A Holistic Approach to Health, Immunity, and Post-COVID-19 Rehabilitation

The Role of Nutrition

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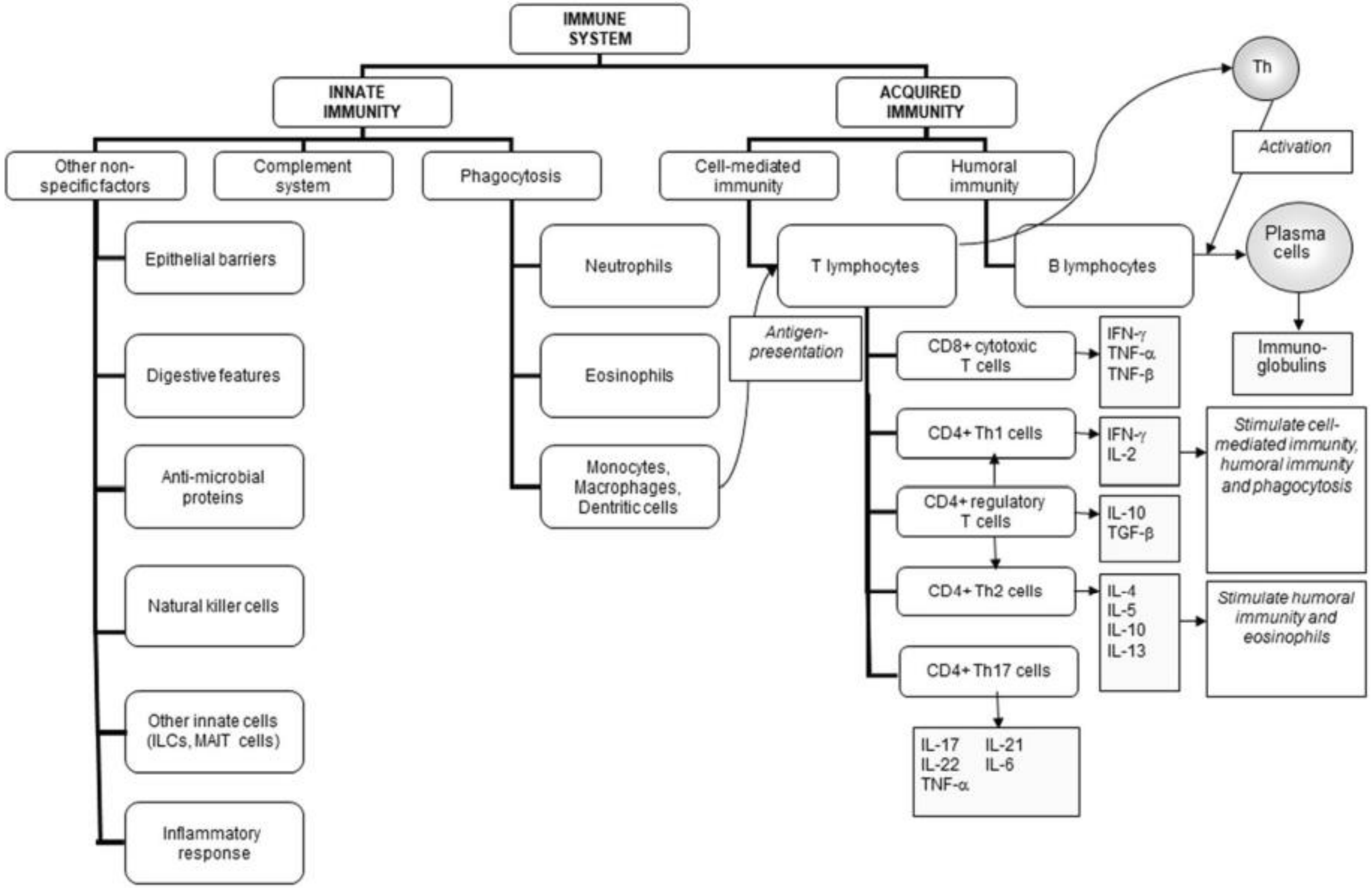
DISCLOSURE

There is no conflict of interest.

