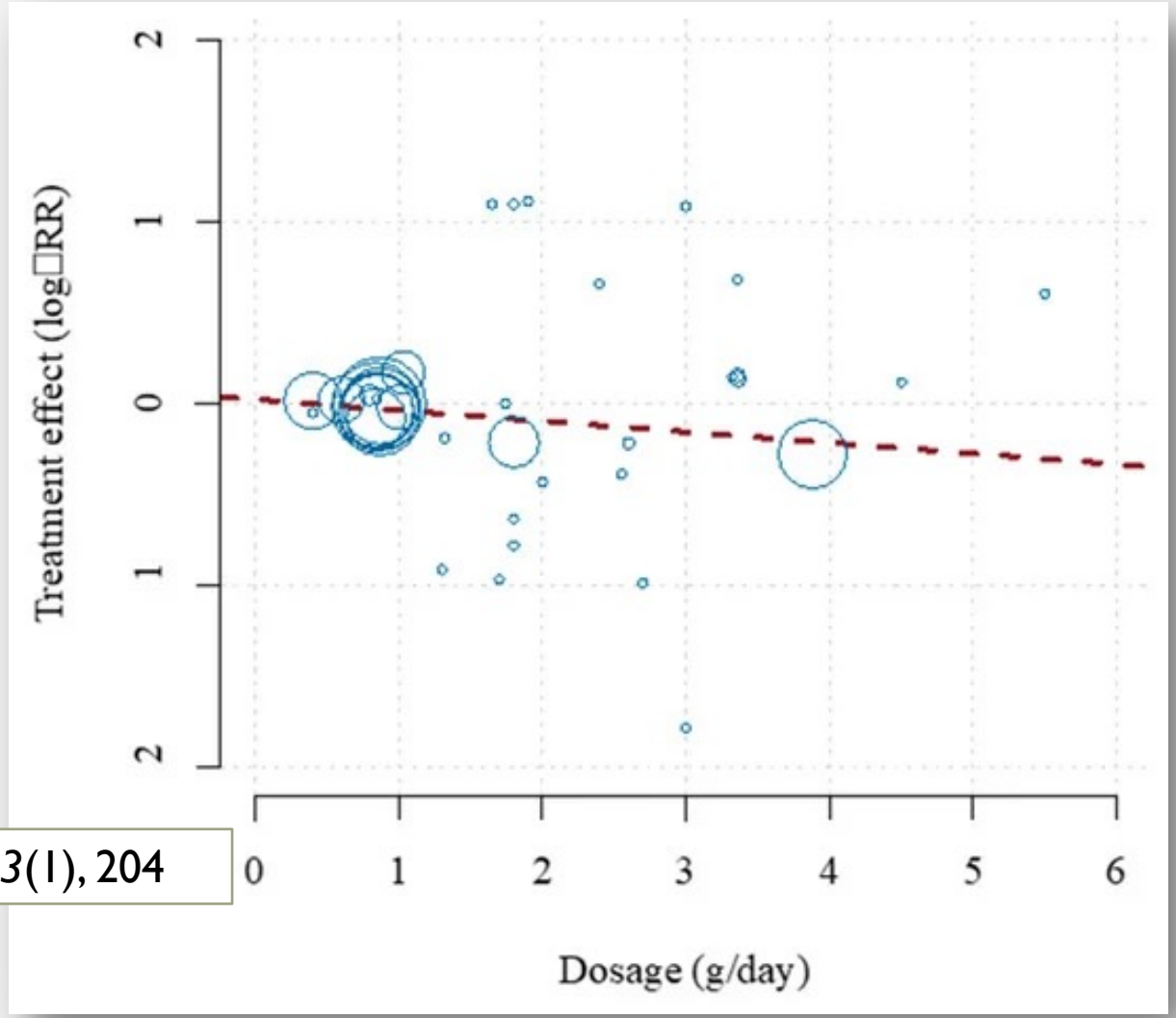
