



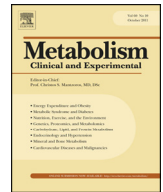
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Contents lists available at ScienceDirect

Metabolism Clinical and Experimental

journal homepage: www.metabolismjournal.com

Editorials

Mediterranean diet as a nutritional approach for COVID-19

Keywords:

COVID-19
 Coronavirus disease 2019
 SARS-CoV-2
 Severe acute respiratory syndrome coronavirus 2
 Mediterranean diet
 Nutrition
 Obesity
 Anti-inflammatory
 Inflammation
 Antioxidant

The 2019 coronavirus (COVID-19) disease pandemic, caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is associated with various clinical, mental, and psychological complications, and has challenged healthcare and social systems at a national and international level [1–3].

We and others have shown that obesity, central fat distribution, and adiposity-associated chronic diseases, e.g., diabetes mellitus and cardiometabolic disorders may lead to poor COVID-19 outcomes [4–6]. Common underlying pathophysiological features such as chronic inflammation, immune dysregulation, oxidative stress, increased cytokine production, endothelial dysfunction, increased number of angiotensin-converting enzyme 2 (ACE2)-expressing adipocytes and the possible role of adipose tissue as a viral reservoir, are among the factors that predispose to worse COVID-19 outcomes [4,6–8].

Obesity is in turn closely associated with lower socioeconomic status and lifestyle habits, with poor diet being one of the most significant contributing factors, building upon a given genetic background.

Disparities in nutrition, closely related to ethnicity, race, socioeconomic status, and other social determinants of health, may result in a suboptimal diet that is associated with several cardiometabolic conditions linked to COVID-19 infection and its prognosis [9]. Following an unhealthy diet has unfavorable implications in terms of inflammation and oxidative stress, and thus may influence the final outcome by affecting the immune system and energy homeostasis. Thus, it would be of paramount importance to adopt healthy eating habits during the COVID-19 outbreak and to maintain balanced dietary practices, as outlined in the recent nutritional advice published by the World Health Organization [10], as well as professional associations, societies, and governments [7].

Current evidence and expert opinion encourage the consumption of fresh and unprocessed plant foods such as vegetables, fruits and whole grain products. Moreover, they highlight the importance of vitamins and minerals such as zinc, vitamin C, D, A and the maintenance of adequate hydration, while they suggest a moderate consumption of fat, preferring unsaturated fats, and avoiding sugar and salt intake.

The Mediterranean diet, one of the healthiest dietary patterns worldwide, reputed for its demonstrated preventive effect of cardiovascular diseases and type-2 diabetes in several trials [11–13] is characterized by the inclusion of mainly plant-derived nutritional components, namely fruits, vegetables, legumes, nuts, and olive oil, all of which are significant sources of bioactive polyphenols. Polyphenols, particularly flavonoids and their metabolites, demonstrate pleiotropic health-promoting effects, especially in cardiovascular and metabolic disorders, due to their antioxidant, anti-inflammatory, and anti-thrombotic properties [14,15]. These properties become even more critical in view of the exaggerated inflammatory and pro-thrombotic milieu associated with COVID-19 severe illness [16,17]. Polyphenols alleviate the immune response, increase antioxidant defenses, improve vascular reactivity, and decrease tissue inflammation and cell infiltration, thus promoting metabolic and cardiovascular health; these beneficial effects appear to be exerted through preventing the activation of the Nuclear factor- κ B (NF- κ B) signaling pathway and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and by reducing the levels of pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor- α [18,19]. Ellagic acid, a particularly bioactive phenolic compound found in some fruits and nuts, also acts via interaction with microbiota and epigenetic regulation [18].

Consumption of nuts and dried fruits such as raisins, which are integral part of the Mediterranean diet, promotes cardiometabolic health through their rich composition in nutrients and bioactive phytochemicals, among which polyphenols play a central role as antioxidant and anti-inflammatory molecules [20]. Both nuts and dried fruits are easily storable and concentrated sources of nutrients; the latter are also portable alternatives to fresh fruits. In particular, Corinthian currants, derived from a specific type of black grape, are characterized by a low to moderate glycemic index [21] and an abundance in minerals, vitamins, fiber, flavonoids and phenolics [22,23]. Ongoing research on potential antimicrobial properties of several Mediterranean foods, such as raisins and olive products, should be considered in the context of current research efforts to elucidate any protective effects of flavonoids and other polyphenols against the coronavirus infection [24,25].