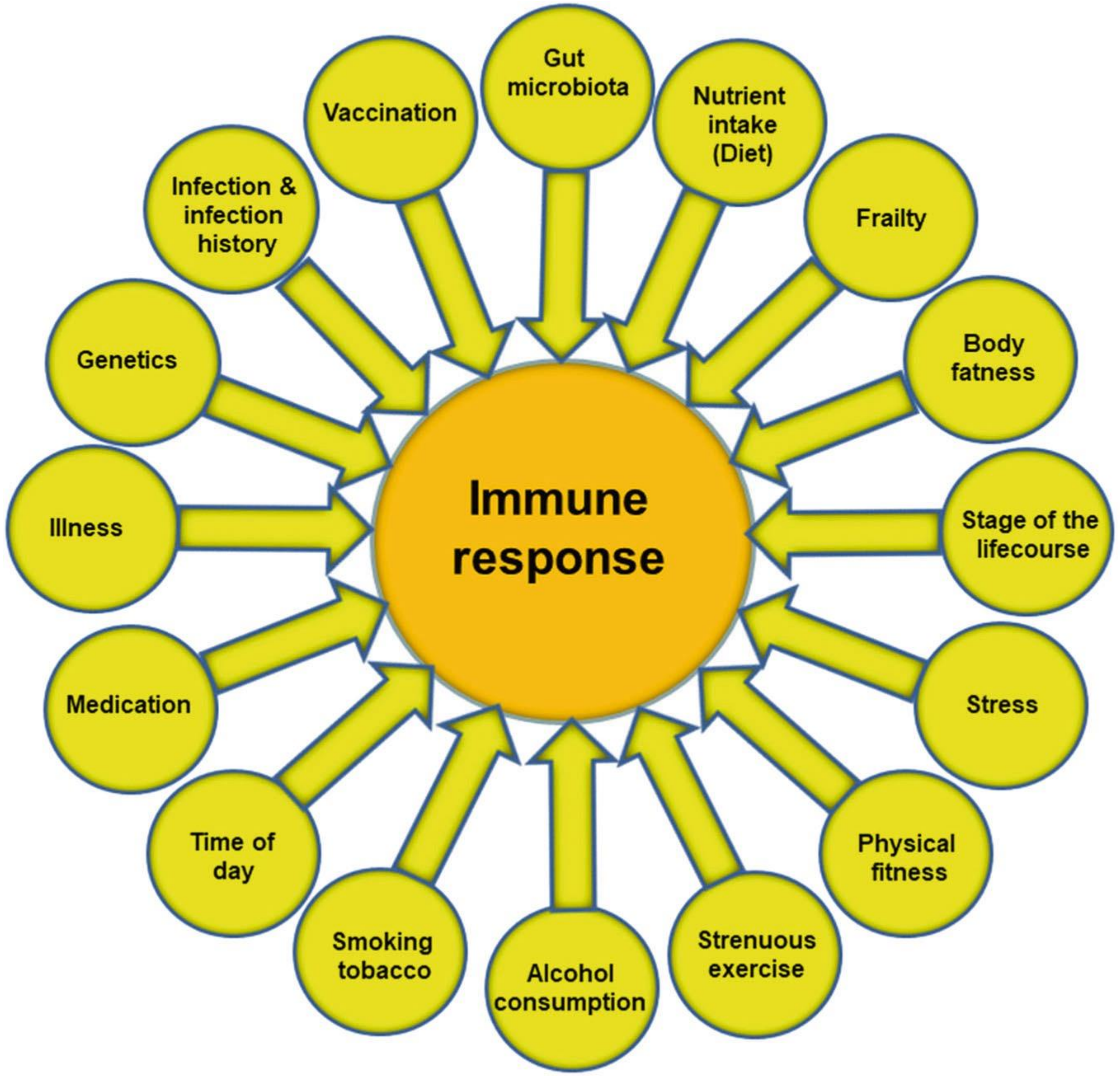
Components of Immune System

- Exclusion barrier
- Identification/recognition
- Elimination
- Memory



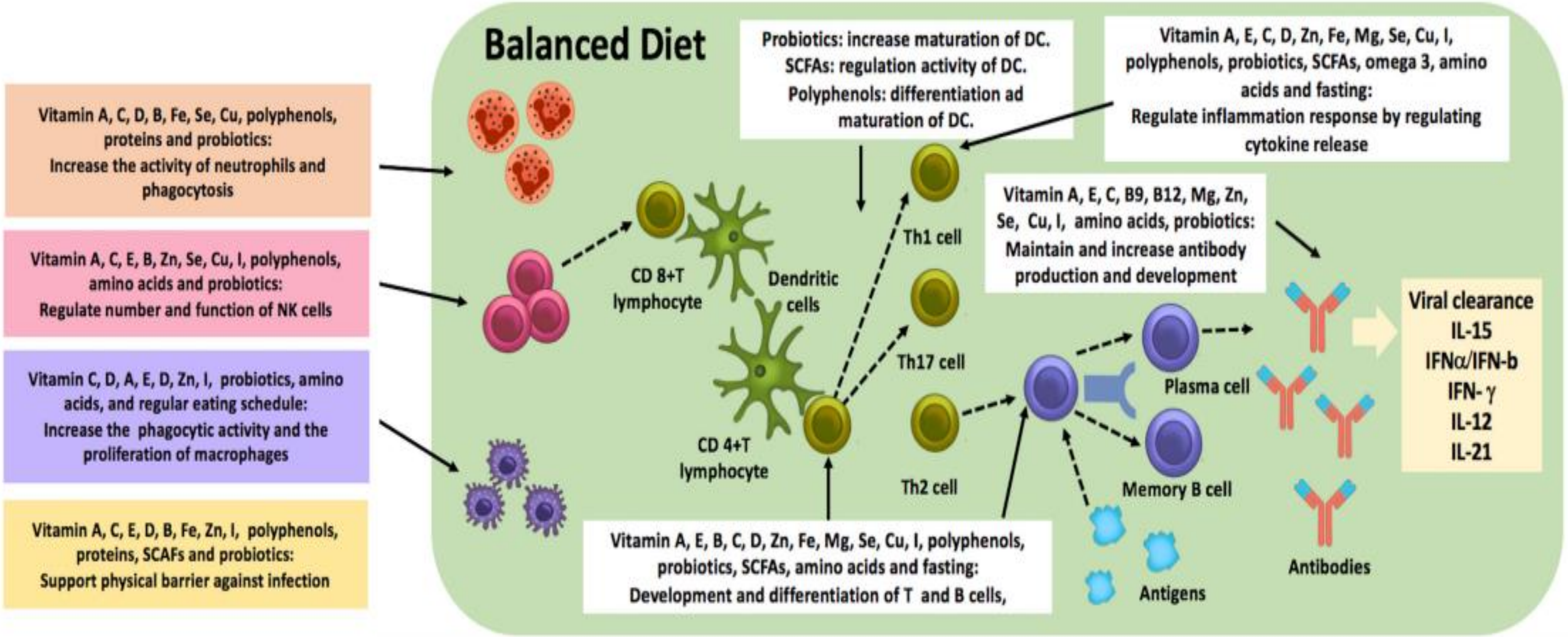
Calder C. European Journal of Clinical Nutrition. 2021;75:1309-1318

Factors Affecting the Immune Response



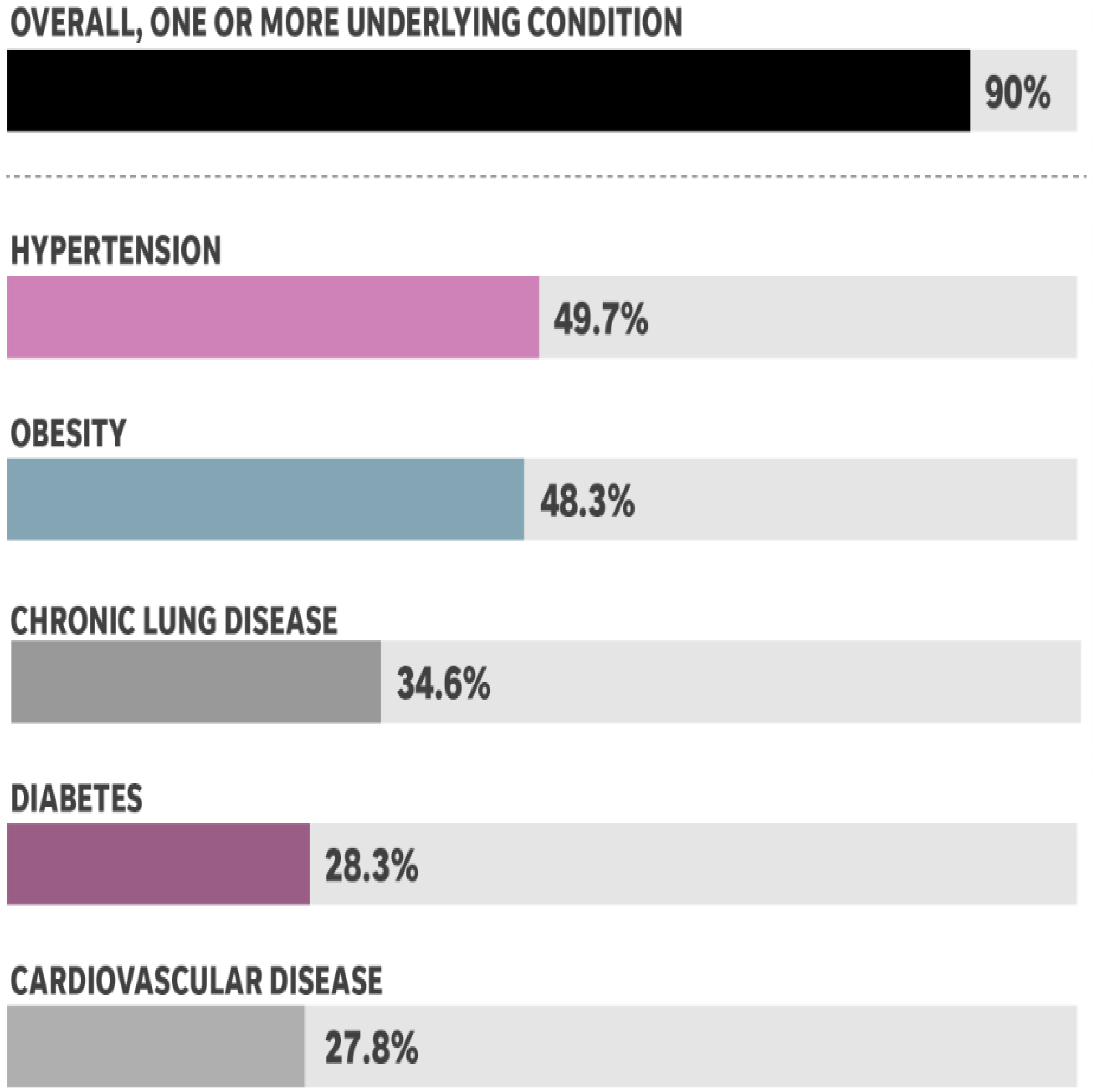
Calder C. European Journal of Clinical Nutrition. 2021;75:1309-1318

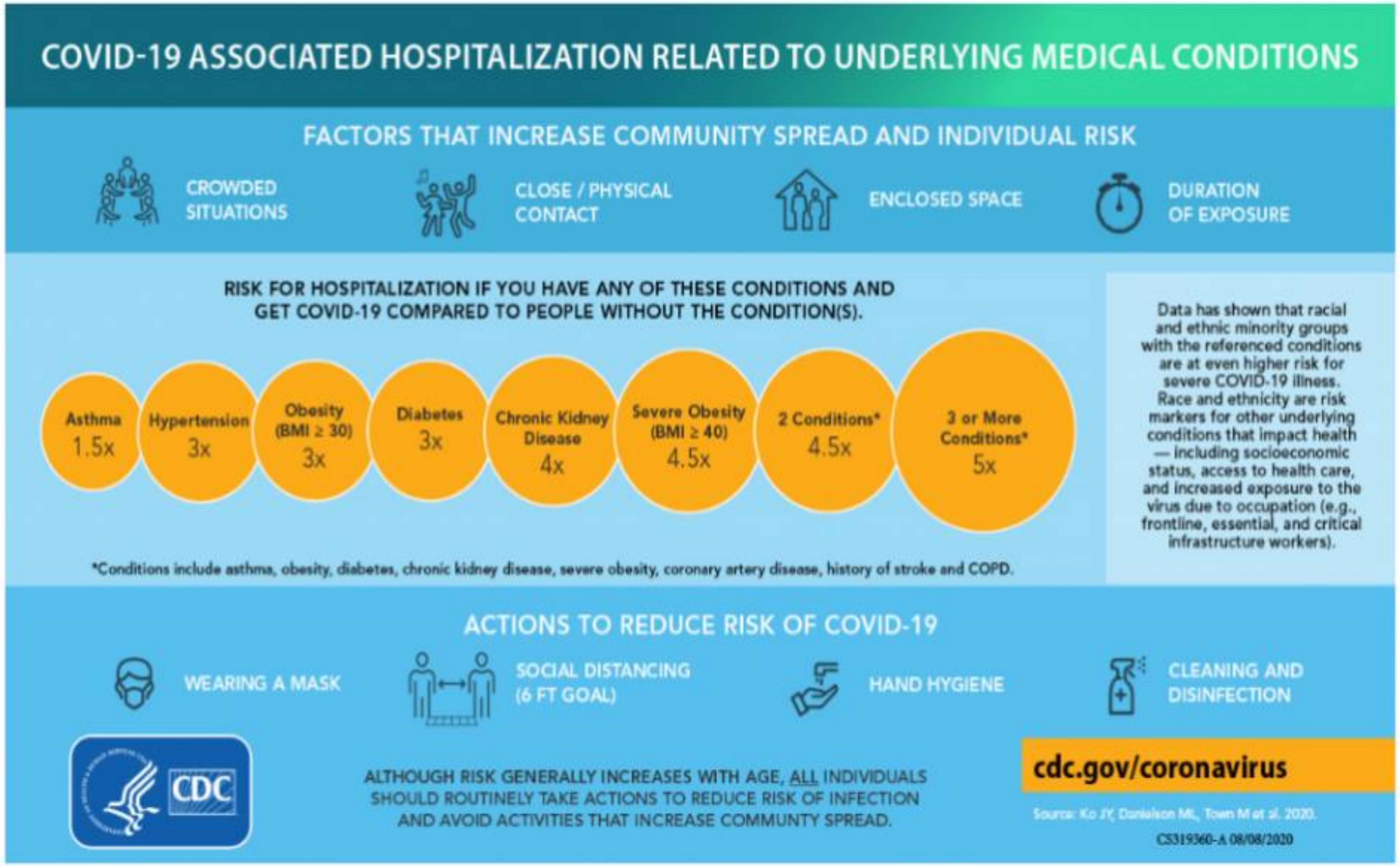
Important Role of Nutrition in Strengthening the Immune System



Chaari A, et al. Front Public Health. 2020;8:476.