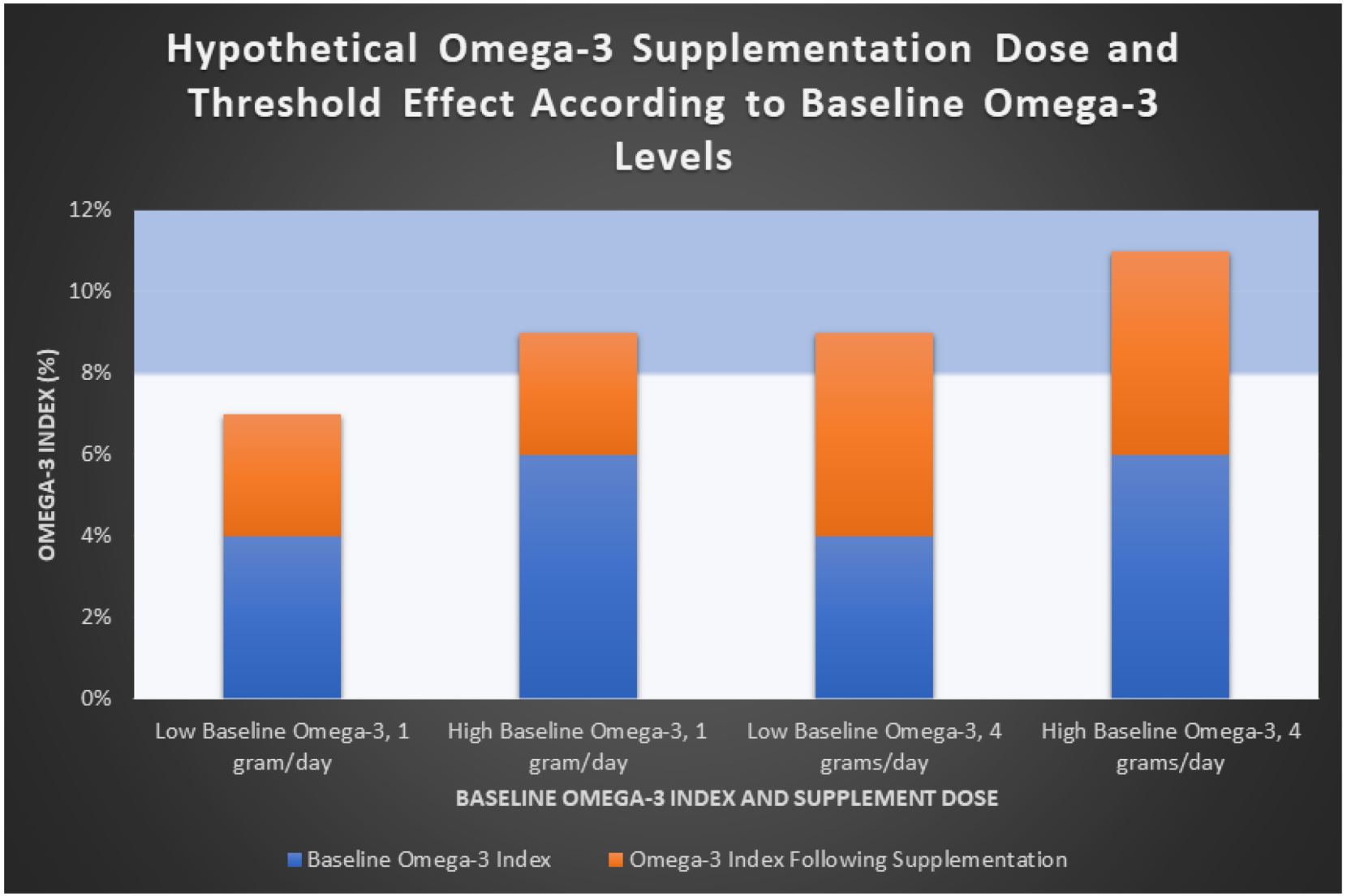
1. Introduction

