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Carballo-Casla, Adrián; Dunk, Michelle M.; Donat-Vargas, Carolina; Xu, Weili

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TITLE PAGE

Title

Could dietary nitrate affect dementia development?

Authors' names and affiliations

Adrián Carballo-Casla, [a,b] Michelle M. Dunk, [a] Carolina Donat-Vargas, [b,c,d,e] Weili Xu [a]

[a] Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet & Stockholm University, Stockholm, Sweden.

[b] Center for Networked Biomedical Research in Epidemiology and Public Health (CIBERESP), Madrid, Spain.

[c] Instituto de Salud Global de Barcelona (ISGlobal), Barcelona, Spain.

[d] Universitat Pompeu Fabra (UPF), Barcelona, Spain.

[e] Unit of Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden.

Authors' contributions

Adrián Carballo-Casla: writing – original draft

Michelle M. Dunk: writing – review & editing

Carolina Donat-Vargas: writing – review & editing

Weili Xu: writing – review & editing

Corresponding author

Adrián Carballo-Casla, PhD

Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet & Stockholm University, Tomtebodavägen 18 A SE-171 77 Stockholm, Sweden.

E-mail: adrian.carballo.casla@ki.se

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For more than a hundred years, nitroglycerine (i.e., glyceryl trinitrate) has been a first-line treatment for angina pectoris and acute myocardial infarction [1]. Its deceptively simple mechanism of action is the elevation of nitric oxide (NO) levels which causes vasodilation, inhibits platelet aggregation, and improves blood circulation [1]. Given that cardiovascular disease is well established in the causal pathway of dementia, several randomized controlled trials (RCTs) have investigated the effect of nitrate or nitrite supplementation (i.e., the two main NO precursors) on cerebral blood perfusion and cognitive performance [2, 3]. Still, these RCTs have yielded inconsistent results, possibly because of small sample sizes and short intervention periods [3].

The large prospective cohort study accompanying this editorial was designed to clarify the relationship between dietary nitrate and dementia [4, 5]. It followed a sample of 9,543 Dutch participants for 14.5 years and showed that higher intake of dietary nitrate from vegetable sources was associated with an approximately 8% lower risk of developing dementia. No association was found, however, for nitrate from non-vegetable sources. Analyses were extensively adjusted for sociodemographic, lifestyle, and dietary variables, as well as for *APOE* ε4 status (a major genetic risk factor for Alzheimer's disease).

Contrary to the authors' expectations, dietary nitrate intake was unrelated to changes in cerebral perfusion or vascular pathology, which raises some questions about the specific mechanisms linking nitrate intake with dementia risk [4]. The authors propose two explanations for these null findings. On one hand, it is possible that NO affects small blood vessels and/or peripheral circulation, which may not be detected in brain imaging. On the other hand, NO could exert a protective effect on metabolic functions (i.e., reducing triglyceride levels, visceral fat accumulation, hyperinsulinemia, and insulin resistance), which

could have an impact on cognition beyond vascular brain health [6]. Though plausible, these hypotheses should be confirmed by additional investigations.

A key finding of this study was that the beneficial association between dietary nitrate intake and dementia was limited to vegetable sources [4]. This is in line with the growing evidence showing that the isolated consumption of specific nutrients or food components may not have the same health effects as the equivalent nutrients from whole foods [5]. In the case of nitrates and nitrites, positive synergies with antioxidants were first described in the 1970s [7]. Specifically, dietary nitrate is reduced to nitrite after ingestion, which can react with amines and amides in the stomach and form N-nitroso compounds (probable carcinogens to humans). Vitamins and polyphenols found in vegetables can, however, inhibit such endogenous nitrosation [8]. Moreover, nitrates and nitrites are precursors of NO, which, notwithstanding its endothelium-relaxing properties, is a free radical, and reactive oxygen species contribute to the pathogenesis of cancer, cardiovascular disease, and neurodegenerative diseases [9]. Then again, some vegetable antioxidants can protect against NO-driven oxidative stress and tissue injury [7].