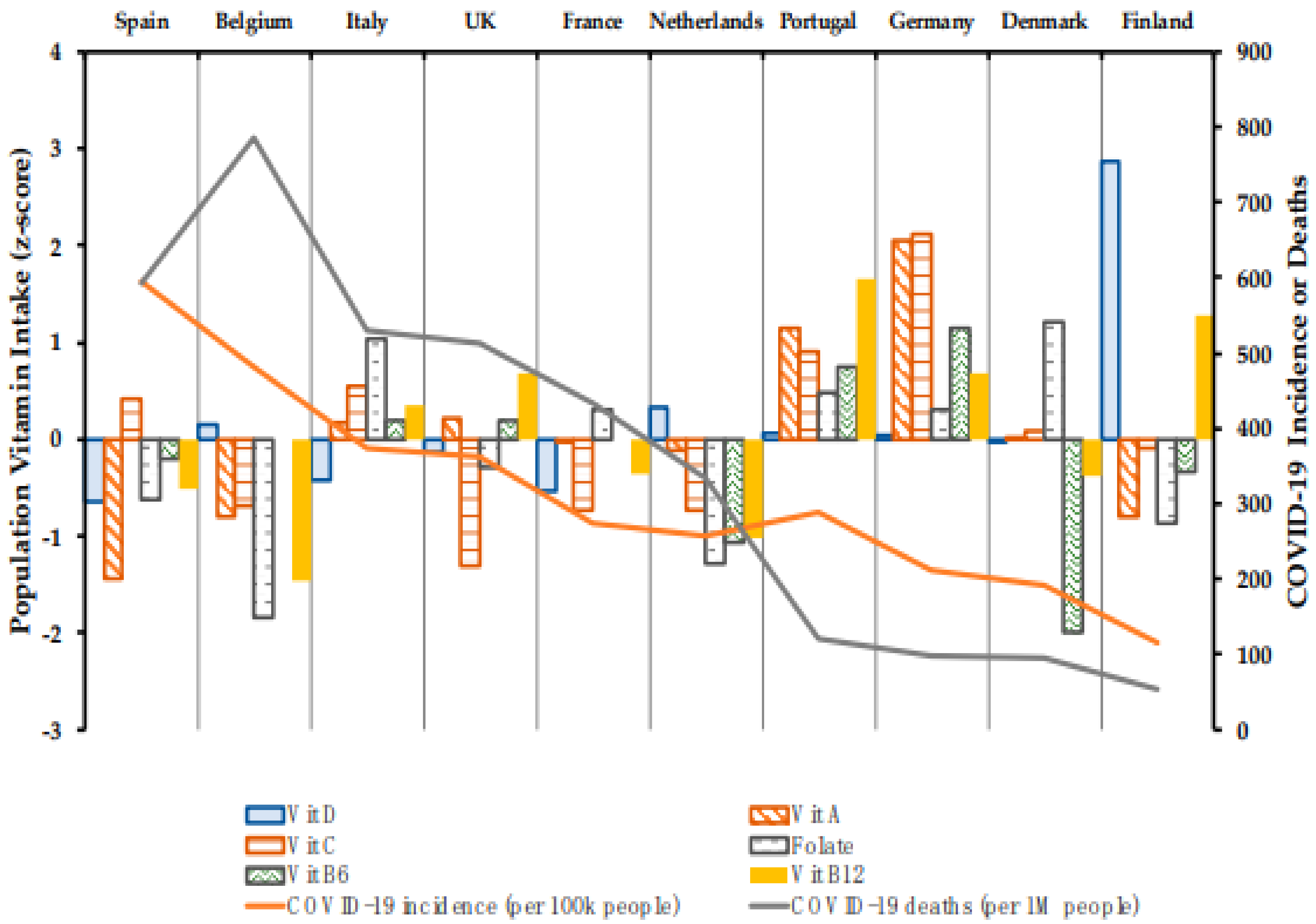
Malnutrition Related Conditions and the US Adult Patients with COVID-19



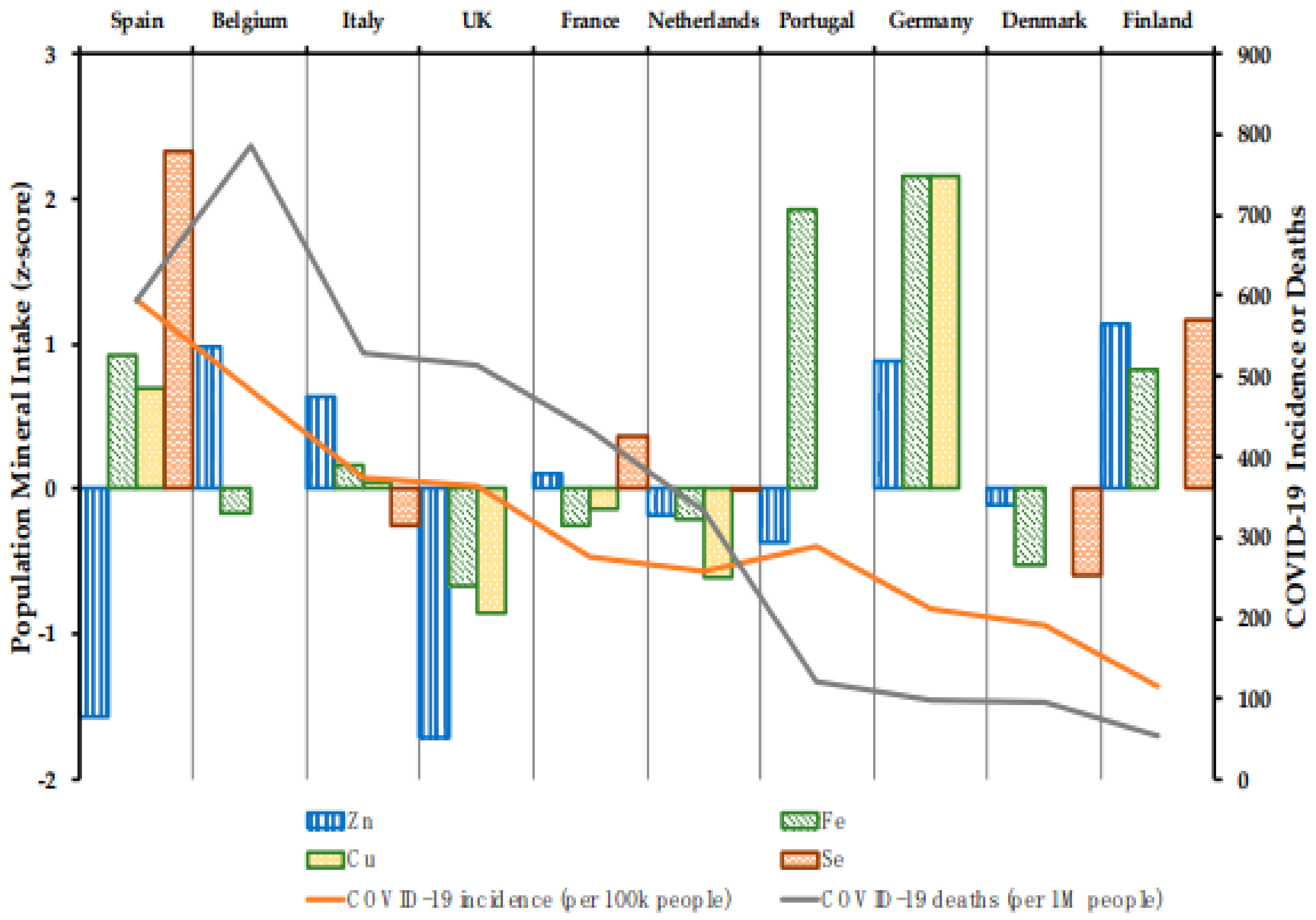


Karina Zaiets and Ramon Padilla.USA TODAY.2020.
CDC.2021. https://www.cdc.gov/aging/covid19-guidance.html

Association between 10 Critical Micronutrients Intake and Prevalence of COVID-19 in Europe



