Plant Sources of Dietary Nitrate as Essential Nutrients

PRESENTED BY

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Presentation Outline

- The conundrum presented by potential health risks and benefits of dietary nitrate and nitrite
- Consideration of plant food-origin nitrate and nitrite as conditionally essential nutrients
- Brief review of dietary and physiological sources of biologically active nitrogen oxides (NO_x) and their functions
- Methemoglobinema risk, sodium nitrite salts and the specter of abuse
- Future directions

The Origins of Dietary Nitrogen

- Nitrate is an essential plant nutrient and a ubiquitous food component
- Plants utilize nitrate to serve as substrates for endogenous amino acid production
- Bacteria and lightning serve as penultimate source of nitrate and nitrite
  - "Fixation" of atmospheric nitrogen by soil bacteria
  - Ammonification, assimilation, nitrification, denitrification are other components of the nitrogen cycle
- Lightning oxidizes atmospheric nitrogen, combines with water to form nitrous acid, rainfall deposits in soil and converted to nitrate

Human Nitrate Intake Levels

Global dietary nitrate intake shows substantial regional variation, reflecting differences in dietary patterns and food sources. This heterogeneity provides natural experiments for understanding dose-response relationships.

Regional Intakes:

- Denmark: 67 mg/day (IQR: 36-105)
- Australia: 65-129 mg/day (range)
- China: 486 mg/day (95% CI: 442-530)
- Japan: >1100 mg/day (95% CI: 980-1220)

Primary sources cited in: Babateen AM, et al. Assessment of dietary nitrate intake in humans: a systematic review. Am J Clin Nutr. 2018;108:878-888. PMID: 29982309

Dietary Sources of Nitrate Exposure

- The majority (60-80%) of dietary nitrate intake comes from vegetables (60-250 mg/day), while drinking water contributes 15-20% (5-50 mg/day), and processed meats account for 5-10% (2-20 mg/day), with other sources providing about 5%.

- Vegetable-derived nitrate exposure consistent with adherence to dietary recommendations (e.g., More Matters®, DASH, AICR) would increase this contribution to ~90%.

Babateen AM, et al. Assessment of dietary nitrate intake in humans: a systematic review. Am J Clin Nutr. 2018;108:878-888. PMID: 29982309

Dietary Sources of Nitrite Exposure

- Dietary nitrite intake primarily comes from processed meats (39-67% of total; 0.3-0.9 mg/day) and vegetables (16-34%; 0.1-0.3 mg/day), with additional exposure from endogenous conversion of dietary nitrate to nitrite in saliva, which can contribute significantly more nitrite than direct dietary sources.
- The average total daily nitrite intake is estimated at 0.7-1.6 mg/day for a typical adult diet.

Babateen AM, et al. Assessment of dietary nitrate intake in humans: a systematic review. Am J Clin Nutr. 2018;108:878-888. PMID: 29982309

Dietary Nitrate: Conundrums and Controversies

Concerns about nitrate and nitrite consumption exist due to:

- legally-mandated additives to processed meats (along with vitamin C or erythorbic acid)

- potential for increased risk of certain GI cancers in adults consuming **processed meats**

American Institute for Cancer Research

- potential health effects of nitrate in drinking water, particularly **methemoglobinemia in infants**

Hord, NG, Tang, YP and Bryan NS (2009) Am J Clin Nutr ;90:1–10

Regulatory Limits on Nitrate and Nitrite Exposure in Drinking Water

- World Health Organization (WHO): 3.7 mg nitrate per kg body weight and 0.07 mg nitrite per kg body weight per day, equivalent to 222 mg nitrate and 4.2 mg nitrite per day, respectively, for a 60-kg adult.[1]
- U.S. Environmental Protection Agency (EPA): Maximum Contaminant Level for nitrate of 44 mg/L or 10 mg nitrate-nitrogen/L.
- The European Union limit for nitrate in water is 50 mg/L.

[1]The WHO's ADI =no-observed-adverse-effect level (NOAEL) of 370 mg/kg body weight/day for methemoglobinaemia in rats, divided by uncertainty factor of 100 applied to account for interspecies and intraspecies variations.

Health Concern: Methemoglobinemia or “Blue Baby” Syndrome

- EPA level was set based on the nitrate concentration in feces-contaminated well water that caused methemoglobinemia in babies.
- The methemoglobinemia was attributed to excess nitrate in well water.
- It is now known that nitrite-mediated oxidation of ferric iron in oxyhemoglobin leads methemoglobin formation and potentially to hypoxia and cyanosis (Fan et al., 1996).
- These observations were likely due to ***bacterial infection-induced iNOS expression*** leading to high NO concentrations and subsequent nitrite-mediated methemoglobinemia.

American Academy of Pediatrics Position: Infant methemoglobinemia

- Breastfed infants are not at risk of nitrate poisoning from mothers who ingest water with high nitrate content (up to 100 ppm nitrate-nitrogen), because nitrate concentration does not increase significantly in the milk.
- Well baby visits should include screening for nitrate exposure via well water.
- Infants should not be exposed to high nitrate vegetables until at least 3 months of age.

Current Nitrite Public Health Issue:

- Surveillance data and publications provide evidence of growing use of sodium nitrite as a poison to attempt suicide.
- The National Poison Data System (NPDS) data from 2017 to 2020 has demonstrated a yearly increase in the number of reported exposures to the sodium nitrite, and among forty-seven cases, the **reported mortality was 30%.**
- Historically, low doses of sodium nitrite (<100 mg/day) have been used in cardiovascular therapeutics, especially blood pressure lowering and heart failure.
- At high doses, sodium nitrite ingestion can cause significant **methemoglobinemia** that can be fatal without antidotal treatment.

Nitrate Use in Foods: A 5000 year history

- In the 19th century it was discovered that the mechanism underlying food preservation was actually the conversion of nitrate to nitrite by bacteria (Binkerd & Kolari, Food Cosmet Toxicol, 1975).
- Nitrite in meat-
  - greatly delays the development of botulinum toxin,
  - develops cured meat flavor and color,
  - retards development of rancidity during storage,
  - inhibits development of warmed-over flavor and preserves flavors of spice and smoke (Binkerd & Kolari, Food Cosmet Toxicol, 1975).

Hormetic effects of nitrate and nitrite

"***Hormesis is a term used by toxicologists to refer to a biphasic dose response to an environmental agent characterized by a low dose stimulation or beneficial effect and a high dose inhibitory or toxic effect.***"
(Mattson, MP Ageing Res Rev. 2008 Jan; 7(1): 1–7)

- Inorganic nitrate and nitrite produce cardiovascular benefits at low (dietary/ food-based) concentrations but negative physiological effects at high concentrations.
- NIH-funded work by Seals (U Colorado) and Gladwin (U Pittsburgh) provide evidence of physiological benefits of nitrite (~80-120 mg/day) for lowered systolic, diastolic, and mean arterial pressures, as well as improved motor and cognitive performance.

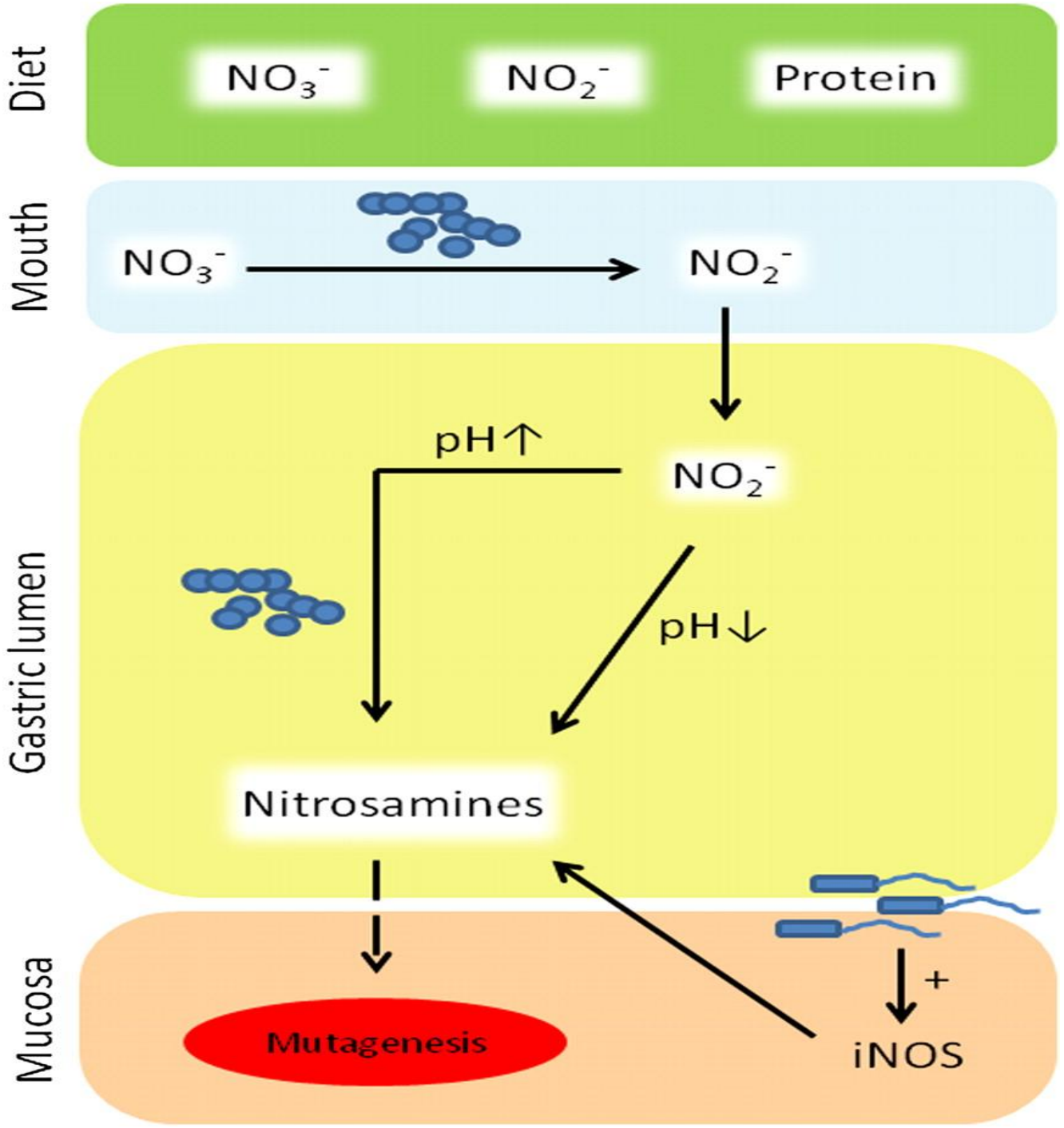
Note that none of these sodium nitrite interventions resulted in methemoglobinemia.

Rossman et al. (2021) Hypertension.Apr;77(4):1212-1222; DeVan AE et al. (2016) J Appl Physiol;120(4):416-25; Justice, JN et al. (2015) J Appl Physiol, Jan 15;118(2):163-9.; Hughan KS et al. (2020) Hypertension, Sep;76(3):866-874.

Nitrate and Nitrite in Processed Meats

- U.S. FDA and U.S.D.A. regulate nitrate and nitrite use in meat products (21 CFR and 9 CFR, respectively) related to risk of gastrointestinal cancer.
- USDA mandates the addition of either 550 ppm ascorbic acid or erythorbic acid to decrease potential to form nitrosamines in storage and cooking.

Gastric Nitrosamine Formation



Lundberg JO
Weitzberg E

Gut doi:10.1136/
gutjnl-2011-301649

Recent advances in basic science
Biology of nitrogen oxides in the gastrointestinal tract

Health Concern: Cured and Processed Meat Consumption and Gastrointestinal Cancer Risk

- A systematic review indicated that up to ’500 g (’18 oz) weekly of red meat can be consumed without cancer risk.
- AICR panelists could not determine a safe consumption level for processed meat.
- Colorectal cancer risk (summary estimate of relative risk per 50 g/d: 1.21; 95% CI: 1.04, 1.42) was shown to increase with any consumption of processed meats based on a meta-analysis of cohort studies.