In summary, adherence to the Mediterranean diet has a favorable impact on cardiovascular diseases and other cardiometabolic disorders, such as diabetes that predispose to COVID-19 infection and related outcomes. The Mediterranean diet, having high antioxidant, anti-inflammatory, and potential antimicrobial and immunomodulatory properties, is a promising and relatively easy method to attenuate the severity of COVID-19 infection. Therefore, there is a critical and imminent need for more in vivo studies and well-designed clinical trials to explore the potentially beneficial effects of the Mediterranean diet and/or some of its key components, such as nuts, dried fruits and olive oil, in preventing COVID-19 infection and/or improving disease-related outcomes.

The COVID-19 pandemic has led to a profound change of food habits and dietary behaviors, both individually and globally. A large Italian

Abbreviations: ACE2, angiotensin-converting enzyme 2; COVID-19, 2019 coronavirus disease; NADPH, nicotinamide adenine dinucleotide phosphate; NF- κ B, nuclear factor- κ B; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

population survey found that during the COVID-19 lockdown 35.8% of the studied subjects consumed less healthy foods, while 48.6% reported weight gain. Of note, greater adherence to the Mediterranean diet was observed in Central and Northern Italy, the epicenter of the pandemic, in which areas the BMI was also lower [26]. Elderly participants reported lower adherence to the Mediterranean diet compared to those aged 18–30 years old. Moreover, according to a Spanish study, female gender, middle age, and higher educational level were associated with higher adherence to the Mediterranean diet during home confinement [27]. Although it appears that relatively younger and more educated individuals increase their adherence to the Mediterranean diet in the middle of the pandemic the beneficial effects of this diet need to be formally and appropriately documented, and if positive as expected, findings need to be disseminated and become part of public health policy.

In conclusion, the Mediterranean diet may represent a potential strategic therapeutic approach to address both short- and long-term conditions associated with COVID-19 infection and severity and improve mortality and the overall well-being of affected populations. From a public health viewpoint, such efforts need to be combined with programs aiming to increase social awareness for obesity and the need to prevent and treat it as well as work required to eliminate health inequalities and to address the lack of access to healthy and nutritious food worldwide.

Funding

None.

Author contribution statement

All authors contributed to the conception and design of the overall commissioned work. This process was chaired by CSM. All authors were involved in the drafting and revision of the report. AMA and CSM lead the drafting and editing process. All authors approved the final version for publication and agree to be held accountable for resolving any future questions related to the integrity or accuracy of the work.

Declaration of competing interest

Drs. Angelidi and Kokkinos have no potential conflicts of interest to disclose.

Dr. Katechaki is employed by the Agricultural Cooperatives' Union of Aeghion (ACUA) but this work was outside her employment duties.

Dr. Ros reports grants, personal fees, non-financial support and other from California Walnut Commission, grants, personal fees, non-financial support and other from Alexion, personal fees, non-financial support and other from Ferrer International, personal fees, non-financial support and other from Danone, outside the submitted work.

Dr. Mantzoros reports grants, personal fees and other from Coherus Inc., grants, personal fees and other from Pangea inc, grants and personal fees from Novo Nordisk, grants and personal fees from Eisai, personal fees and non-financial support from Ansh, personal fees and non-financial support from PES, personal fees and non-financial support from California Walnut Commission, personal fees from Genfit, personal fees from Astra Zeneca, personal fees from Aegerion, personal fees from Regeneron, personal fees from CardioMetabolic Health Conference - The Metabolic Institute of America, personal fees from Alexion, non-financial support from Amarin, non-financial support from Jansen, non-financial support from Boehringer Ingelheim, outside the submitted work.