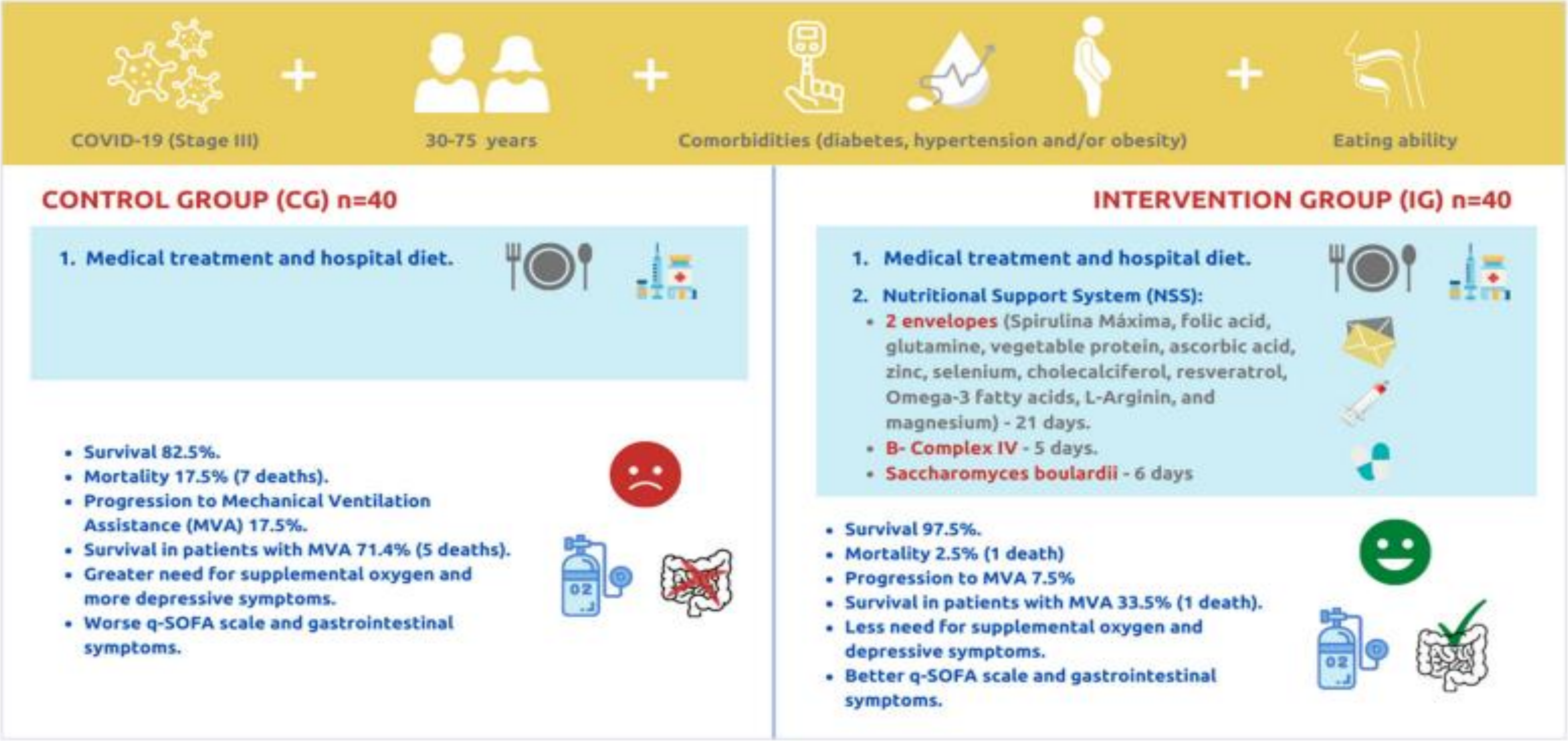
Population intake (z-score) of relevant **vitamins** and epidemiological COVID-19 features



Population intake (z-score) of relevant **minerals** and epidemiological COVID-19 features

Karina Zaiets and Ramon Padilla.USA TODAY.2020.
CDC.2021. https://www.cdc.gov/aging/covid19-guidance.html

The Nutritional Support System Increases Survival and Decreases Mortality in Severe Patients with COVID-19



Leal-Martínez F, et al. Int J Environ Res Public Health. 2022;19(3):1172.

Healthy Plant-based Diet and Risk & Severity of COVID-19

Study Design:

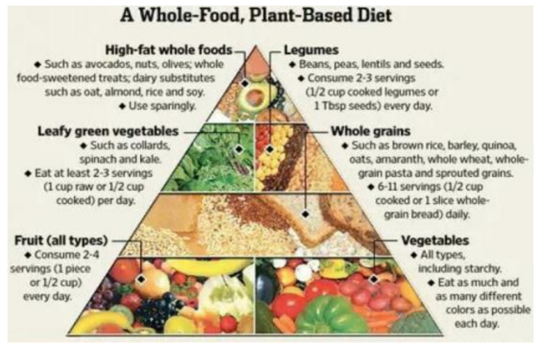
A prospective cohort study

Participants:

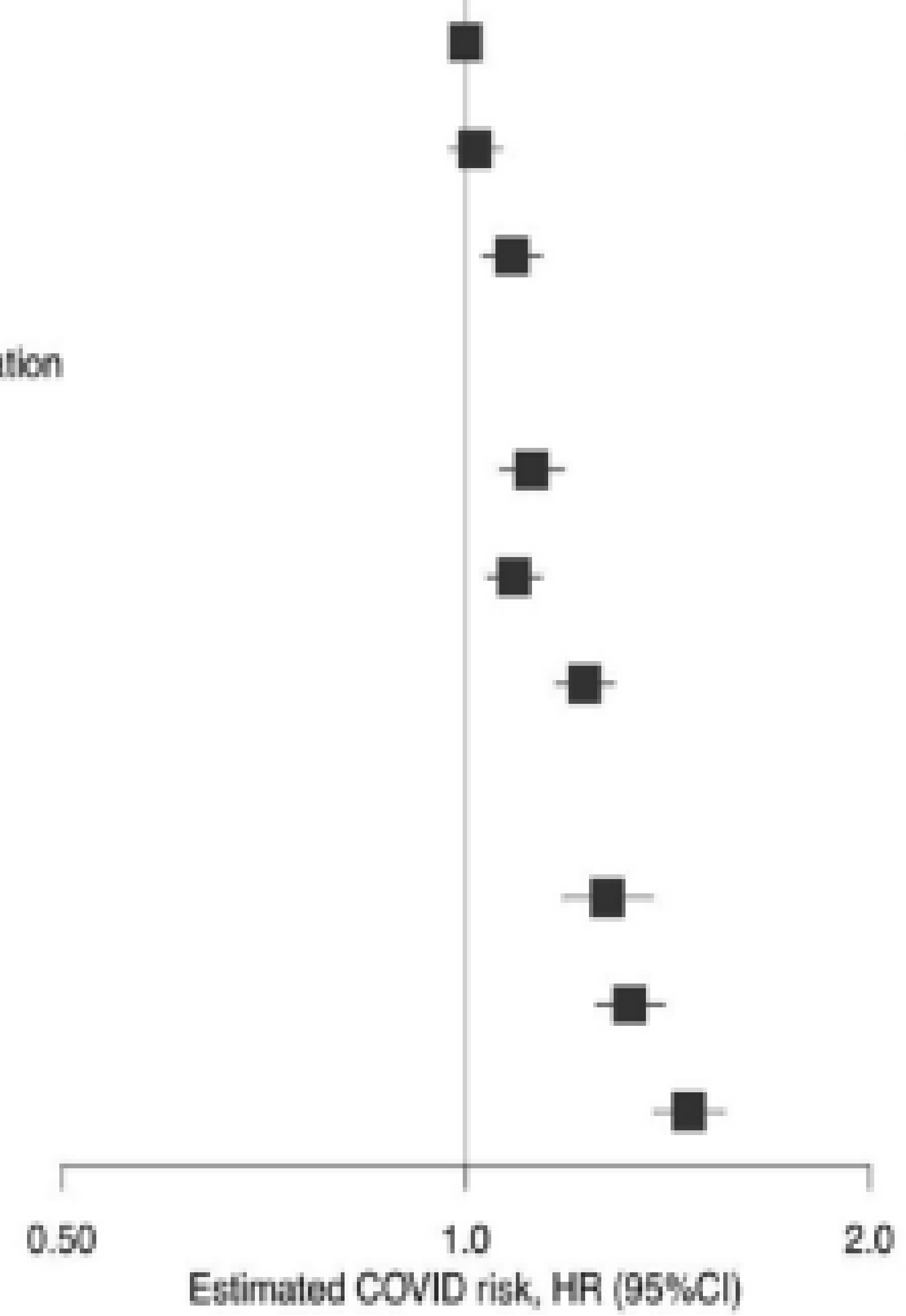
592,571 adults in the UK & US

What are the new findings:

- Higher healthy plant-based foods intake was associated with lower risk and severity of COVID-19.
- This association may be particularly evident among individuals living in areas with higher socioeconomic deprivation.