Nitrate Intake Source and Cancer Risk

- Consumption of red and processed meats is associated with an increased risk of certain types of cancer and chronic obstructive pulmonary disease (Sanatrelli et al., 2008; Jiang et al., 2008).
- The American Institute for Cancer Research's Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective contains the following recommendation:

"***Limit consumption of red meats (such as beef, pork and lamb) and avoid processed meats.***"

Work Group Summary: Drinking-Water Nitrate and Human Health

(Ward, MH et al., Int. J. Environ. Res. Public Health 2018, 15, 1557)

- Risk of numerous health conditions are consistently associated with drinking-water nitrate concentrations, some at concentrations lower than regulatory limits.

- A recent review identified the strongest evidence for a relationship between drinking water nitrate ingestion and adverse health outcomes (besides **methemoglobinemia**) are for **colorectal cancer, thyroid disease, and neural tube defects**.

- Future studies of these and other health outcomes should include improved **exposure assessment** and accurate characterization of **individual factors that affect endogenous nitrosation**.

….the food form of nitrate exposure affects the metabolic disposition and health effects as well….

World Health Organization Acceptable Daily Intake Limits:

Maximum Limits or Minimum Intake Recommendations for Nitrate and Nitrite?

WHO Acceptable Daily Intake	ADI per 60-kg adult	Nitrate concentration to achieve putative blood pressure lowering
Nitrate (0-3.7mg/kg/d)	0-222 mg (0-3.6 mmol)	3.5 mmol (hypertensive individuals)[1] 4.0 mmol (normotensive individuals)[2]
Nitrite (0-.07mg/kg/d)	0-4.2 mg (0-0.09 mmol)	

[1] Ghosh et al. (2013) Hypertension 61: 1091-1102.

[2] Kapil et al. (2010) Hypertension 56: 274-281.

[3] The WHO's ADI =no-observed-adverse-effect level (NOAEL) of 370 mg/kg body weight/day for methemoglobinaemia in rats, divided by uncertainty factor of 100 applied to account for interspecies and intraspecies variations.

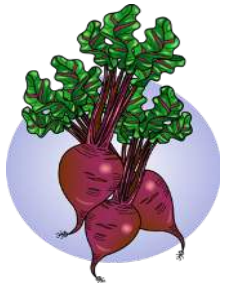
WHO Acceptable Daily Intake	ADI per 60-kg adult	Nitrate concentration to achieve putative blood pressure lowering
Nitrate (0-3.7mg/kg/d)	0-222 mg (0-3.6 mmol)	3.5 mmol (hypertensive individuals)[1] 4.0 mmol (normotensive individuals)[2] → ~250 mg nitrate
Nitrite (0-.07mg/kg/d)	0-4.2 mg (0-0.09 mmol)	

[1] Ghosh et al. (2013) Hypertension 61: 1091-1102.

[2] Kapil et al. (2010) Hypertension 56: 274-281.

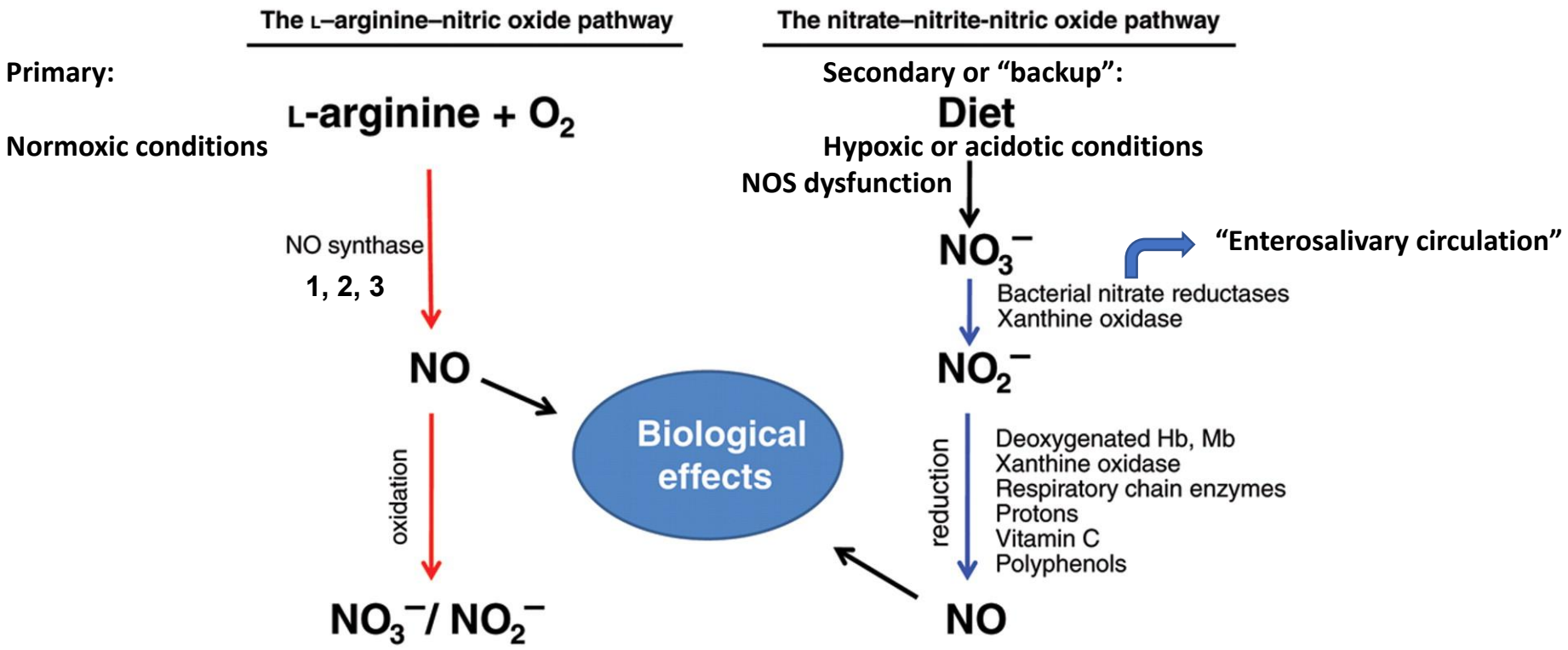
European Food Standards Agency Panel Recommendation:

“Overall, the estimated exposures to nitrate from vegetables are unlikely to result in appreciable health risks, therefore the recognized beneficial effects of consumption of vegetables prevail." (EFSA, 2008).



How can dietary nitrate can serve as an endogenous source of biologically active nitrogen oxides, including nitric oxide?