References

- [1] Bi Q, Wu Y, Mei S, Ye C, Zou X, Zhang Z, et al. Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study [published correction appears in *Lancet Infect Dis*. 2020 Jul;20(7):e148]. *Lancet Infect Dis*. 2020;20(8):911–9. [https://doi.org/10.1016/S1473-3099\(20\)30287-5](https://doi.org/10.1016/S1473-3099(20)30287-5).
- [2] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med*. 2020;382(8):727–33. <https://doi.org/10.1056/NEJMoa2001017>.
- [3] Mukhtar S, Mukhtar S. Letter to the editor: mental health and psychological distress in people with diabetes during COVID-19. *Metabolism*. 2020;108:154248. <https://doi.org/10.1016/j.metabol.2020.154248>.
- [4] Palaiodimos L, Kokkinidis DG, Li W, Karamanis D, Ognibene J, Arora S, et al. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. *Metabolism*. 2020;108:154262. <https://doi.org/10.1016/j.metabol.2020.154262>.
- [5] Sattar N, McInnes IB, McMurray JJV. Obesity is a risk factor for severe COVID-19 infection: multiple potential mechanisms. *Circulation*. 2020;142:4–6.
- [6] Angelidi AM, Belanger MJ, Mantzoros CS. Commentary: COVID-19 and diabetes mellitus: what we know, how our patients should be treated now, and what should happen next. *Metabolism*. 2020;107:154245. <https://doi.org/10.1016/j.metabol.2020.154245>.
- [7] de Faria Coelho-Ravagnani C, Corgosinho FC, Sanches FFZ, Prado CMM, Laviano A, Mota JF. Dietary recommendations during the COVID-19 pandemic [published online ahead of print, 2020 Jul 12]. *Nutr Rev*. 2020:nuaa067. <https://doi.org/10.1093/nutrit/nuaa067>.
- [8] Kruglikov IL, Scherer PE. The role of adipocytes and adipocyte-like cells in the severity of COVID-19 infections. *Obesity (Silver Spring)*. 2020;28(7):1187–90. <https://doi.org/10.1002/oby.22856>.
- [9] Belanger MJ, Hill MA, Angelidi AM, Dalamaga M, Sowers JR, Mantzoros CS. Covid-19 and disparities in nutrition and obesity. *N Engl J Med*. 2020;383(11):e69. <https://doi.org/10.1056/NEJMp2021264>.
- [10] World Health Organization. Nutrition advice for adults during the COVID-19 outbreak. <http://www.emro.who.int/nutrition/nutrition-infocus/nutrition-advice-for-adults-during-the-covid-19-outbreak.html>; 2020. (Accessed date: 10 October 2020).
- [11] Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med*. 2018;378(25):e34. <https://doi.org/10.1056/NEJMoa1800389>.
- [12] Salas-Salvadó J, Bulló M, Estruch R, Ros E, Covas MI, Ibarrola-Jurado N, et al. Prevention of diabetes with Mediterranean diets: a subgroup analysis of a randomized trial [published correction appears in *Ann Intern Med*. 2018 Aug 21;169(4):271–272]. *Ann Intern Med*. 2014;160(1):1–10. <https://doi.org/10.7326/M13-1725>.
- [13] Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. *N Engl J Med*. 2003;348(26):2599–608. <https://doi.org/10.1056/NEJMoa025039>.
- [14] Mozaffarian D, Wu JHY. Flavonoids, dairy foods, and cardiovascular and metabolic health: a review of emerging biologic pathways. *Circ Res*. 2018;122:369–84.
- [15] Del Rio D, Rodriguez-Mateos A, Spencer JP, Tognolini M, Borges G, Crozier A. Dietary (poly)phenolics in human health: structures, bioavailability, and evidence of protective effects against chronic diseases. *Antioxid Redox Signal*. 2013;18(14):1818–92. <https://doi.org/10.1089/ars.2012.4581>.
- [16] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):1033–4. [https://doi.org/10.1016/S0140-6736\(20\)30628-0](https://doi.org/10.1016/S0140-6736(20)30628-0).
- [17] Hanff TC, Mohareb AM, Giri J, Cohen JB, Chirinos JA. Thrombosis in COVID-19 [published online ahead of print, 2020 Aug 28]. *Am J Hematol*. 2020. <https://doi.org/10.1002/ajh.25982>.