Subgroup	Total No. of participants	COVID–19 cases Person–Month	Adjusted HR [95% CI]	P Value
Low Socioeconomic Deprivation				
High hPDI	66,714	2,916 / 446,623	1.00[Reference]	
Intermediate hPDI	133,557	6,139 / 892,602	1.02[0.97–1.06]	0.481
Low hPDI	60,759	3,499 / 398,407	1.08[1.03–1.14]	0.002
Intermediate Socioeconomic Deprivation				
High hPDI	56,354	2,905 / 372,964	1.12[1.06–1.18]	<0.001
Intermediate hPDI	110,890	5,660 / 731,895	1.09[1.04–1.15]	<0.001
Low hPDI	56,143	3,810 / 359,896	1.23[1.17–1.29]	<0.001
High Socioeconomic Deprivation				
High hPDI	15,053	9,79 / 97,708	1.28[1.18–1.37]	<0.001
Intermediate hPDI	31,590	2,152 / 202,751	1.33[1.25–1.40]	<0.001
Low hPDI	20,752	1,787 / 126,752	1.47[1.38–1.56]	<0.001



hPDI, healthful Plant-Based Diet Index.

Merino J, et al. Gut. 202;70(11):2096-2104.
https://plantbasedhealthprofessionals.com/plant-based-diet-index.


Almond
(Prunus dulcis)


Ginseng
(Panax ginseng)


Purple Angelica
(Angelica atropurpurea)


Tarragon
(Artemisia dracunculus)


Basil
(Ocimum basilicum)


Black Pepper
(Piper nigrum)


Celery Seed
(Apium graveolens)


Cinnamon
(Cinnamomum verum)


Clove
(Syzygium aromaticum)


Coriander
(Coriandrum sativum)


Gamboge
(Garcinia mangostana)


Garlic
(Allium sativum)


Ginger
(Zingiber officinale)


Licorice
(Glycyrrhiza glabra)


Green Pepper
(Capsicum annuum)


Horseradish
(Armoracia rusticana)


Kokum
(Garcinia indica)


Onion
(Allium cepa)


Red Chili
(Capsicum annuum)


Sage
(Salvia officinalis)


Turmeric
(Curcuma longa)

Anti-Inflammatory and Immune-Enhancing Dietary Components

- Allicin - onions
- Catechins - green tea
- Cinnamaldehyde - cinnamon
- Curcumin - turmeric
- Lycopene - tomato products, watermelon
- Omega-3 fatty acids
- Polyphenols - tea, berries
- Resveratrol - grapes
- Sulforaphane and di-indolylmethane - broccoli/cruciferae

Kannappan R, et al. Mol Neurobiol.2011;44:142-159.
Cardozo L, Biochimie, 2013
Immune Boosting Nutrition: Uncovering New Lifestyle Behaviors

Mediterranean Diet and Risk & Severity of COVID-19

Study Design:

A prospective cohort study

Participants:

42,935 nurses and health professionals aged 55-99 years in the US

What are the new findings:

Adherence to a Mediterranean-style dietary pattern was inversely associated with risk of COVID-19 infection and its severity.

Table 1. Associations (ORs and 95% CIs) between dietary quality scores and **risk** of SARS-CoV-2 infection in the Nurses' Health Study II and Health Professionals Follow-up Study1

	Q1	Q4	*P*-trend[2]	Continuous[3]
AMED				
Cases/noncases,[4] *n*	495/3678	417/4690		1941/17,813
Model 1[5]	1 (ref.)	0.67 (0.58, 0.77)	<0.0001	0.85 (0.82, 0.90)
Model 2[6]	1 (ref.)	0.76 (0.65, 0.89)	0.0008	0.89 (0.84, 0.94)
Model 3[7]	1 (ref.)	0.78 (0.67, 0.92)	0.0032	0.90 (0.85, 0.95)
Model 3 + IPW[8]	1 (ref.)	0.79 (0.67, 0.94)	0.0091	0.90 (0.85, 0.96)

[1]AMED, alternative Mediterranean Diet; [2-8]Multivariable logistic regression models were used. IPW: probability of receiving a COVID-19 test. Q, quartile

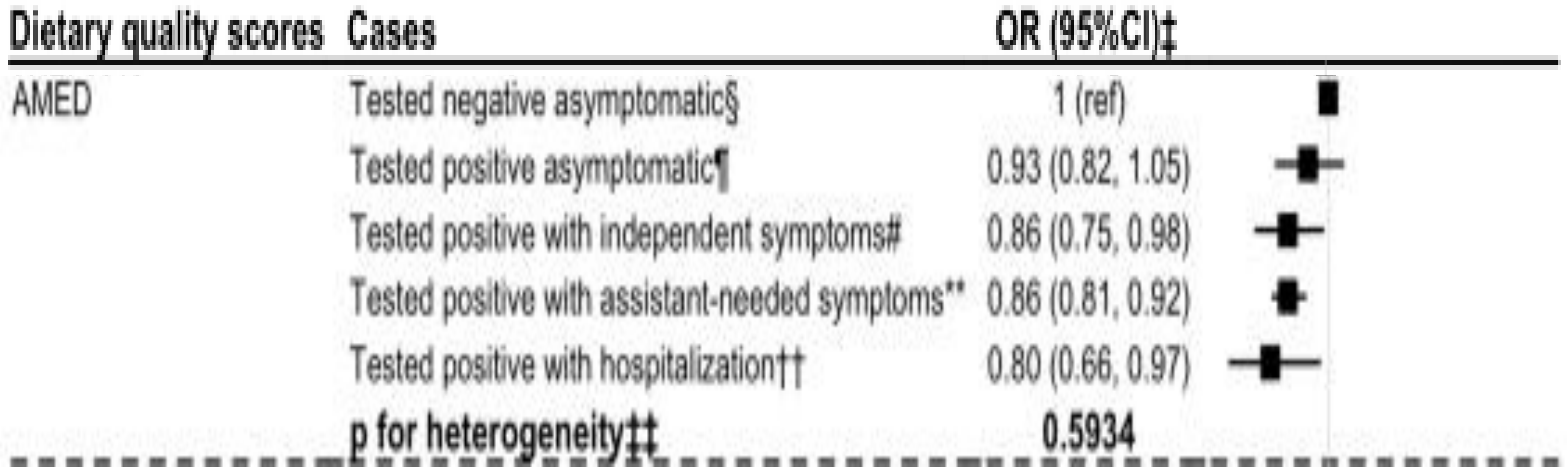
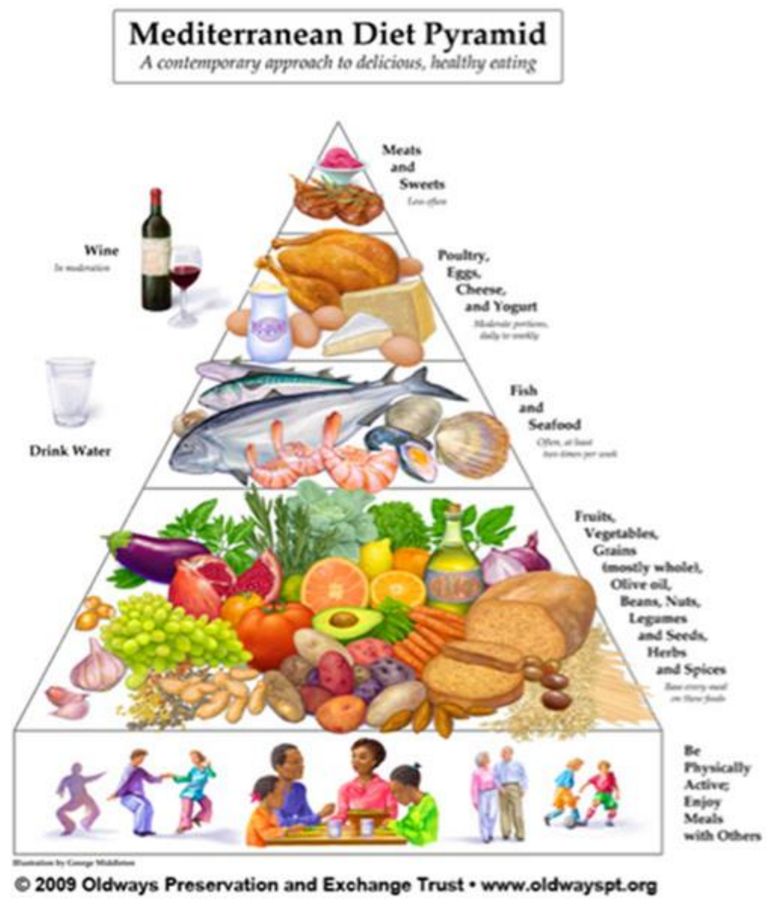
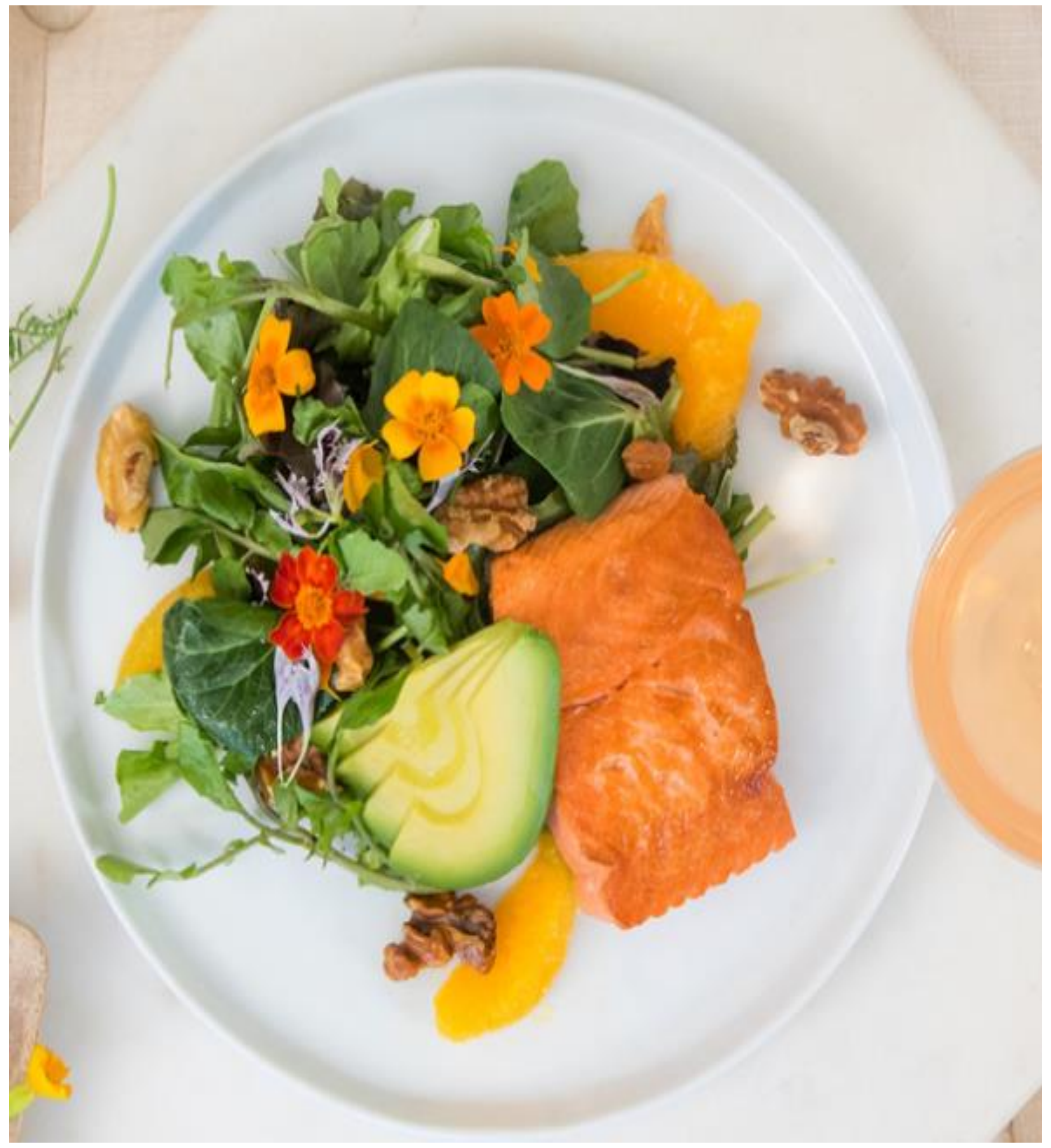