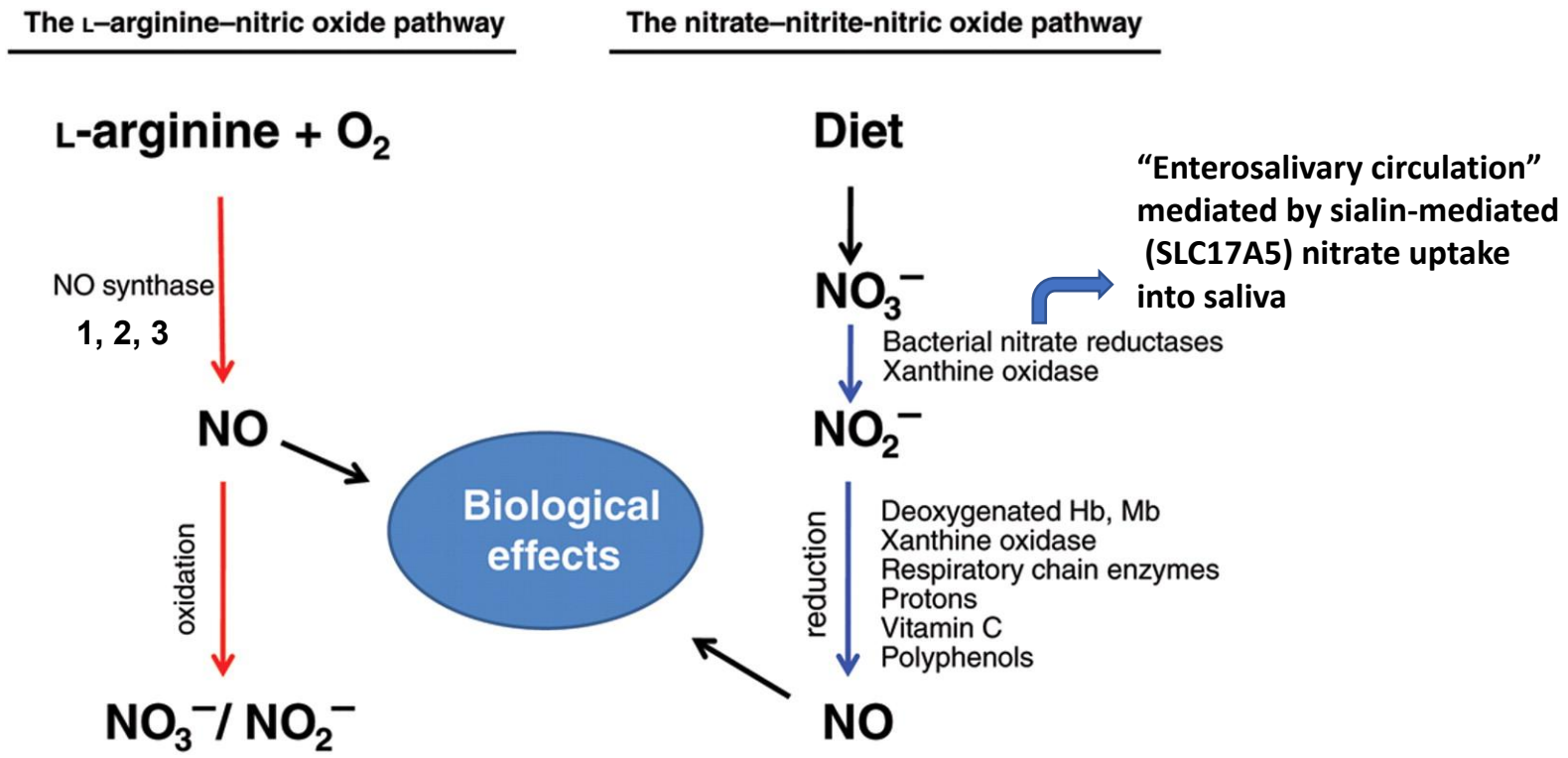
Two parallel pathways for NO formation



Lundberg J O et al. Cardiovasc Res 2011;89:525-532

Cardiovascular Research

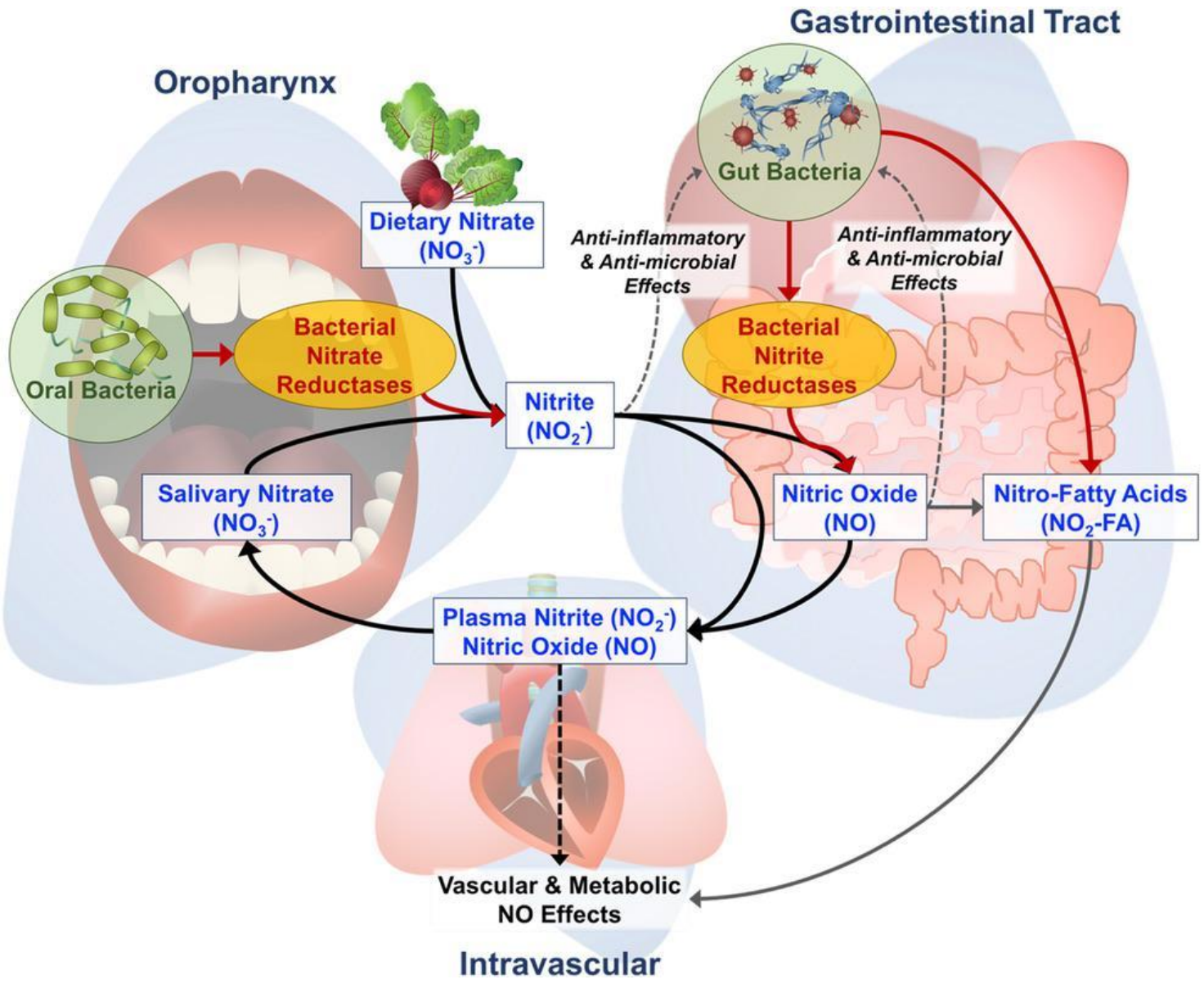
Two parallel pathways for NO formation



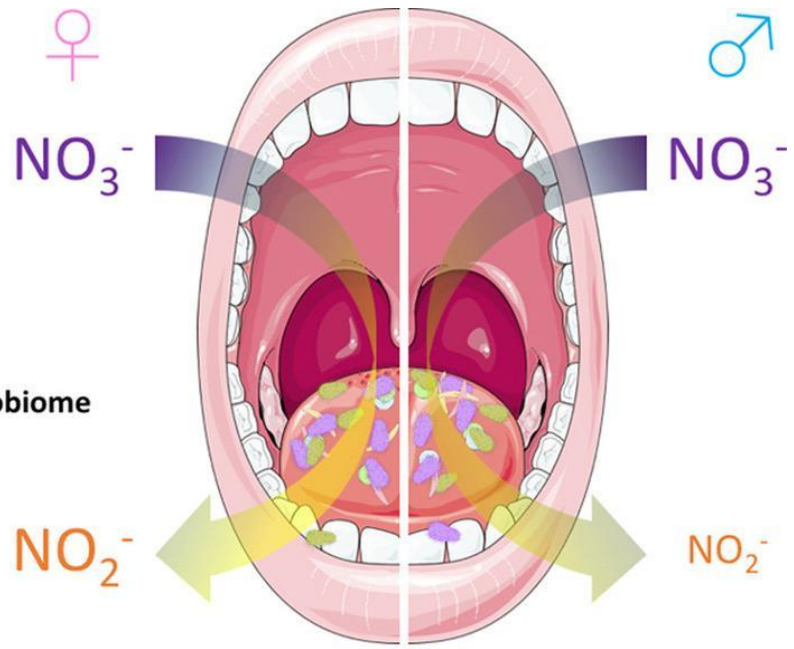
Lundberg J O et al. Cardiovasc Res 2011;89:525-532

Cardiovascular Research

Enterosalivary circulation, gastric acidity and the oral microbiome collaborate to NO bioavailability from plant food sources of nitrate



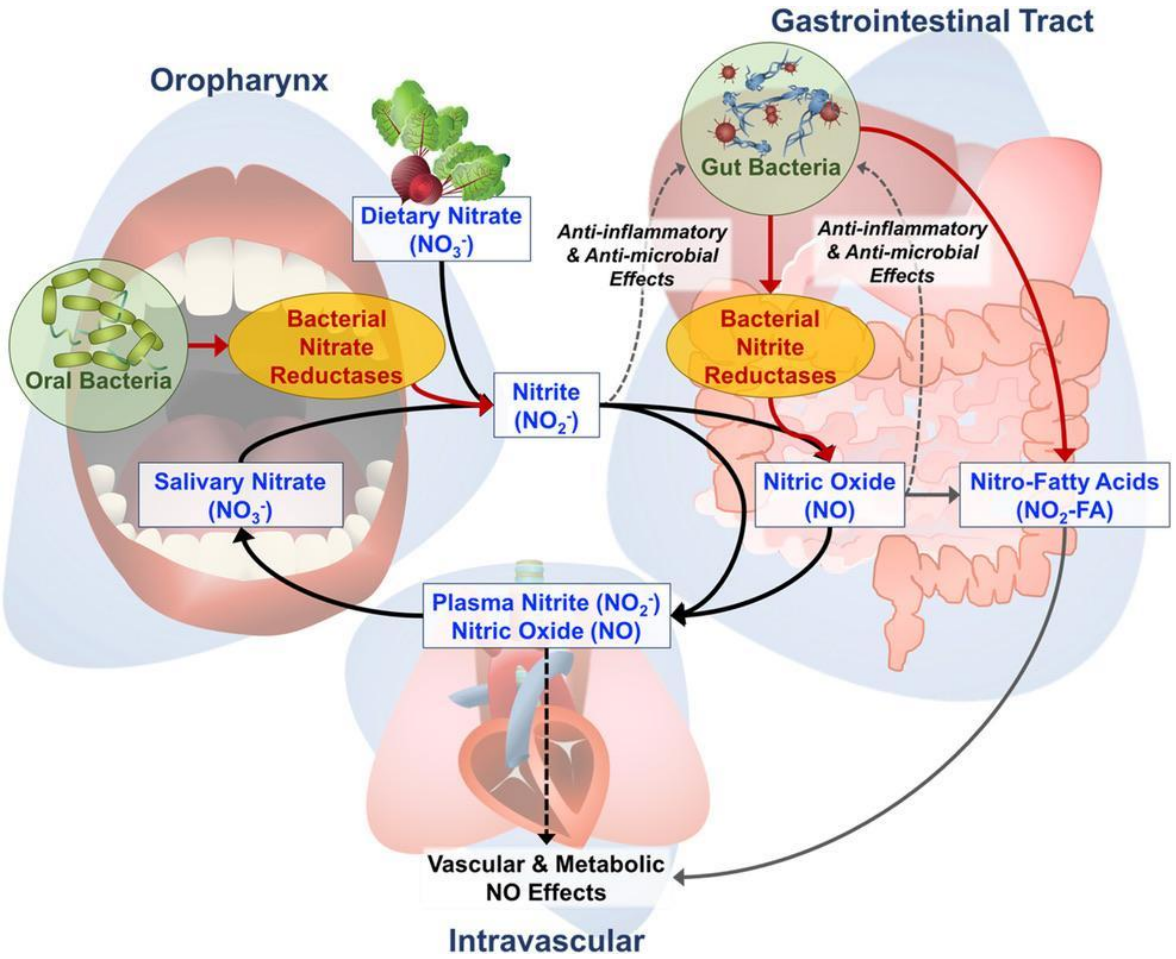
Enterosalivary circulation, gastric acidity and the oral microbiome collaborate to NO bioavailability from plant food sources of nitrate



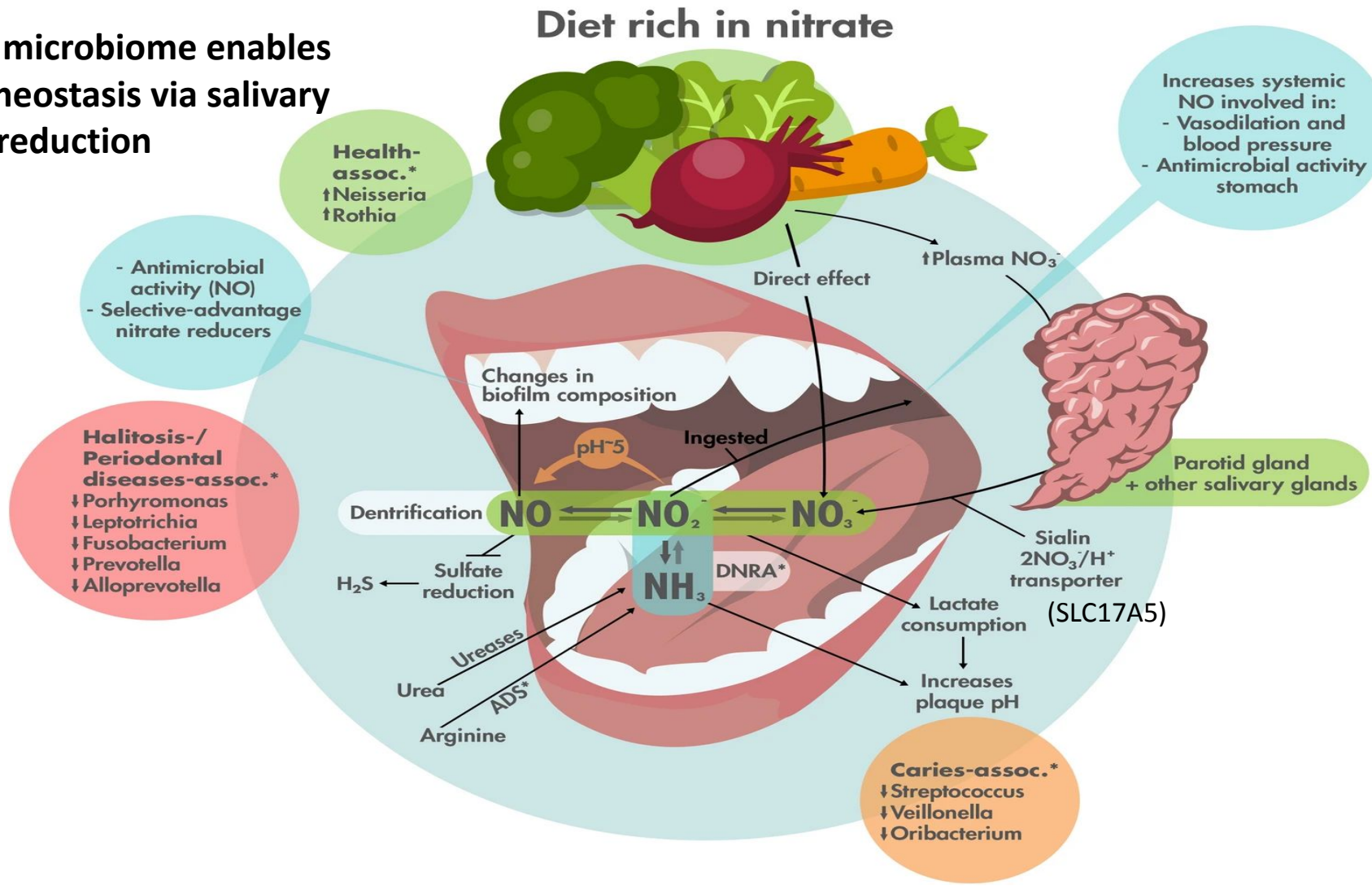
No sex difference in **microbiome community structure**