As early as 1944, Sinclair described the rarity of coronary heart disease (CHD) amongst Greenland Eskimos, who consumed a diet rich in fish, seal and whale [1]. More than 40 years ago, Bang and Dyerberg reported that despite low consumption of fruit, vegetables and complex carbohydrates in exchange for a diet high in saturated fat and cholesterol, serum cholesterol and triglyceride (TG) levels were lower in Greenland Inuit than in age-matched residents of Denmark, who also demonstrated lower risk of myocardial infarction (MI) [2]. These and other similar observations sparked interest in the potential benefits of increased dietary fish intake, particularly the benefits of or[illegible] acids (Ω-3), for cardiovascular (CV) health.

Ω-3 confer CV benefits through TG reduction, anti-infla[illegible] effects, vasodilation, reduced blood pressure, improved art[illegible] favorable autonomic tone, and reduced platelet aggregation [3–5]. In particular, TG levels are a historically well-studied, independent risk factor for CHD. Ω-3 or fish oil diet supplementation is evidenced to lower TG levels in a dose-dependent fashion, whereby 3–4 g/day of eicosapentaenoic acid (EPA) or a combined EPA and docosahexaenoic acid (DHA) reduces blood levels by 20–50% in those with high TGs [6].



Nutrients **2021**, *13*(1), 204



Nutrients **2021**, *13*(1), 204

Multiple trials continue to use an Ω-3 intervention dose of 1 g/day of EPA + DHA, which demonstrated significant CVD benefits in the landmark GISSI-P trial. However, trials demonstrating a benefit with this low dose, such as GISSI-P, GISSI-HF and JELIS, were performed in Italian and Japanese populations with higher baseline Ω-3 intake in their regular diet, which may account for their ability to reach a therapeutic level of Ω-3 which confers CVD benefits. The efficacy of modern medical therapy for CVD can further confound the benefits of Ω-3 supplementation due to reduced overall CVD events. Patients in Western nations or nations with lower Ω-3 intake in general may require higher-dose interventions (e.g., 2–4 g/day of EPA + DHA) to reach a therapeutic effect of Ω-3.

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Review

The Differential Effects of Eicosapentaenoic Acid and Docosahexaenoic Acid on Cardiometabolic Risk Factors: A Systematic Review