Figure 1. Associations (ORs and 95% CIs) between 1-SD increments of AMED scores and COVID-19 **severity** in the Nurses' Health Study II and Health Professionals Follow-up Study.



Yue Y, et al. Am J Clin Nutr.2022:nqac219.
Martínez-González MA, et al. Circ Res. 2019;124:779–798.

Which Salmon Do You Like?



Inappropriate cooking could destroy anti-inflammatory and immune-enhancing nutrients.

https://40aprons.com/blackened-salmon/
https://www.diabetesfoodhub.org/recipes/alaska-salmon-with-orange-and-watercress.html

Why Are the Results Different?

nutrients MDPI

Article

Positive Effects of Vitamin D Supplementation in Patients Hospitalized for COVID-19: A Randomized, Double-Blind, Placebo-Controlled Trial

Sophie De Niet [1,*], Mickaël Trémège [1], Monte Coffiner [1], Anne-Francoise Rousseau [2], Doriane Calmes [3], Anne-Noelle Frix [3], Fanny Gester [3], Muriel Delvaux [3], Anne-Francoise Dive [3], Elora Guglielmi [3], Monique Henket [3], Alicia Staderoli [3], Didier Maesen [4], Renaud Louis [3], Julien Guiot [3] and Etienne Cavalier [5]

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Citation: De Niet, S.; Trémège, M.; Coffiner, M.; Rousseau, A.-F.; Calmes, D.; Frix, A.-N.; Gester, F.; Delvaux, M.; Dive, A.-F.; Guglielmi, E.; et al. Positive Effects of Vitamin D Supplementation in Patients Hospitalized for COVID-19: A Randomized, Double-Blind, Placebo-Controlled Trial. *Nutrients* **2022**, *14*, 3048. https://doi.org/10.3390/nu14153048

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Abstract: Retrospective studies showed a relationship between vitamin D status and COVID-19 severity and mortality, with an inverse relation between SARS-CoV-2 positivity and circulating calcifediol levels. The objective of this pilot study was to investigate the effect of vitamin D supplementation on the length of hospital stay and clinical improvement in patients with vitamin D deficiency hospitalized with COVID-19. The study was randomized, double blind and placebo controlled. A total of 50 subjects were enrolled and received, in addition to the best available COVID therapy, either vitamin D (25,000 IU per day over 4 consecutive days, followed by 25,000 IU per week up to 6 weeks) or placebo. The length of hospital stay decreased significantly in the vitamin D group compared to the placebo group (4 days vs. 8 days; $p = 0.003$). At Day 7, a significantly lower percentage of patients were still hospitalized in the vitamin D group compared to the placebo group (19% vs. 54%; $p = 0.0161$), and none of the patients treated with vitamin D were hospitalized after 21 days compared to 14% of the patients treated with placebo. Vitamin D significantly reduced the duration of supplemental oxygen among the patients who needed it (4 days vs. 7 days in the placebo group; $p = 0.012$) and significantly improved the clinical recovery of the patients, as assessed by the WHO scale ($p = 0.0048$). In conclusion, this study demonstrated that the clinical outcome of COVID-19 patients requiring hospitalization was improved by administration of vitamin D.

Keywords: vitamin D; cholecalciferol; calcifediol; COVID-19; SARS-CoV-2; hospitalization

JAMA | **Original Investigation**

Effect of a Single High Dose of Vitamin D_3 on Hospital Length of Stay in Patients With Moderate to Severe COVID-19
A Randomized Clinical Trial

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Editorial page 1047
Supplemental content

IMPORTANCE The efficacy of vitamin D_3 supplementation in coronavirus disease 2019 (COVID-19) remains unclear.

OBJECTIVE To investigate the effect of a single high dose of vitamin D_3 on hospital length of stay in patients with COVID-19.

DESIGN, SETTING, AND PARTICIPANTS This was a multicenter, double-blind, randomized, placebo-controlled trial conducted in 2 sites in Sao Paulo, Brazil. The study included 240 hospitalized patients with COVID-19 who were moderately to severely ill at the time of enrollment from June 2, 2020, to August 27, 2020. The final follow-up was on October 7, 2020.

INTERVENTIONS Patients were randomly assigned to receive a single oral dose of 200 000 IU of vitamin D_3 (n = 120) or placebo (n = 120).

MAIN OUTCOMES AND MEASURES The primary outcome was length of stay, defined as the time from the date of randomization to hospital discharge. Prespecified secondary outcomes included mortality during hospitalization; the number of patients admitted to the intensive care unit; the number of patients who required mechanical ventilation and the duration of mechanical ventilation; and serum levels of 25-hydroxyvitamin D, total calcium, creatinine, and C-reactive protein.