♀: higher **oral nitrate** reduction

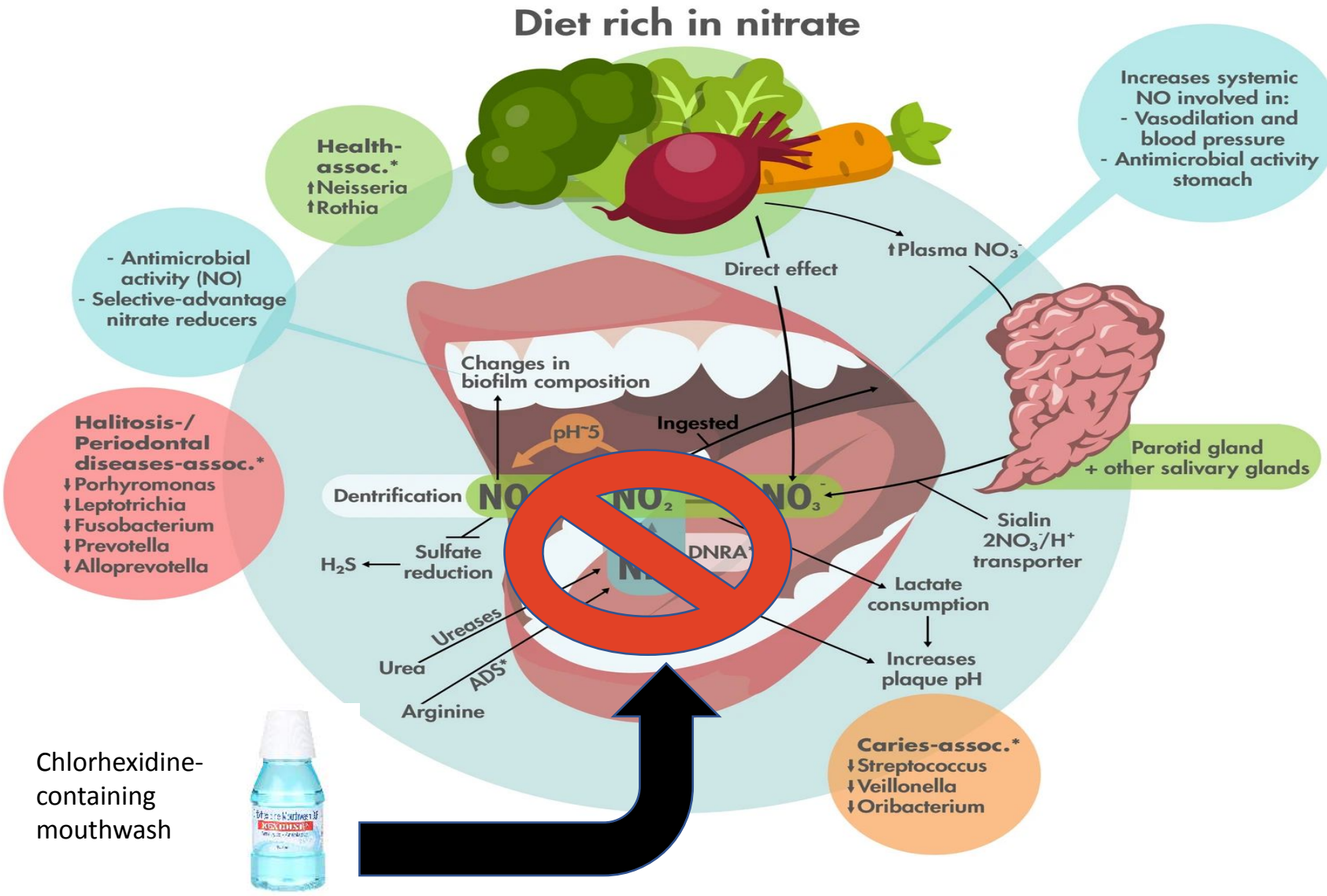
♀: ⬆ systemic **nitrite**



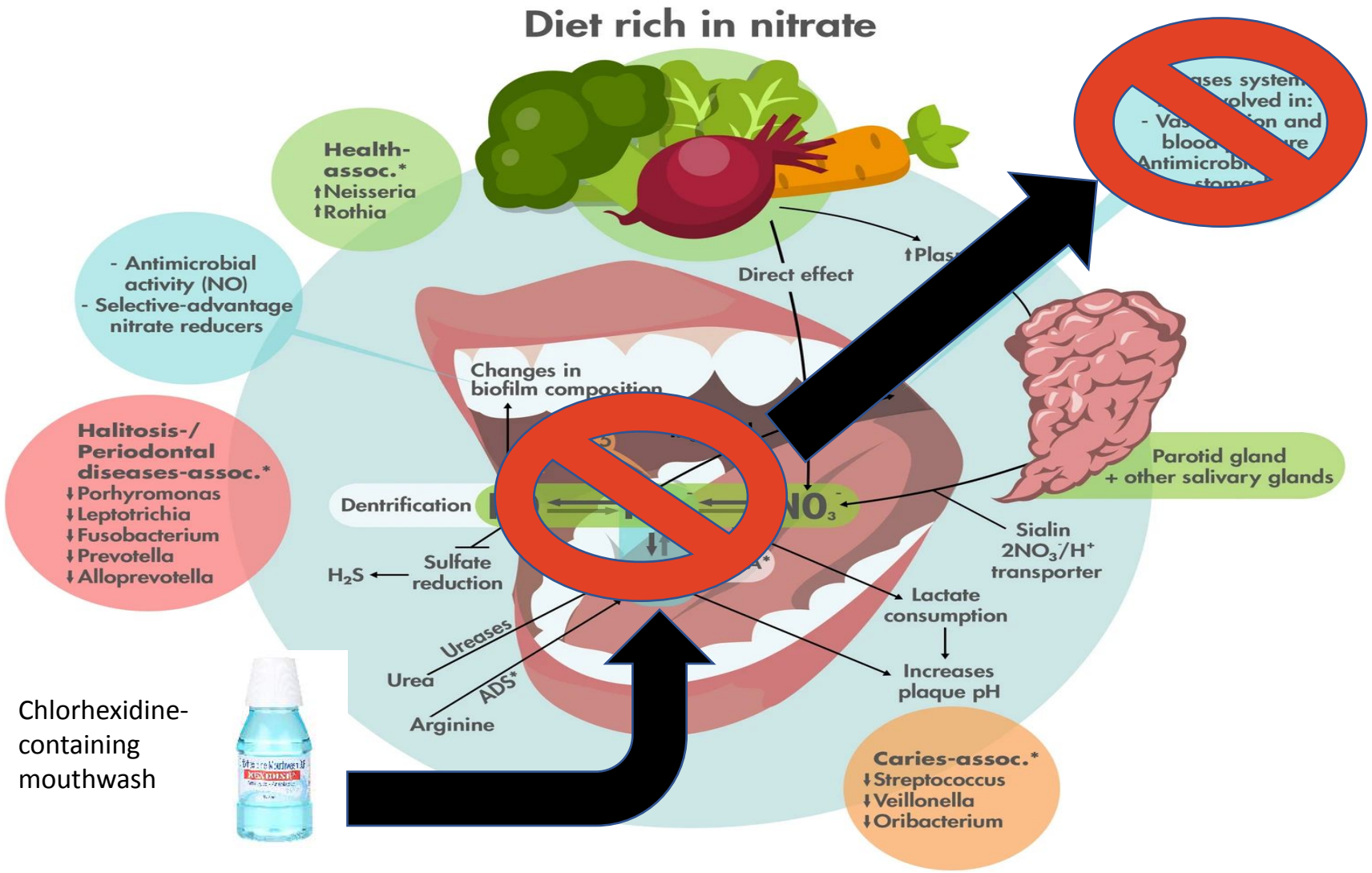
Lingual microbiome enables NO homeostasis via salivary nitrate reduction



Rosier et al. Scientific Reports (2020) 10:12895-12900



Rosier et al. Scientific Reports (2020) 10:12895-12900



Chlorhexidine-containing mouthwash

Oral health improvements occur with consumption of plant-based nitrate foods:

- Reduced acidification
- Enhanced pH buffering
- Decreased caries-associated bacteria
- Reduced periodontitis-associated bacteria.

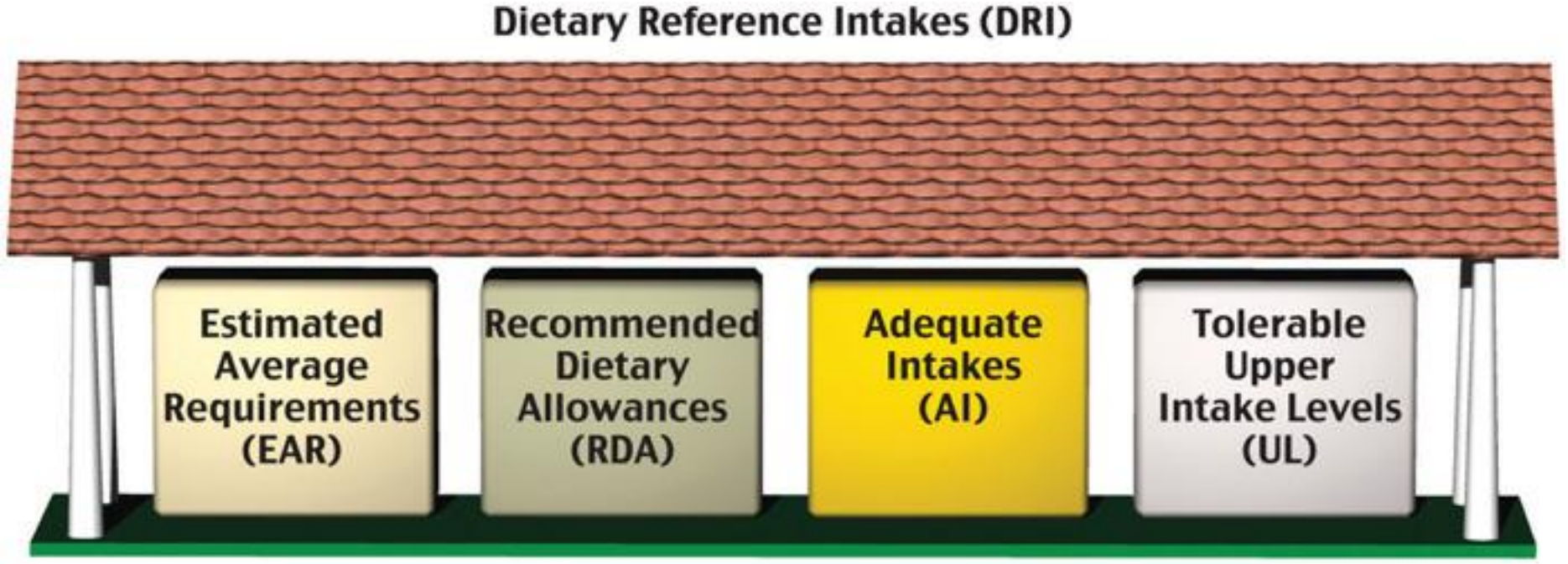
Kapadia, R. S., Salzman, A. L., & Reynolds, M. S. (2021). The oral microbiome and nitric oxide homoeostasis. Nature Reviews Microbiology, 19(5), 307-319. https://doi.org/10.1038/s41579-020-00487-3. PMID: 33664503

How could dietary nitrate and nitrite serve as conditionally essential nutrients?