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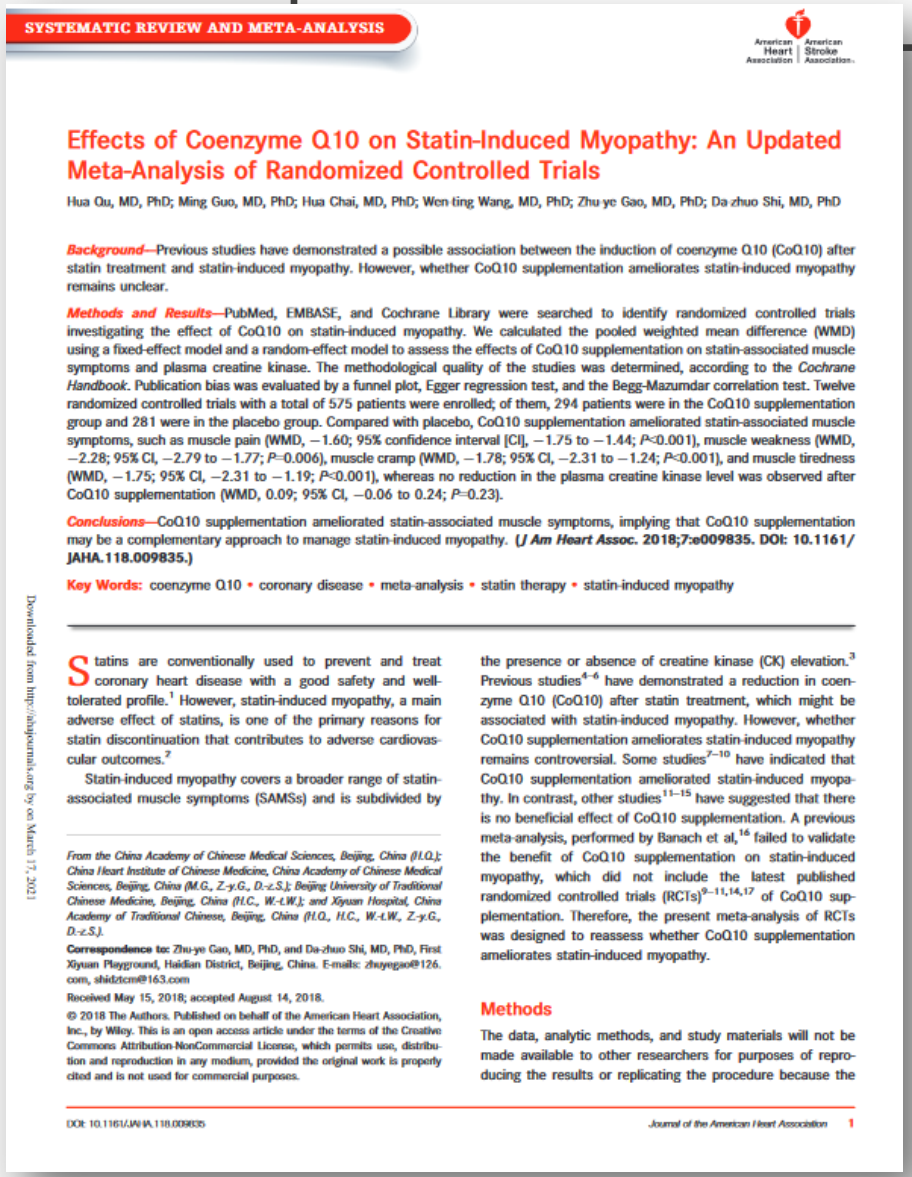
Abstract: A large body of evidence supports the cardioprotective effects of the long-chain omega-3 polyunsaturated fatty acids (PUFAs), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). There is increasing interest in the independent effects of EPA and DHA in the modulation of cardiometabolic risk factors. This systematic review aims to appraise the latest available evidence of the differential effects of EPA and DHA on such risk factors. A systematic literature review was conducted up to May 2017. Randomised controlled trials were included if they met strict eligibility criteria, including EPA or DHA > 2 g/day and purity ≥ 90%. Eighteen identified articles were included, corresponding to six unique studies involving 527 participants. Both EPA and DHA lowered triglyceride concentration, with DHA having a greater triglyceride-lowering effect. Whilst total cholesterol levels were largely unchanged by EPA and DHA, DHA increased high-density lipoprotein (HDL) cholesterol concentration, particularly HDL_2, and increased low-density lipoprotein (LDL) cholesterol concentration and LDL particle size. Both EPA and DHA inhibited platelet activity, whilst DHA improved vascular function and lowered heart rate and blood pressure to a greater extent than EPA. The effects of EPA and DHA on inflammatory markers and glycaemic control were inconclusive; however both lowered oxidative stress. Thus, EPA and DHA appear to have differential effects on cardiometabolic risk factors, but these need to be confirmed by larger clinical studies.

Int. J. Mol. Sci. 2018, 19(2), 532; https://doi.org/10.3390/ijms19020532

STATIN USE: COQ10 AND VITAMIN K2



SYSTEMATIC REVIEW AND META-ANALYSIS

American Heart Association | American Stroke Association

Effects of Coenzyme Q10 on Statin-Induced Myopathy: An Updated Meta-Analysis of Randomized Controlled Trials

Hua Qu, MD, PhD; Ming Guo, MD, PhD; Hua Chai, MD, PhD; Wen-ting Wang, MD, PhD; Zhu-ye Gao, MD, PhD; Da-zhuo Shi, MD, PhD

Background—Previous studies have demonstrated a possible association between the induction of coenzyme Q10 (CoQ10) after statin treatment and statin-induced myopathy. However, whether CoQ10 supplementation ameliorates statin-induced myopathy remains unclear.