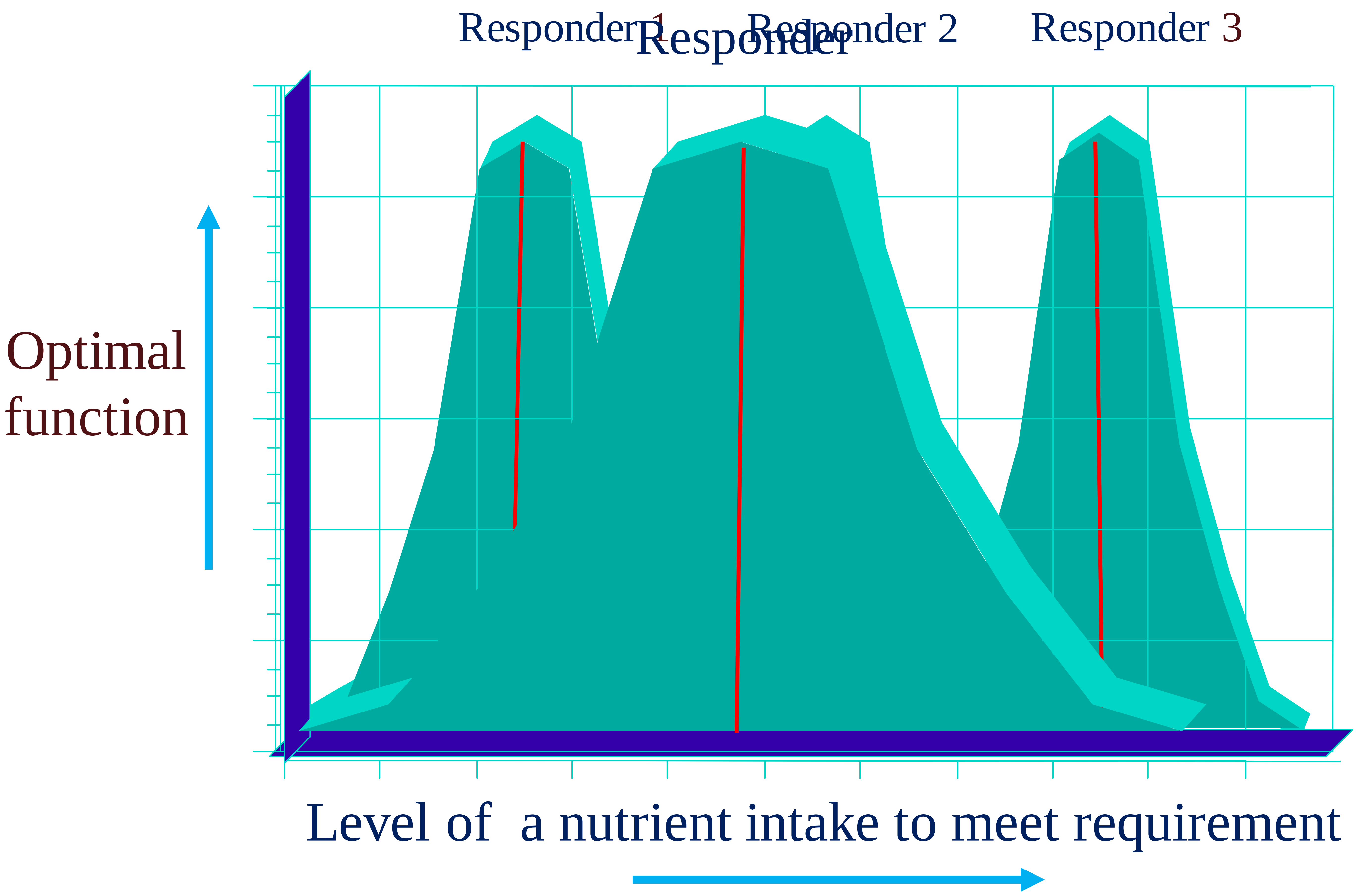
RESULTS Of 240 randomized patients, 237 were included in the primary analysis (mean [SD] age, 56.2 [14.4] years; 104 [43.9%] women; mean [SD] baseline 25-hydroxyvitamin D level, 20.9 [9.2] ng/mL). Median (interquartile range) length of stay was not significantly different between the vitamin D_3 (7.0 [4.0-10.0] days) and placebo groups (7.0 [5.0-13.0] days) (log-rank $P = .59$; unadjusted hazard ratio for hospital discharge, 1.07 [95% CI, 0.82-1.39]; $P = .62$). The difference between the vitamin D_3 group and the placebo group was not significant for in-hospital mortality (7.6% vs 5.1%; difference, 2.5% [95% CI, −4.1% to 9.2%]; $P = .43$), admission to the intensive care unit (16.0% vs 21.2%; difference, −5.2% [95% CI, −15.1% to 4.7%]; $P = .30$), or need for mechanical ventilation (7.6% vs 14.4%; difference, −6.8% [95% CI, −15.1% to 1.2%]; $P = .09$). Mean serum levels of 25-hydroxyvitamin D significantly increased after a single dose of vitamin D_3 vs placebo (44.4 ng/mL vs 19.8 ng/mL; difference, 24.1 ng/mL [95% CI, 19.5-28.7]; $P < .001$). There were no adverse events, but an episode of vomiting was associated with the intervention.

CONCLUSIONS AND RELEVANCE Among hospitalized patients with COVID-19, a single high dose of vitamin D_3, compared with placebo, did not significantly reduce hospital length of stay. The findings do not support the use of a high dose of vitamin D_3 for treatment of moderate to severe COVID-19.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT04449718

Author Affiliations: Author affiliations are listed at the end of this article.

Personalized Nutrition
Identifying Metabolic Individuality



Why?

Gene Polymorphisms

Gut bacteria

Health Status

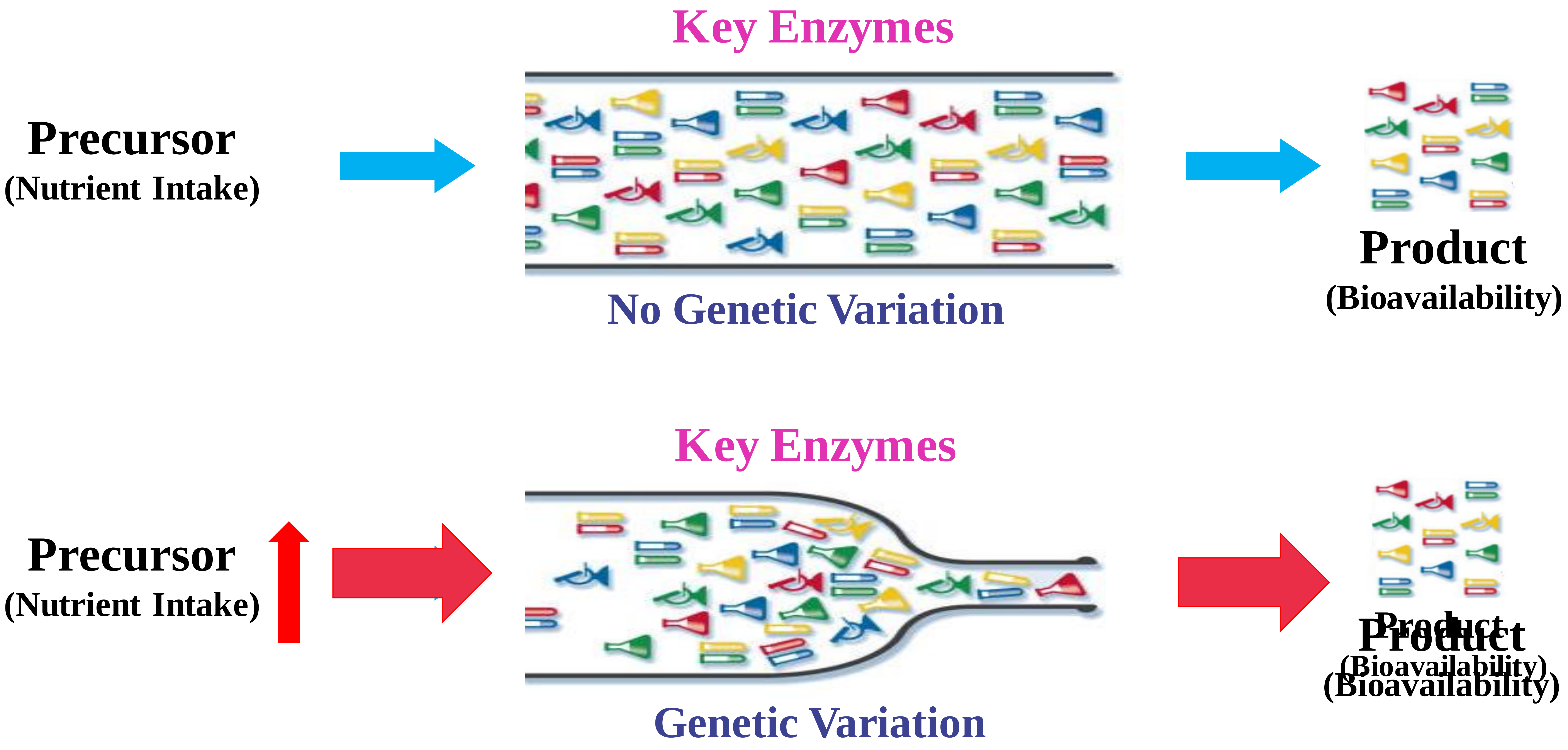
Gender

Age

...

Da-Costa KA, et al. FASEB J. 2014;28(7):2970-8.
Zeisel SH, et al. Adv Nutr. 2018,9(1):58-60.

Personalized Nutrition
Genetic variation can create metabolic inefficiency.



Zeisel SH, et al. Adv Nutr. 2018,9(1):58-60.