Dietary Reference Intakes (DRI)

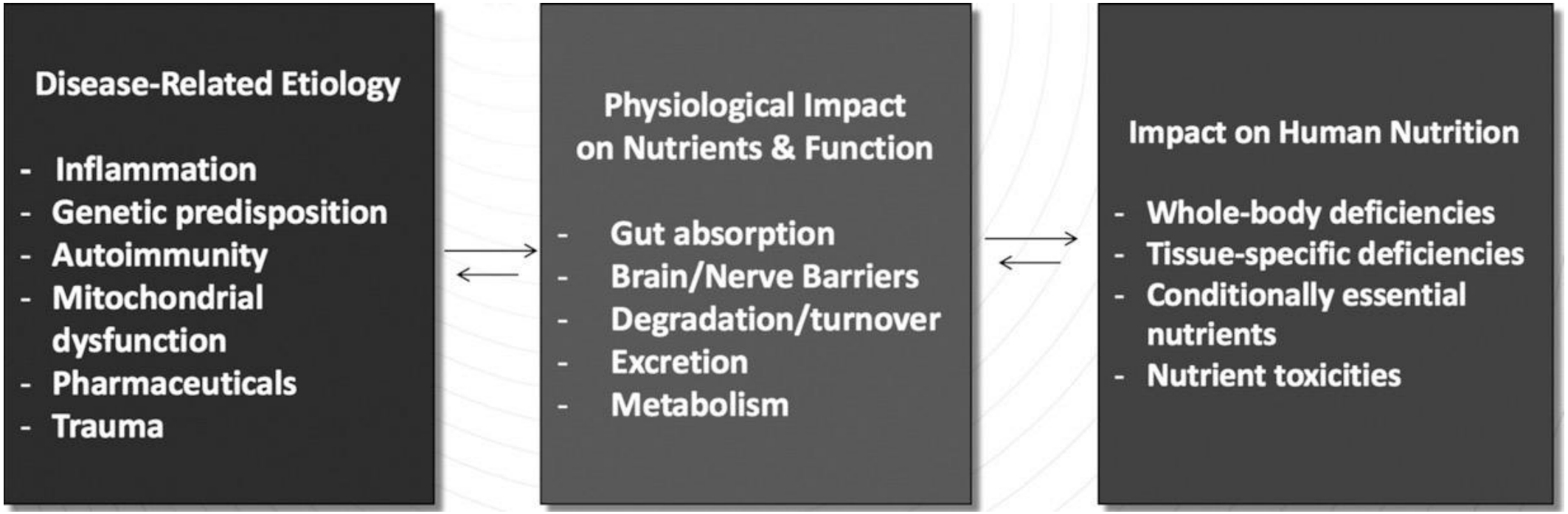
Standards for essential nutrients, such as the Dietary Reference Intakes (DRI) are established for healthy individuals within populations classified according to age group and sex.

The DRIs are nutrient reference values that serve as the scientific basis for food guidance in the United States and Canada including many program, policy, and regulatory initiatives.



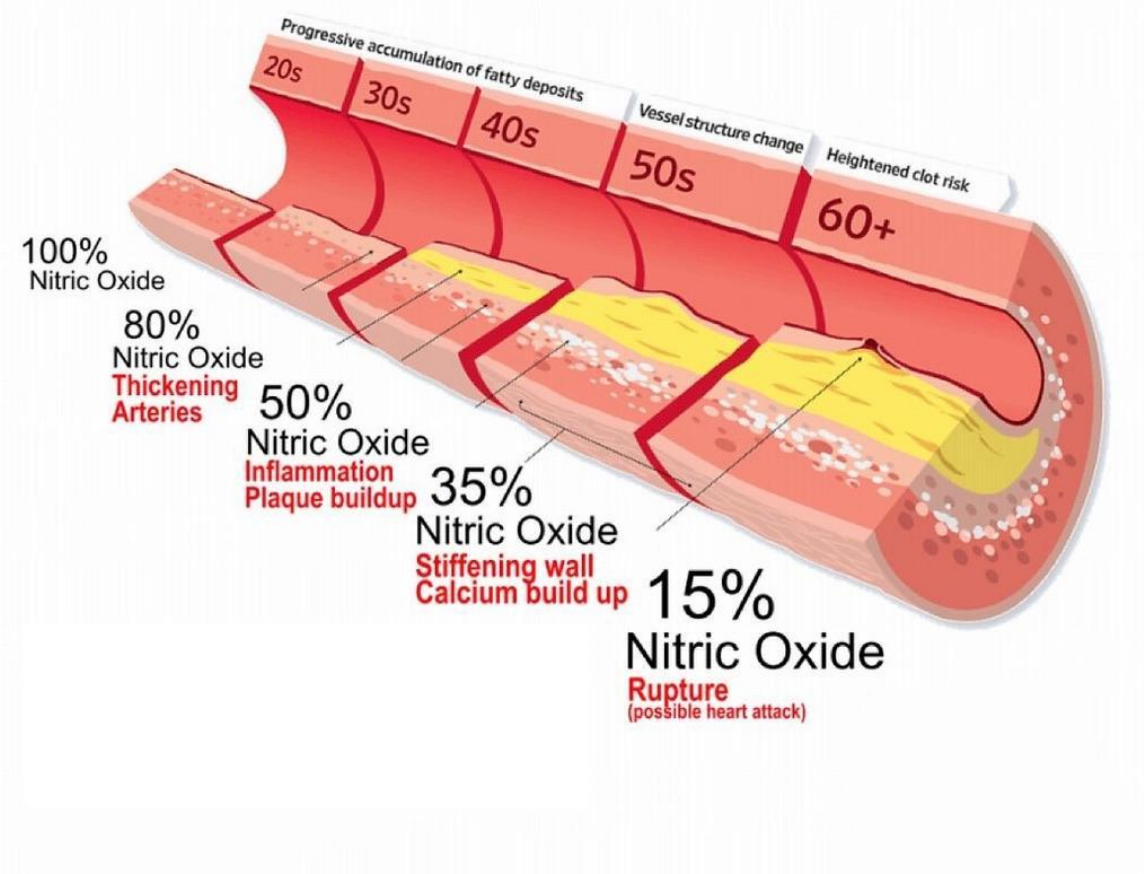
Conditionally essential nutrients become indispensable under specific physiological conditions or disease states where endogenous production cannot meet metabolic demands. This framework provides context for evaluating dietary nitrate's role in health maintenance.

Disease-Related Etiologies Impact Physiological Functions and Nutrient Needs



Stover PJ, Garza C, Durga J, Field MS. Emerging concepts in nutrient needs. J Nutr. 2020;150(Suppl 1):2593S-2601S. PMID: 31851302

Decreased bioavailability of nitric oxide is a hallmark of atherosclerosis



Hypertension: 31% reduction (95% CI: 27-35%) (Forte P, et al. Lancet. 1997;349:837-842. PMID: 9121261)

- Chronic Renal Failure: 61% reduction (95% CI: 55-67%)
(Wever R, et al. Arterioscler Thromb Vasc Biol. 1999;19:1168-1172. PMID: 10323766)

- Chronic Heart Disease: 73% reduction (95% CI: 68-78%)
(Katz SD, et al. Circulation. 1999;99:2113-2117. PMID:

Two Primary Pathophysiological Processes Drive Cardiorenal Disease Risk

Endothelial Dysfunction

- Förstermann U, Münzel T. Endothelial nitric oxide synthase in vascular disease: from marvel to menace. Circulation. 2006;113(13):1708-1714. PMID: 16585403
- Shaito A, Aramouni K, Assaf R, Parenti A, Orekhov A, El Yazbi A, Eid AH. Oxidative stress-induced endothelial dysfunction in cardiovascular diseases. Front Biosci (Landmark Ed). 2022;27(3):105. PMID: 35317843

Oxidative Stress

- Münzel T, Daiber A. Vascular redox signaling, eNOS uncoupling and endothelial dysfunction in the setting of transportation noise exposure or chronic treatment with organic nitrates. Antioxid Redox Signal. 2023;38(13-15):1001-1021. PMID: 36264290
- Förstermann U, Xia N, Li H. Roles of vascular oxidative stress and nitric oxide in the pathogenesis of atherosclerosis. Circ Res. 2017;120(4):713-735. PMID: 28209797

Conditionally essential nutrients refer to certain nutrients whose endogenous production cannot meet physiological needs in conditions such as neonatal growth, catabolic stress, or disease conditions, requiring exogenous supplementation (for example, through diet).

In this context, standards for conditionally essential nutrients are referred to as **Specialized Nutrient Requirements** by the National Academies of Sciences, Engineering and Medicine.

Examining special nutritional requirements in disease states: proceedings of a workshop [Internet]., Washington (DC) [Updated June 29, 2018; cited 8/16/2023]. Available from: https://nap.nationalacademies.org/ catalog/25164/examining-special-nutritional-requirements-in- disease-states-proceedings-of-a.

P.J. Stover, C. Garza, J. Durga, M.S. Field, Emerging concepts in nutrient needs, J. Nutr. 150 (Suppl 1) (2020) 2593S–2601S.

Dietary nitrate has potential to act as a conditionally essential nutrient in conditions that involve:

- low dietary nitrate
- decreased NOS expression
- dysfunctional NOS activity, and/or
- increased NO auto-oxidation

……..all ultimately result in decreased NO bioavailability.

Kapil V, Khambata RS, Jones DA, Rathod K, Primus C, Massimo G, Fukuto JM, Ahluwalia A. The noncanonical pathway for in vivo nitric oxide generation: The nitrate-nitrite-nitric oxide pathway. Pharmacol Rev. 2020 Jul;72(3):692-766. PMID: 32554512.

Nitrate: A Conditionally Essential Nutrient?

(Hord et al. Am J Clin Nutr. 2009 Jul;90(1):1-10)

- Nitrate-free diets in rodent models lead to hyperglycemia, adiposity and premature death due to cardiovascular disease (Kina-Tanada et al. Diabetologica (2017) 60: 1138-1151).
- Dietary nitrate and nitrite restore NO homeostasis in NO-deficient models (e.g., eNOS knockout models, NO deficiency in aging, atherosclerosis and T2DM models).
- Over 30 active clinical trials registered with NIH testing nitrate or nitrite as treatment (ClinicalTrials.gov)
  - Hypertension
  - Coronary artery disease
  - Obstructive sleep apnea
  - * Heart failure (pEF)
  - * Pulmonary hypertension

TABLE 1
Study characteristics and results of population-based observational studies on the association between dietary nitrate intake and cardiovascular disease outcomes

First author	Year	Number of participants	Population/cohort	Follow-up length	Comparator	Outcome	Results
Z. Bahadoran [91]	2016	2799	Adults (≥20 y old) Tehran Lipid and Glucose Study	5.8 y	Lowest (<6.04 mg/d) vs. highest (≥12.7 mg/d) tertile	Incident HTN and CKD	Dietary nitrate: no association with HTN or CKD Dietary nitrite: OR 0.58 (95% CI: 0.33, 0.98) for HTN; OR 0.50 (95% CI: 0.24, 0.89) for CKD
L. Blekkenhorst [92]	2017	1226	Older adults (70–85 y old)	15 y	1-SD increase from the mean (67.0 ± 29. 2 mg/d)	ASVD and all-cause mortality	ASVD mortality: HR 0.79 (95% CI: 0.68, 0.93; $P = 0.004$) All-cause mortality: HR 0.87 (95% CI: 0.78, 0.97; $P = 0.011$)
J. Jackson [93]	2019	62,535	Female adults (30–55 y old) Nurses' Health Study	26 y	Lowest (<86 mg/d) vs. highest (>195 mg/d) quintile	CHD risk	RR 0.91 (95% CI: 0.80, 1.04; $P = 0.27$)
A. Liu [94]	2019	2229	Adults (≥49 y old) Blue Mountains Eye Study	14 y	Lowest (<69.5 mg/d) vs. highest (>137.8 mg) quartile	CVD mortality	HR 0.63 (95% CI: 0.41, 0.95)
C. Bondonno [95]	2021	53,150	Adults (≥49 y old) Danish Diet, Cancer, and Health Study	23 y	Lowest (median intake: 23 mg/d) vs. highest (median intake: 141 mg/d) quintile	BP and CVD risk	SBP: −2.58 mmHg (95% CI: −3.12 to −2.05 mmHg) DBP: −1.38 mmHg (95% CI: −1.66 to −1.10 mmHg) CVD risk: HR 0.86 (95% CI: 0.82, 0.91)

Abbreviations: ASVD, atherosclerotic vascular disease; BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; HR, hazard ratio; HTN, hypertension; RR, risk ratio; SBP, systolic blood pressure.