Methods and Results—PubMed, EMBASE, and Cochrane Library were searched to identify randomized controlled trials investigating the effect of CoQ10 on statin-induced myopathy. We calculated the pooled weighted mean difference (WMD) using a fixed-effect model and a random-effect model to assess the effects of CoQ10 supplementation on statin-associated muscle symptoms and plasma creatine kinase. The methodological quality of the studies was determined, according to the *Cochrane Handbook*. Publication bias was evaluated by a funnel plot, Egger regression test, and the Begg-Mazumdar correlation test. Twelve randomized controlled trials with a total of 575 patients were enrolled; of them, 294 patients were in the CoQ10 supplementation group and 281 were in the placebo group. Compared with placebo, CoQ10 supplementation ameliorated statin-associated muscle symptoms, such as muscle pain (WMD, −1.60; 95% confidence interval [CI], −1.75 to −1.44; $P<0.001$), muscle weakness (WMD, −2.28; 95% CI, −2.79 to −1.77; $P=0.006$), muscle cramp (WMD, −1.78; 95% CI, −2.31 to −1.24; $P<0.001$), and muscle tiredness (WMD, −1.75; 95% CI, −2.31 to −1.19; $P<0.001$), whereas no reduction in the plasma creatine kinase level was observed after CoQ10 supplementation (WMD, 0.09; 95% CI, −0.06 to 0.24; $P=0.23$).

Conclusions—CoQ10 supplementation ameliorated statin-associated muscle symptoms, implying that CoQ10 supplementation may be a complementary approach to manage statin-induced myopathy. (***J Am Heart Assoc.* 2018;7:e009835. DOI: 10.1161/JAHA.118.009835.**)

Key Words: coenzyme Q10 • coronary disease • meta-analysis • statin therapy • statin-induced myopathy

Statins are conventionally used to prevent and treat coronary heart disease with a good safety and well-tolerated profile.[1] However, statin-induced myopathy, a main adverse effect of statins, is one of the primary reasons for statin discontinuation that contributes to adverse cardiovascular outcomes.[2]

Statin-induced myopathy covers a broader range of statin-associated muscle symptoms (SAMSs) and is subdivided by the presence or absence of creatine kinase (CK) elevation.[3] Previous studies[4–6] have demonstrated a reduction in coenzyme Q10 (CoQ10) after statin treatment, which might be associated with statin-induced myopathy. However, whether CoQ10 supplementation ameliorates statin-induced myopathy remains controversial. Some studies[7–10] have indicated that CoQ10 supplementation ameliorated statin-induced myopathy. In contrast, other studies[11–15] have suggested that there is no beneficial effect of CoQ10 supplementation. A previous meta-analysis, performed by Banach et al,[16] failed to validate the benefit of CoQ10 supplementation on statin-induced myopathy, which did not include the latest published randomized controlled trials (RCTs)[9–11,14,17] of CoQ10 supplementation. Therefore, the present meta-analysis of RCTs was designed to reassess whether CoQ10 supplementation ameliorates statin-induced myopathy.