Genetic Variants Influence Essential Nutrients' Bioavailability Associated with the Healthy Immune System

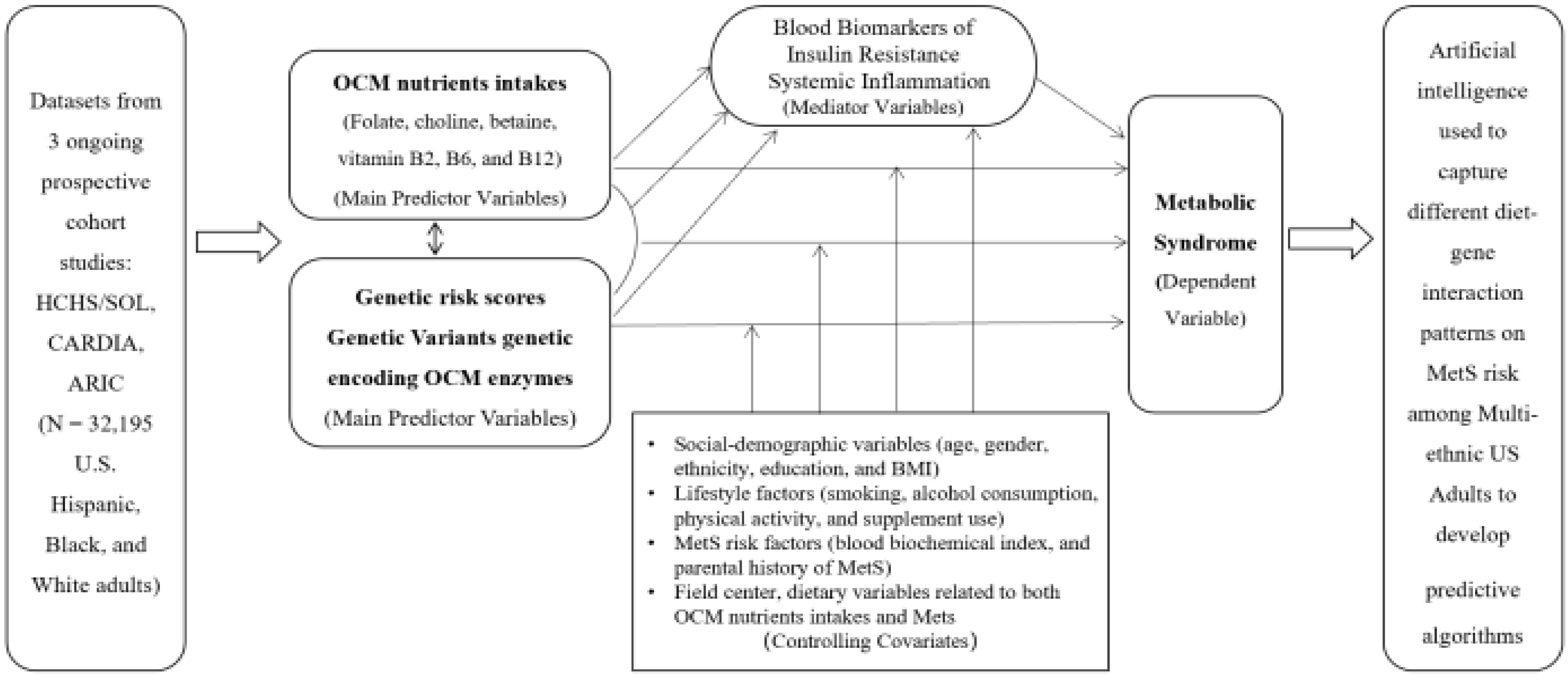
Table 2. List of nutrients with contribution to the functioning of the immune system endorsed by the European Food Safety Authority.

Micronutrient [EFSA Cite]	EFSA DRVs	SNP Affecting Status (Gene)	Associated Trait	Risk Allele	Population Based Discovery	Cite
Vitamin D [3,4]	AI: 15 µg/day UL: 100 µg/day	rs7041 (GC)	↑ vitamin D-binding protein ↓ Serum Vitamin D **	C C	1380 European 8541 African American or Afro-Caribbean	[16,17]
		rs1155563 (GC)	↓ Serum Vitamin D	C	761 European	[18]
		rs12785878 (NADSYN1)	Vitamin D Deficiency	C	16125 European	[19]
Vitamin A (and ß-carotene) [3]	PRI: 650 (w)/50 (m) µg RE/day UL: 3000 µg RE/day	rs6564851 (BCO1)	↓ Serum Carotenoids	T	1191 European	[20]
Vitamin C [3,4]	PRI: 95 (w)/110 (m) mg/day UL: ND	rs33972313 (SLC23A1)	↓ Serum Vitamin C	A	9234 European	[21]
Folate [5]	PRI: 330 µg DFE/day UL: 1000 µg DFE /day	rs1801133 (MTHFR)	↓ Folic acid in red blood cells	T	2232 European	[22]
Vitamin B_6 [5]	AI: 1.6 (w)/1.7 (m) mg/day UL: 25 mg/day	rs4654748 (NBPF3)	↓ Serum vitamin B_6	C	2934 European	[23]
Vitamin B_{12} [5]	PRI: 4 µg/day UL: ND	rs11254363 (CUBN) rs526934 (TCN1) rs602662 (FUT2)	↓ Serum vitamin B_{12} ↓ Serum vitamin B_{12} ↓ Serum vitamin B_{12}	A G G	2934 European 2934 European 2934 European	[23]
			↓ Serum vitamin B_{12}	G	1001 South Asian	[24]
Zinc [6]	PRI*: 10.1 (w)/12.9 (m) mg/day UL: 25 mg/day	rs2120019 (PPCDC)	↓ Serum Zinc	C	2603 European	[25]

SNP, Single Nucleotide Polymorphism; AI, Average Intake; PRI, Population Reference Intake; UL, Tolerable Upper Intake Level; RE, Retinol Equivalents; ND, Not defined; DFE, Dietary Folate Equivalent.

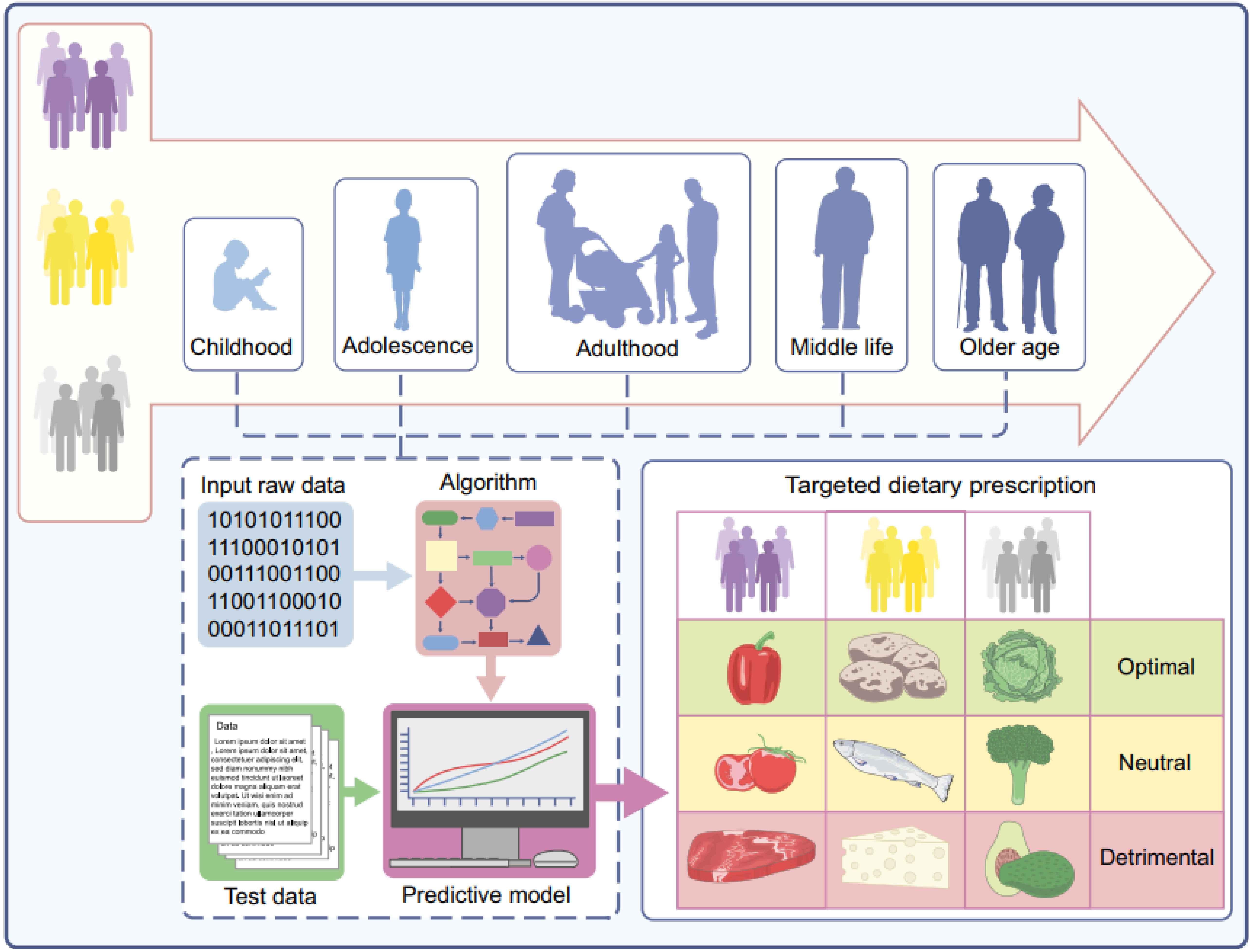
Galmés S, et al. Nutrients. 2020 Sep 8;12(9):2738.

One-carbon Metabolism Nutrients Intakes and Genetic Susceptibility on Risk of Metabolic Syndrome among Multi-ethnic US Adults



This research project aligns with the highlighted research focus:
“Precision Nutrition” in 2020–2030 Strategic Plan for NIH Nutrition Research.

A Framework for Implementing Personalized Nutrition in Heathy Immunity Promotion/Disease Prevention



Merino J, et al. Diabetologia.2022;65(11):1839-1848..

Thank you!

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