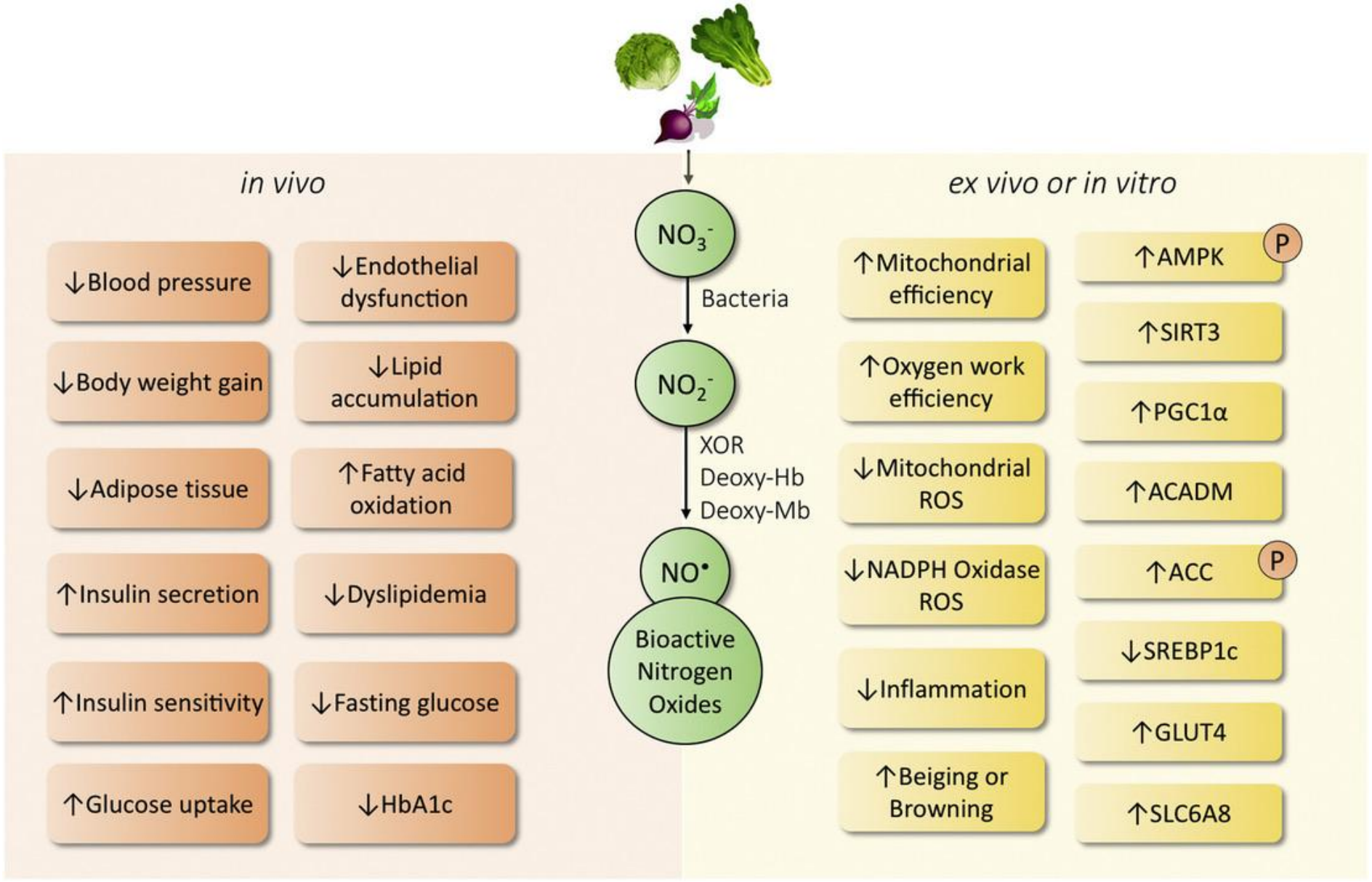
Pinaffi-Langley AC, Dajani RM, Prater MC, Nguyen HVM, Vrancken K, Hays FA, Hord NG. Dietary Nitrate from Plant Foods: A Conditionally Essential Nutrient for Cardiovascular Health. Adv Nutr. 2024;15(1):100158. PMID: 37116849

TABLE 2
Study characteristics and results of meta-analyses on the effect of nitrate supplementation on outcomes related to cardiovascular disease risk factors

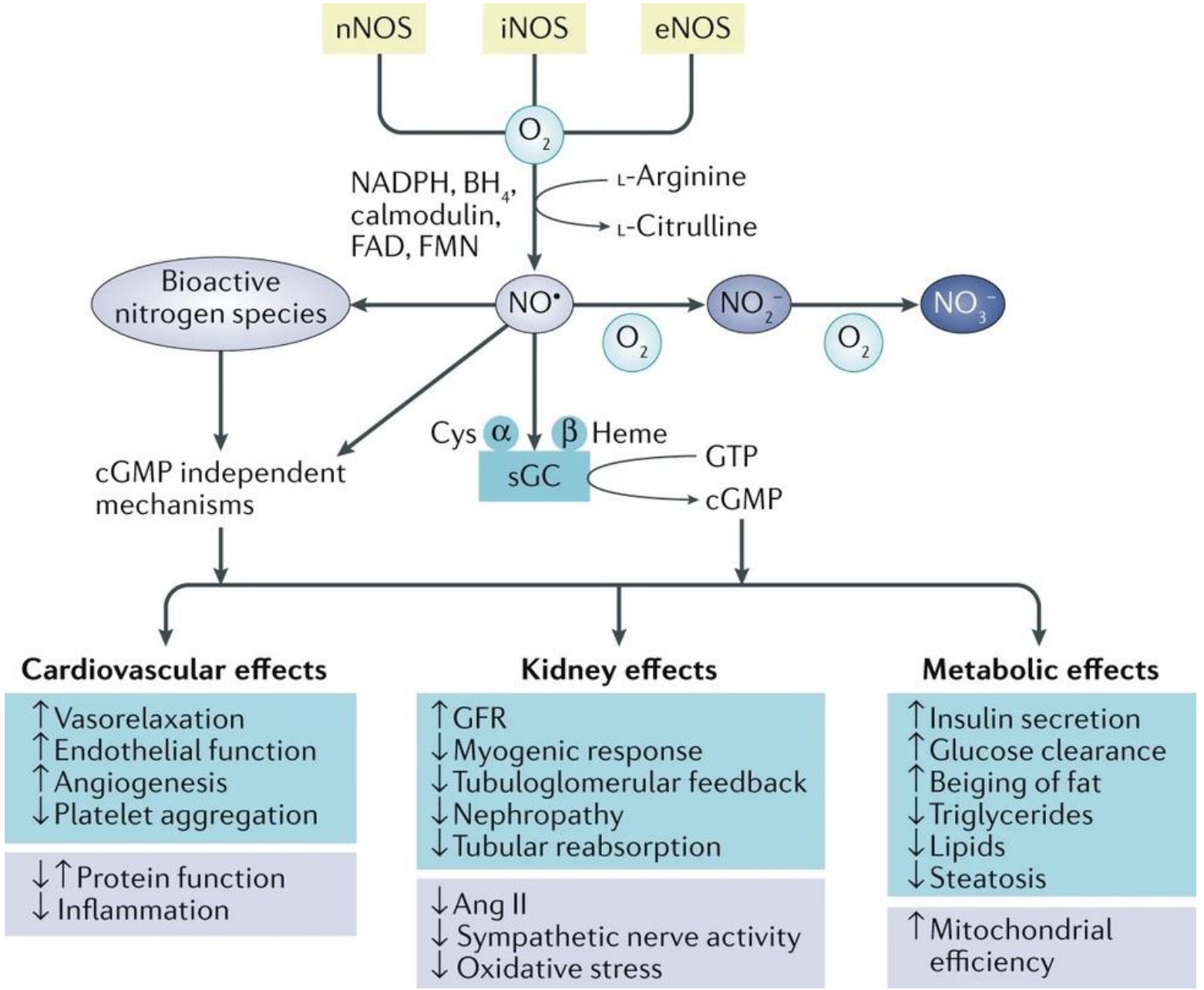
First author	Year	Number of studies (total number of participants)	Study population	Duration range	Nitrate source	Dose range (mg per dose)	Main outcomes	Results
M. Siervo [99]	2013	16 (254)	Adults	2 h to 15 d	Nitrate salt or beetroot juice	157–1488	Blood pressure	SBP: −4.4 mmHg ($P < 0.001$); DBP: −1.1 mmHg ($P = 0.06$)
J. Lara [100]	2016	12 (246)	Adults	90 min to 28 d	Nitrate salt or beetroot supplementation	68–1488	Vascular function parameters	Endothelial function: 0.4 ($P < 0.001$)
A. W. Ashor [101]	2017	13 (325)	Adults	1 to 6 wk	Nitrate salt or beetroot juice	322–620	Blood pressure	SBP: −4.1 mmHg ($P < 0.001$); DBP: −2.0 mmHg ($P < 0.001$)
J. K. Jackson [106]	2018	34 (813)	Adults	2 h to 70 d	Nitrate salt or dietary sources	55–1490	Blood pressure	SBP: −4.8 mmHg ($P < 0.0001$); DBP: −1.7 mmHg ($P = 0.001$)
D. Li [107]	2020	47 (1101)	Adults	3 to 168 d	Nitrate salt or dietary sources	150–1000	Blood pressure	SBP: −2.9 mmHg ($P < 0.001$); DBP: −1.5 mmHg ($P < 0.001$)
L. S. Bahrami [108]	2021	27 (765)	Adults	1 h to 6 wk	Beetroot supplementation	70–1500	Cardiovascular disease risk factors	SBP: −0.7 mmHg ($P = 0.3$); DBP: −1.3 ($P = 0.06$); HR: 8.6 bpm ($P = 0.08$); AIX: −3.3% ($P = 0.1$); FMD: 0.6% ($P = 0.002$)
Y. He [102]	2021	22 (372)	Older adults (>60 y old)	45 min to 4 wk	Nitrate salt or beetroot juice	25–840	Blood pressure	SBP: −3.9 mmHg ($P < 0.001$); DBP: −2.6 mmHg ($P < 0.005$)
Y. Zhang [103]	2023	19 (1069)	Adults	1 d to 4 wk	Nitrate salt or dietary sources	248–1165	Blood pressure	Healthy individuals: SBP: −2.42 mmHg ($P = 0.01$); DBP: −0.58 mmHg ($P = 0.36$) Hypertensive individuals: SBP: −0.82 mmHg ($P = 0.35$); DBP: −0.03 mmHg ($P = 0.97$)

Results are expressed as mean/standardized mean differences. All meta-analyses included in this table utilized randomized controlled trials and/or placebo-controlled trials and a significance level of 5%.
Abbreviations: AIX, augmentation index; AOS, arterial oxygen saturation; DBP, diastolic blood pressure HR, heart rate; SBP, systolic blood pressure.

Pinaffi-Langley AC, Dajani RM, Prater MC, Nguyen HVM, Vrancken K, Hays FA, Hord NG. Dietary Nitrate from Plant Foods: A Conditionally Essential Nutrient for Cardiovascular Health. Adv Nutr. 2024;15(1):100158. PMID: 37116849



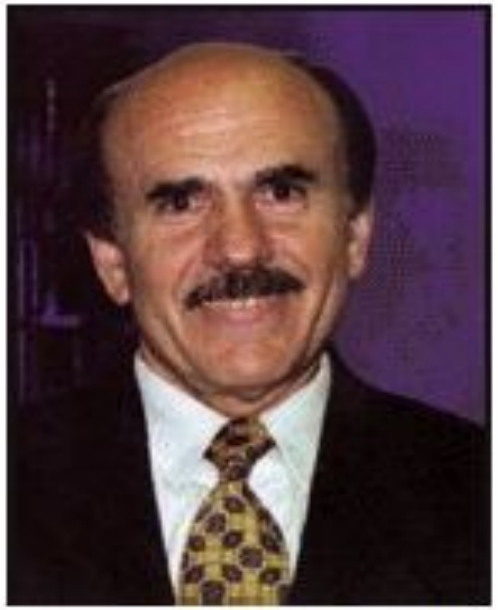
Kapil V, Khambata RS, Jones DA, Rathod K, Primus C, Massimo G, Fukuto JM, Ahluwalia A. The noncanonical pathway for in vivo nitric oxide generation: The nitrate-nitrite-nitric oxide pathway. Pharmacol Rev. 2020 Jul;72(3):692-766. PMID: 32554513



PMID: 32554512

The Nobel Prize in Physiology or Medicine 1998

Robert F Furchgott, born 1916
Dept. of Pharmacology,
SUNY Health Science Center
New York