With regards to non-vegetable nitrate sources, on one hand, nitrates and nitrites are added to meat as antimicrobial agents (i.e., to inhibit the growth of *Clostridium Botulinum*), and nitrites are used in meat and fish products for their color-fixing and flavoring properties. On the other hand, nitrates in drinking water are increasingly common due to the use of nitrogen fertilizers in intensive farming. Nitrate ingested via these two sources does not necessarily benefit from the protection conferred by vitamins and polyphenols and has been consistently linked to several types of cancer [10, 11]. Not only the negative effects of nitrites and NO could partially explain the differential associations of vegetable and non-vegetable nitrate

intake with dementia in this study, but also the lack of consistent and beneficial effects of nitrate supplementation in RCTs.

In the accompanying original research, dietary nitrate intake was estimated through a self-reported food frequency questionnaire [4]. Despite potential variations in nitrate content between organically and conventionally grown vegetables, between those grown undercover and in open fields, as well as between seasons, the authors' methodology has previously been validated against urinary samples. In any case, the use of urine nitrate would not have allowed for differentiation between dietary versus endogenously produced nitrate or between dietary sources, and -unless repeated measures are taken- it may not be a good indicator of long-term nitrate intake. It is worth mentioning that the frequency questionnaire collected information on individual foods and cooking techniques, as nitrate concentrations differ substantially within food groups and between food processing methods.

Some limitations are inherent to this study. First, the database used for non-vegetable nitrate calculations was less detailed and updated than that on vegetable nitrate. Second, the authors did not seem to account for nitrate present in drinking water, which can contribute to 12-15% of total dietary nitrate intake [10]. Third, participants were under continuous surveillance for dementia, but not for other forms of cognitive impairment, which precluded the use of cognitive decline and incident cognitive impairment in the analyses. Lastly, the correlations of total and vegetable nitrate intake with vegetable consumption (a source of fiber, vitamins, minerals, and other phytochemicals), and that between non-vegetable nitrate and animal products (e.g., processed meats, red meat, and high-fat dairy) do not allow to rule out dietary residual confounding [12, 13]. To minimize this bias, the authors alternatively adjusted the analyses for a diet quality score, a plant-based dietary index, and total vegetable consumption. Although these adjustments had little effect on the magnitude of the

associations between total and vegetable nitrate intake and dementia, the latter approach made them nonsignificant, possibly because of overadjustment.

The finding of lower dementia risk in relation to nitrate intake exclusively from vegetable sources -namely vegetables and legumes- complements a key trend that has emerged over time in the study of diet and dementia. Lower dementia risk has consistently been observed in relation to dietary patterns which are high in minimally processed plant-based foods (vegetables, fruits, whole grains, legumes, nuts, and seeds), with moderate amounts of fish and olive oil, and minimal amounts of animal-based (especially red meat and high-fat dairy, which are high in saturated fat), processed, and fried foods [13, 14]. The new findings by de Crom *et al.* suggest that higher nitrate intake from a diet rich in vegetables and legumes may be one key contributing factor to previous reports of dietary-related dementia risk [4].

This study is even more relevant because no pharmacological therapies for dementia exist aside from those aimed at symptom management [15]. Despite the potential of monoclonal antibodies for reducing amyloid markers and slowing cognitive and functional decline in early-stage Alzheimer's disease, they may not come without adverse events, to the point that some widely anticipated therapies have not been authorized on the grounds of the risks potentially outweighing the benefits [16, 17]. In this context of limited therapeutical options for disease modification or reversal, the prospect of a dietary intervention for dementia prevention with a focus on nitrate intake is exciting and underscores the importance of diet in mitigating dementia risk.

Further research is now needed to corroborate these findings, including examinations in other large samples which account for changes in dietary nitrate intake over time, investigation of specific underlying mechanisms using experimental studies, and RCTs to strengthen causal inference from the associations between vegetable nitrate and subsequent dementia risk.

Future directions also include the use of cerebrospinal fluid and blood-based biomarkers of dementia and Alzheimer's disease, which might highlight alternative mechanisms of action of dietary nitrate [18]. The role of microbiota should also be explored, given that oral bacteria are responsible for the metabolization of dietary nitrate to nitrite, while the gut microbiome could play a protective role against nitrosamines [10]. Finally, gene-diet interactions could operate in the liberation, absorption, distribution, metabolism, and excretion of nitrate, nitrite, and NO [19]. Studies on nitrate and dementia are far from over.

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