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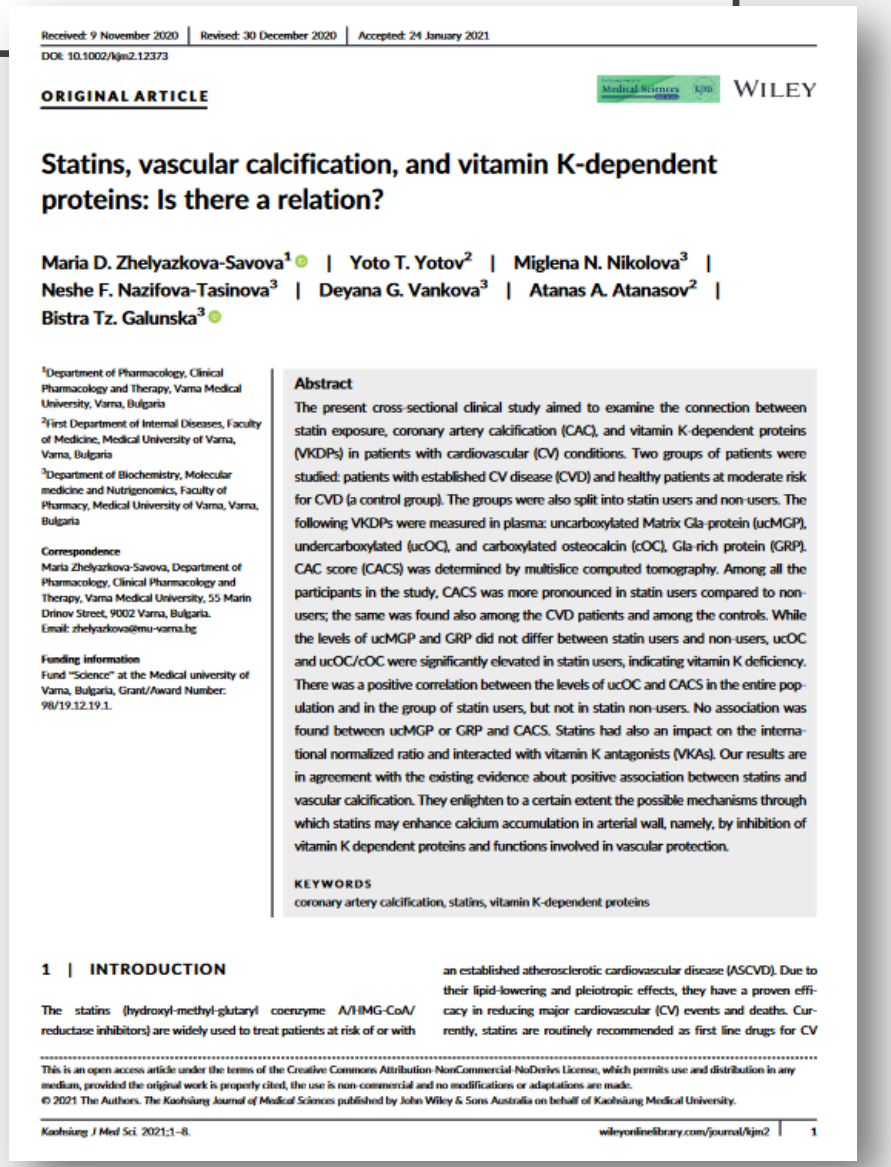
Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure because the



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ORIGINAL ARTICLE

Medical Sciences KJM WILEY

Statins, vascular calcification, and vitamin K-dependent proteins: Is there a relation?

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Abstract

The present cross-sectional clinical study aimed to examine the connection between statin exposure, coronary artery calcification (CAC), and vitamin K-dependent proteins (VKDPs) in patients with cardiovascular (CV) conditions. Two groups of patients were studied: patients with established CV disease (CVD) and healthy patients at moderate risk for CVD (a control group). The groups were also split into statin users and non-users. The following VKDPs were measured in plasma: uncarboxylated Matrix Gla-protein (ucMGP), undercarboxylated (ucOC), and carboxylated osteocalcin (cOC), Gla-rich protein (GRP). CAC score (CACS) was determined by multislice computed tomography. Among all the participants in the study, CACS was more pronounced in statin users compared to non-users; the same was found also among the CVD patients and among the controls. While the levels of ucMGP and GRP did not differ between statin users and non-users, ucOC and ucOC/cOC were significantly elevated in statin users, indicating vitamin K deficiency. There was a positive correlation between the levels of ucOC and CACS in the entire population and in the group of statin users, but not in statin non-users. No association was found between ucMGP or GRP and CACS. Statins had also an impact on the international normalized ratio and interacted with vitamin K antagonists (VKAs). Our results are in agreement with the existing evidence about positive association between statins and vascular calcification. They enlighten to a certain extent the possible mechanisms through which statins may enhance calcium accumulation in arterial wall, namely, by inhibition of vitamin K dependent proteins and functions involved in vascular protection.