Louis J Ignarro, born 1941
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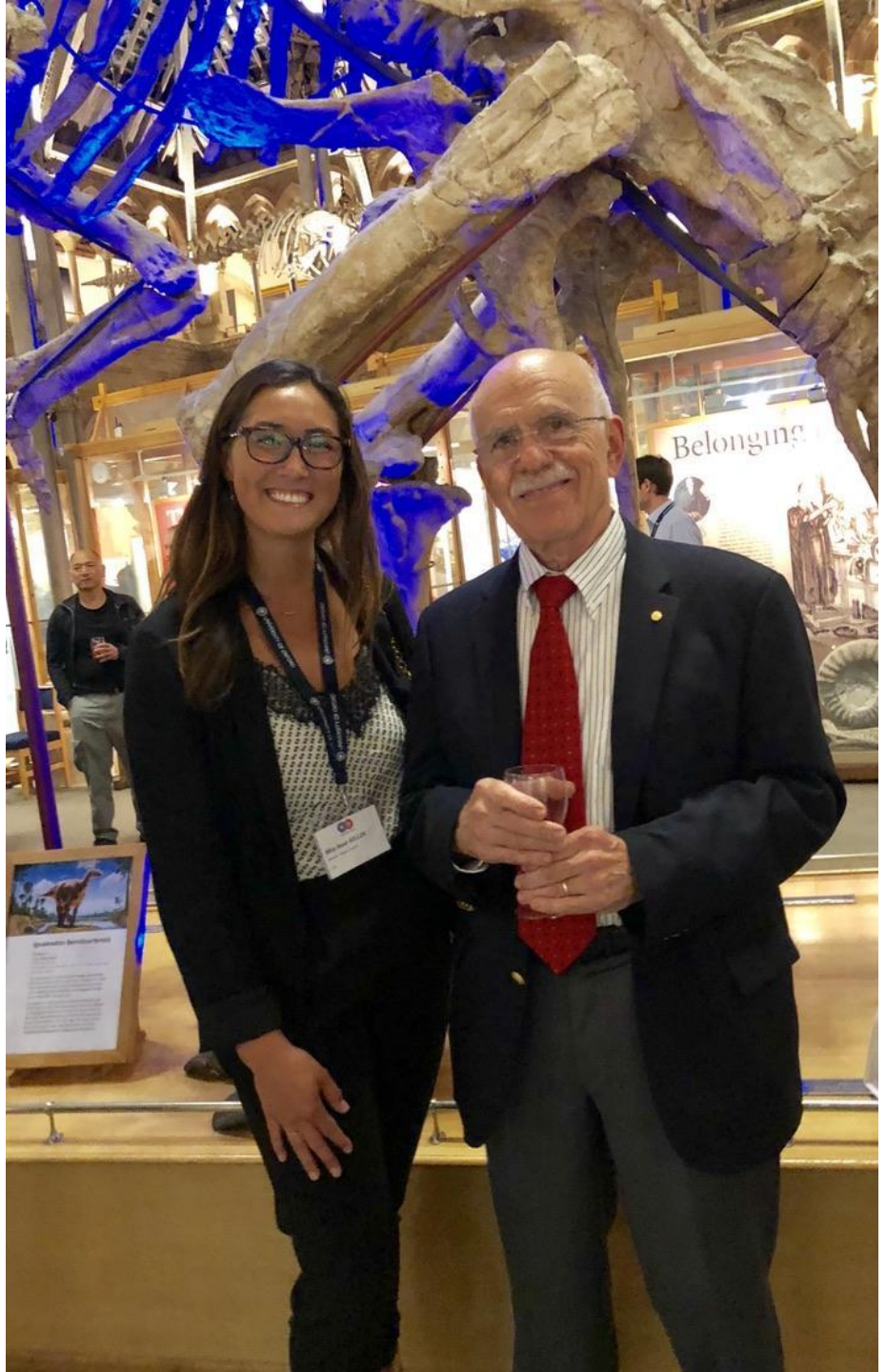
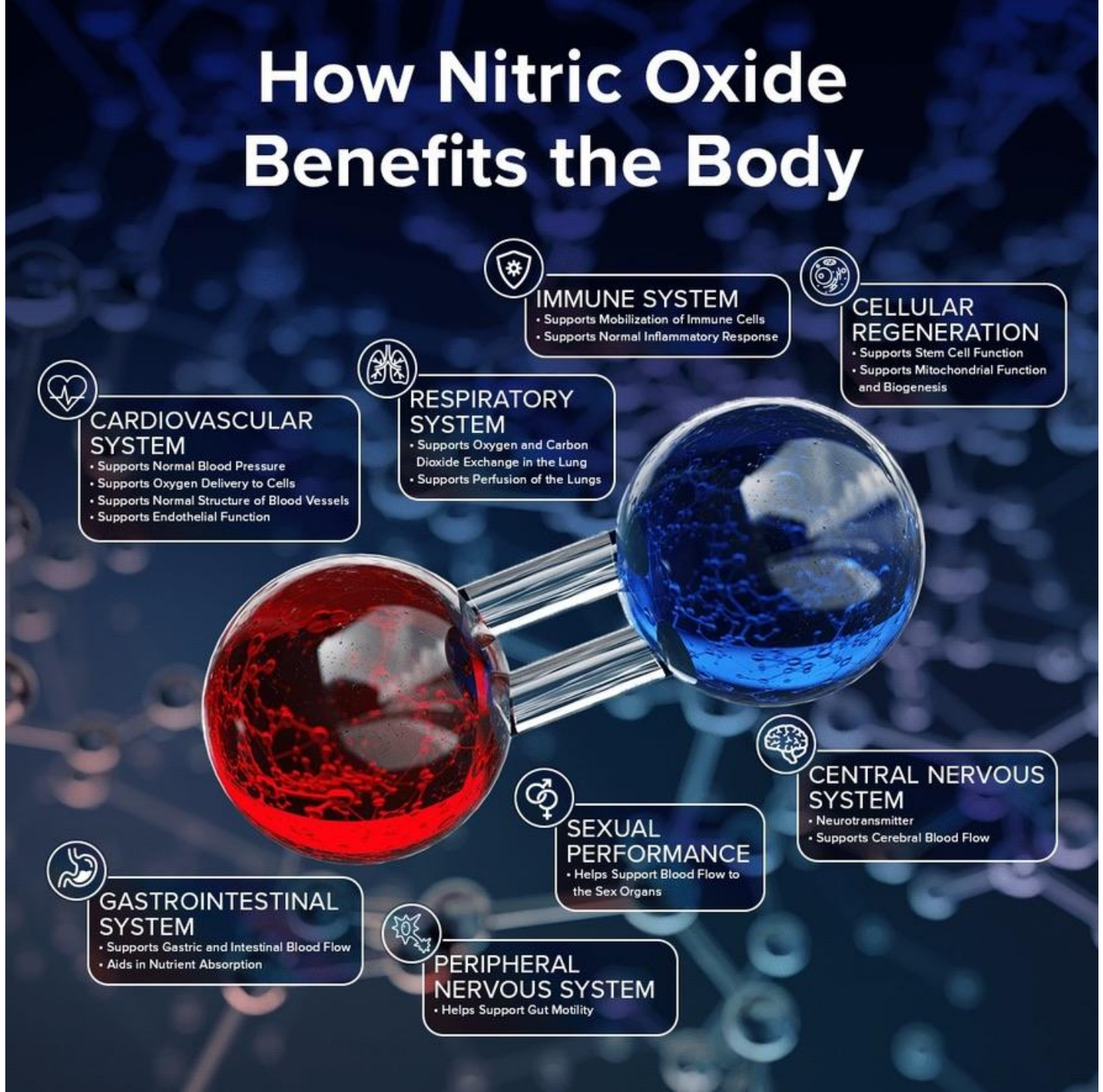

Belonging

Dietary Supplement Advertisement

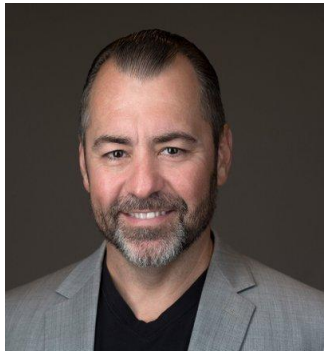


Amrita Ahluwalia, M.D.
Queen Mary University of London

Mark Gladwin, MD
University of Pittsburgh School of Medicine

Andrew Jones, PhD
University of Exeter

Jon Lundberg, MD, PhD
Karolinska Institutet



Nathan Bryan, PhD
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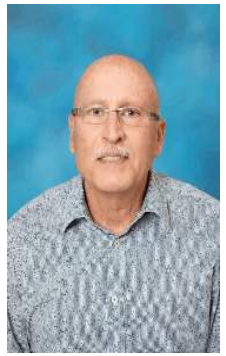

Bruce Freeman, PhD
University of Pittsburgh

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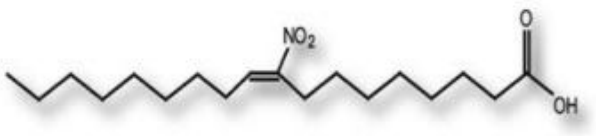
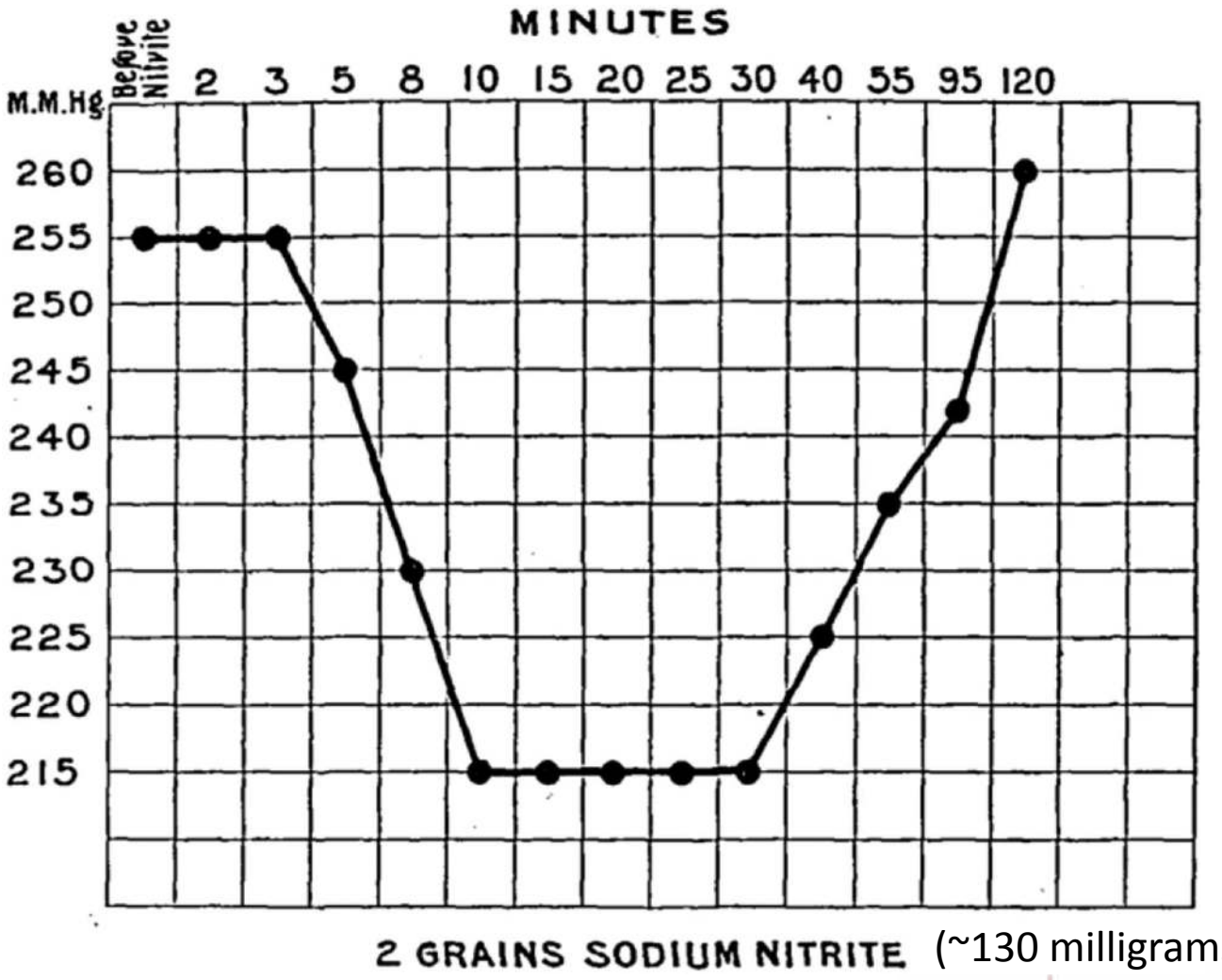


Nitro-oleic acid

Oral inorganic nitrite and acute BP response (Matthew, 1909).