- [18] Kang I, Buckner T, Shay NF, Gu L, Chung S. Improvements in metabolic health with consumption of ellagic acid and subsequent conversion into urolithins: evidence and mechanisms. *Adv Nutr*. 2016;7(5):961–72. <https://doi.org/10.3945/an.116.012575>.
- [19] Andriantsitohaina R, Auger C, Chataigneau T, Étienne-Selloum N, Li H, Martínez MC, et al. Molecular mechanisms of the cardiovascular protective effects of polyphenols. *Br J Nutr*. 2012;108(9):1532–49. <https://doi.org/10.1017/S0007114512003406>.
- [20] Alasalvar C, Salas-Salvadó J, Ros E. Bioactives and health benefits of nuts and dried fruits. *Food Chem*. 2020;314:126192.
- [21] Kanellos PT, Kaliora AC, Liaskos C, Tentolouris NK, Perrea D, Karathanos VT. A study of glycemic response to Corinthian raisins in healthy subjects and in type 2 diabetes mellitus patients. *Plant Foods Hum Nutr*. 2013;68(2):145–8. <https://doi.org/10.1007/s11130-013-0348-y>.
- [22] Chiou A, Panagopoulou EA, Gatzali F, De Marchi S, Karathanos VT. Anthocyanins content and antioxidant capacity of Corinthian currants (*Vitis vinifera* L., var. Apyrena). *Food Chem*. 2014;146:157–65. <https://doi.org/10.1016/j.foodchem.2013.09.062>.
- [23] Nikolaidaki EK, Chiou A, Christea M, Gkegka AP, Karvelas M, Karathanos VT. Sun dried Corinthian currant (*Vitis Vinifera* L., var. Apyrena) simple sugar profile and macronutrient characterization. *Food Chem*. 2017;221:365–72. <https://doi.org/10.1016/j.foodchem.2016.10.070>.
- [24] Annunziata G, Sanduzzi Zamparelli M, Santoro C, Ciampaglia R, Stornaiuolo M, Tenore GC, et al. May polyphenols have a role against coronavirus infection? An overview of in vitro evidence. *Front Med (Lausanne)*. 2020;7:240. <https://doi.org/10.3389/fmed.2020.00240>.
- [25] Mendonca P, Soliman KFA. Flavonoids activation of the transcription factor Nrf2 as a hypothesis approach for the prevention and modulation of SARS-CoV-2 infection severity. *Antioxidants (Basel)*. 2020;9(8):659. <https://doi.org/10.3390/antiox9080659>.
- [26] Di Renzo L, Gualtieri P, Pivari F, Soldati L, Attinà A, Cinelli G, et al. Eating habits and lifestyle changes during COVID-19 lockdown: an Italian survey. *J Transl Med*. 2020;18(1):229. <https://doi.org/10.1186/s12967-020-02399-5>.

- [27] Rodríguez-Pérez C, Molina-Montes E, Verardo V, Artacho R, García-Villanova B, Guerra-Hernández E, et al. Changes in dietary behaviours during the COVID-19 outbreak confinement in the Spanish COVIDiet Study. *Nutrients*. 2020;12(6):1730. Published 2020 Jun 10 <https://doi.org/10.3390/nu12061730>.

Angeliki M. Angelidi

Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA

Alexander Kokkinos

First Department of Propaedeutic Internal Medicine and Diabetes Center, Medical School, National and Kapodistrian University of Athens, Laiko General Hospital, Athens 11527, Greece

Eleftheria Katechaki

Agricultural Cooperatives' Union of Aeghion, Corinthou 201, Aeghion 25100, Greece

Emilio Ros

*Lipid Clinic, Department of Endocrinology and Nutrition, Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), Hospital Clínic, Barcelona 08036, Spain
CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Madrid 28029, Spain*

Christos S. Mantzoros

*Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA
Section of Endocrinology, VA Boston Healthcare System, Harvard Medical School, Boston, MA 02115, USA*

Corresponding author at: Beth Israel Deaconess Medical Center, 330 Brookline Ave, Boston, MA 02215, United States of America

E-mail address: cmantzor@bidmc.harvard.edu