KEYWORDS
coronary artery calcification, statins, vitamin K-dependent proteins

1 | INTRODUCTION

The statins (hydroxyl-methyl-glutaryl coenzyme A/HMG-CoA/reductase inhibitors) are widely used to treat patients at risk of or with an established atherosclerotic cardiovascular disease (ASCVD). Due to their lipid-lowering and pleiotropic effects, they have a proven efficacy in reducing major cardiovascular (CV) events and deaths. Currently, statins are routinely recommended as first line drugs for CV

Table 7: Lipid and Lipoprotein Effects of Various Nutrients and Botanicals

	Monograph Page #	TC	LDL-C	HDL-C	TG	LDL Particle Size	LDL Particle Number	Lp(a)
Berberine	175	↓↓	↓↓	↑	↓↓	ND	ND	ND
Bergamot	184	↓↓	↓↓	↑	↓	↑↑	ND	ND
CoQ10	203	↔	↔	↔	↔ / ↓	ND	ND	↓
Garlic	226	↓	↓	↔	↔	↔	↔	↔
Gugulipids	235	↔	↔	↔	↔	ND	ND	ND
Niacin	266	↓↓	↓↓↓	↑↑	↓↓↓	↑↑	↓	↓↓
Omega-3 EPA	275	↔	↔	↔	↓↓↓	↔	↓	ND
Omega-3 DHA	275		↑	↑		↑↑		
Policosanols	287	↑↓	↑↓	↑↓	↑↓	ND	ND	ND
RYR*	296	↓↓	↓↓	↑	↓	ND	ND	ND
Sterols/Stanols	282	↓	↓↓	↔	↓	↑	ND	ND
Tocotrienols	301	↑↓	↑↓	↑↓	↑↓	ND	ND	ND

* RYR data is complicated by the regulatory status of RYR, this measure assumes active monacolin K; see RYR monograph on page 296.

KEY

↑, ↑↑, ↑↑↑ Relative Increase and Data Reliability

↓, ↓↓, ↓↓↓ Relative Decrease and Data Reliability

↔ No Effect

↑↓ Data is too heterogeneous to suggest reliable increase or decrease

ND No Data

Table 8: Anti-Hypertensive Effects of Various Nutrients and Botanicals

		Monograph Page #	Systolic	Diastolic	Endothelial Function	Arterial Compliance
Arginine		168	↓	↓	↑↑	↑
Berberine (HCl)		175	↓	↔	↑	ND
Bergamot		184	ND	ND	↑	ND
Citrulline		171	↓	↓	↑	↑
Coenzyme Q10		203	↓	↓	↑	ND
Garlic†		226	↓↓	↓	↑↑	↑↑
Hawthorn		240	↓	↓	↔	ND
Alpha Lipoic Acid (LA)		245	↔	↔	↑	ND
Magnesium		254	↓	↓	↑	ND
Omega-3	DHA	269	↓↓	↓	↑	↑
	EPA	269	↓	↓	↑	↑
Probiotics		291	↓ / ↔*	↓ / ↔*	ND	ND
Vitamin D		312	↓	↓	↑	ND
Vitamin E		323	↑↓	↑↓	↑	↔
Vitamin K		335	ND	ND	ND	↑

* The beneficial data on probiotics and blood pressure mostly centers on fermented dairy products and may not be universal to all probiotic formulations, this data is preliminary

† Highly dependent on the type and dose of garlic preparation

KEY

↑, ↑↑, ↑↑↑ Relative Increase and Data Reliability

↓, ↓↓, ↓↓↓ Relative Decrease and Data Reliability

↔ No Effect

↑↓ Data is too heterogeneous to suggest reliable increase or decrease

ND No Data

THE TYPE OF MEDICINE YOU PRACTICE IS GREATLY INFLUENCED BY HOW YOU MEASURE RISK

THANK YOU