(~130 milligrams; 85 mg NO_2))

V. Kapil et al. Pharmacol Rev 2020;72:692-766

ASPET | PHARMACOLOGICAL REVIEWS

International Olympic Committee Consensus Statement

International Journal of Sport Nutrition and Exercise Metabolism, 2018, 28, 104-125
https://doi.org/10.1123/ijsnem.2018-0020

Human Kinetics
CONSENSUS STATEMENT

IOC Consensus Statement: Dietary Supplements and the High-Performance Athlete

Ronald J. Maughan
St Andrews University

Louise M. Burke
Australian Institute of Sport and
Mary MacKillop Institute
for Health Research

Jiri Dvorak
Schulthess Clinic

D. Enette Larson-Meyer
University of Wyoming

Peter Peeling
University of Western Australia and
Western Australian Institute of Sport

Stuart M. Phillips
McMaster University

Current Limitations

Summary of Workshop on Dietary Nitrates and the Epidemiology of Hypertension and Cardiovascular Disease

Ahluwalia, A, Hord, NG et al. (2016) Journal of the American Heart Association, Jul; 5(7): e003402.

1) **improvements in the standard dietary databases** used in epidemiological research are required to include estimates of the nitrate content of commonly eaten vegetables,
2) **incorporate measures of drinking water nitrate content** to observational cohort data collection is critical to take account of variations in exposure
3) **large cohort studies** assessing nitrate exposure through direct measurement in plasma, saliva or urine along with nitrate and nitrite content in the diet are essential
4) there is an urgent need to examine the effects of sports supplement consumption upon **endogenous production of carcinogenic N-nitroso compounds**.

Nitrate, Nitrite and Nitrosamine Database Development

The Nitr-Navigator database represents a significant advancement in understanding dietary nitrate exposure, containing comprehensive data on nitrate content in foods across multiple regions and conditions.

Database Characteristics:
- 129,000+ nitrate values
- 800+ foods documented
- 80+ countries represented
- Seasonal variations tracked
  - Processing effects documented
  - Based on publications: PMID: 35753259, PMID: 34792849, PMID: 28105786, PMID: 33884541

New Nitrate, Nitrite and Nitrosamine Database (http://nitr-navigator.com)

Population Studies and Epidemiological Evidence

Danish Diet, Cancer, and Health Study

Large prospective cohort study (N=53,150) demonstrated significant cardiovascular benefits associated with higher dietary nitrate intake, with dose-dependent reductions in both blood pressure and cardiovascular disease risk.

Key Findings:
- Systolic BP reduction: -2.5 mmHg (95% CI: -3.3 to -1.7)
- Diastolic BP reduction: -1.4 mmHg (95% CI: -2.0 to -0.8)
- CVD risk reduction: 15% (95% CI: 10-20%)
- Median follow-up: 23 years

Bondonno CP, et al. Vegetable nitrate intake, blood pressure and incident cardiovascular disease: Danish Diet, Cancer, and Health Study. Eur J Epidemiol. 2021;36:813-825. PMID: 33899149

Australian Cohort Outcomes

Analysis of the prospective Australian Diabetes, Obesity and Lifestyle Study (n=11,000 with 5 and 12 year follow-ups) revealed significant reductions in mortality outcomes associated with higher vegetable nitrate intake.

Primary Outcomes:
- All-cause mortality reduction: 12% (95% CI: 8-16%)
- Cardiovascular mortality: 15% (95% CI: 10-20%)
- Dose-dependent effects observed
- Population base: N=2,229

Rajendra A, et al. Habitual dietary nitrate intake and cognition in the Australian Imaging, Biomarkers and Lifestyle Study of ageing. Front Nutr. 2024;11:1327042. PMID: 38299824

Current Work: Development of USDA Special Interest Database

- Current work in proceeding to develop a database of nitrate and nitrite concentrations in foods and dietary supplements

Franklin Hays, Michelle Nguyen, Ana Clara Langley, Norman Hord, Diane Whitehead

Pamela R Pehrsson, PhD
Methods and Application of Food Composition Laboratory
USDA

Consideration of plant sources of nitrate as a conditionally essential nutrient

- Considering the available evidence, we suggest 2 different approaches to providing dietary guidance on nitrate from plant-based dietary sources as a nutrient:
  - the Dietary Reference Intakes developed by the National Academies of Sciences, Engineering, and Medicine,
  - the dietary guidelines evaluated by the Academy of Nutrition and Dietetics.
- Our proposal underscores the need for food-based dietary guidelines to capture the complex and context-dependent relationships between nutrients, particularly dietary nitrate, and health.

Plant-based sources of nitrate: dietary bioactive guideline

Crowe-White KM, Evans LW, Kuhnle GGC, Milenkovic D, Stote K, Wallace T, Handu D, Senkus KE. Flavan-3-ols and Cardiometabolic Health: First Ever Dietary Bioactive Guideline. Adv Nutr. 2022; 13(6):2070-83. doi: 10.1093/advances/nmac105. PubMed PMID: 36190328; PMCID: PMC9776652.

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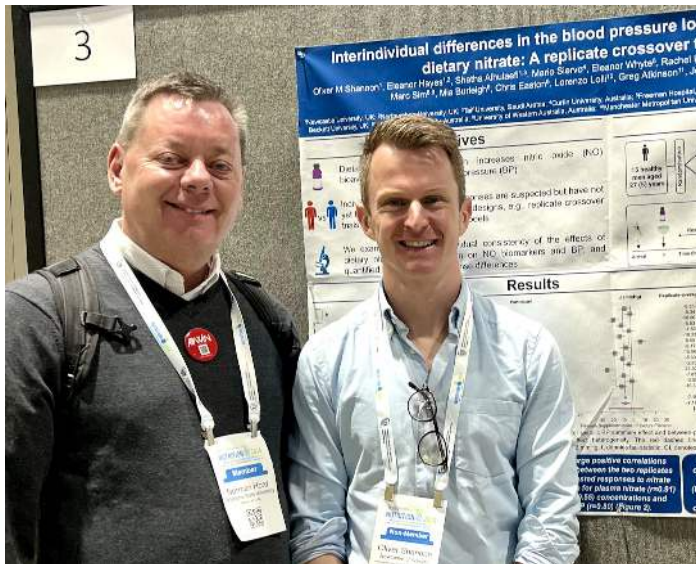
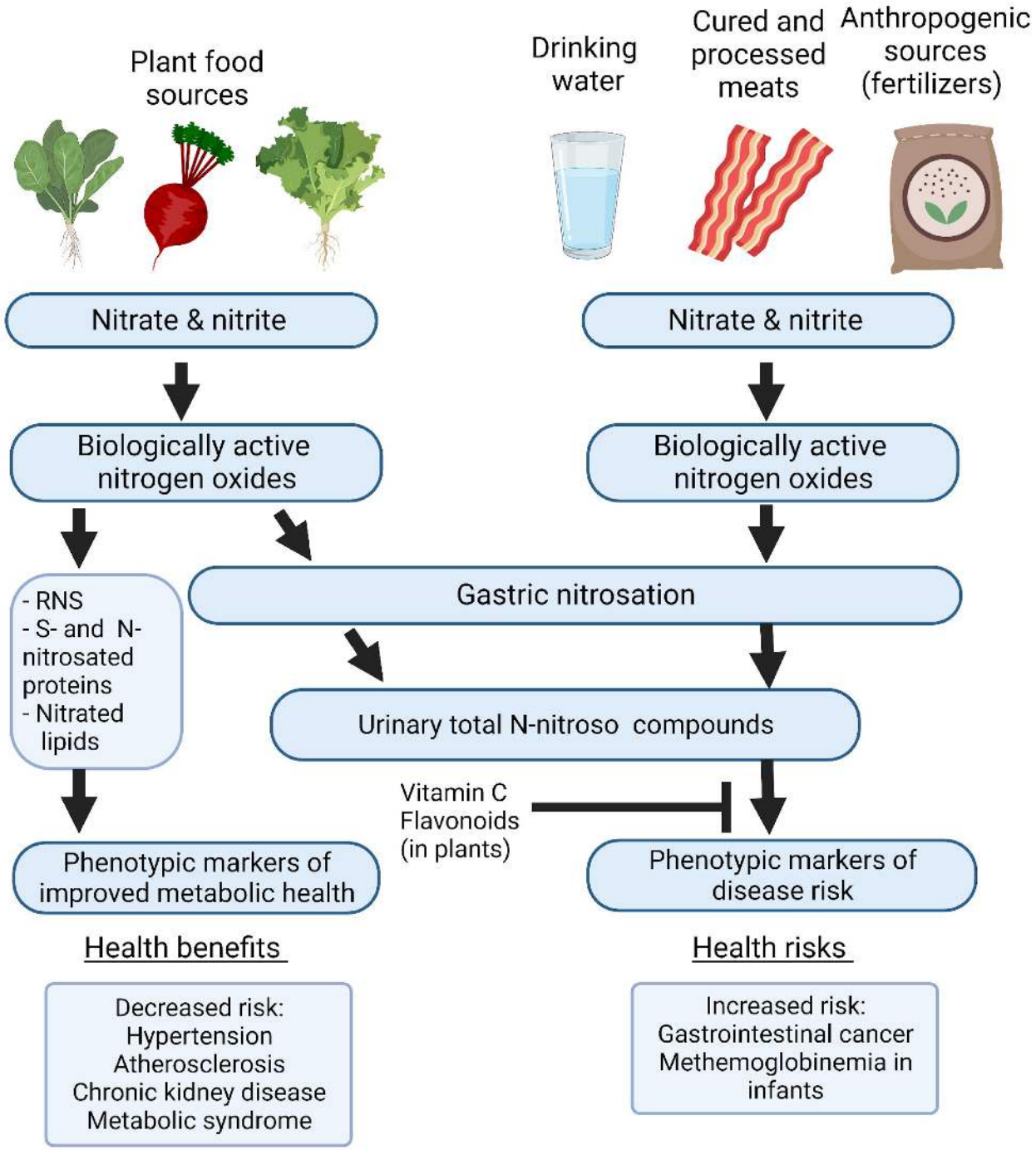


Summary of Metabolic Effects Of Dietary Nitrate & Nitrite



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Concluding Points

Advances in Nutrition 15 (2024) 100158

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Perspective

Dietary Nitrate from Plant Foods: A Conditionally Essential Nutrient for Cardiovascular Health

Ana Clara da C Pinaffi-Langley [1], Rosa M Dajani [2], M Catherine Prater [3], Hoang Van M Nguyen [1], Kurt Vrancken [4], Franklin A. Hays [1], Norman G Hord [1,5,*]

[1] *Department of Nutritional Sciences, College of Allied Health, University of Oklahoma Health Sciences Center, Oklahoma City, OK, United States;* [2] *Nutrition and Food Services, San Francisco Health, University of California, San Francisco, CA, United States;* [3] *Department of Foods and Nutrition, Dawson Hall, University of Georgia, Athens, GA, United States;* [4] *Independent Researcher, Brooklyn, NY, United States;* [5] *Department of Nutritional Sciences, College of Education and Human Sciences, Oklahoma State University, Stillwater, OK, United States*

- The established vasoprotective, blood pressure lowering, and antiplatelet aggregation properties of nitrite alone, or of nitrite originating from dietary nitrate, requires a new regulatory paradigm that incorporates the concepts of physiological deficiency, sufficiency and excess.

- There is a need to engage an independent panel of experts from academia, industry, and governmental and non-governmental sectors to undertake the first comprehensive, systematic review of the potential **health risks and potential benefits** of dietary sources of nitrates and nitrites.

- U.S. Institute of Medicine's Dietary Reference Intake paradigm may be a useful guide to the development of coherent dietary nitrate and nitrite intake recommendations.

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