Contribution of biological age-predictive biomarkers to nutrition research: A systematic review of the current evidence and implications for future research

Dr George Siopis, PhD & Prof Judi Porter, PhD

Online Supplementary Material

Table of contents

Supplementary methods

i. Supplementary Table 1. Complete search strategy for studies assessing the effect of nutritional biomarkers on biological ageing in older adults

Ovid MEDLINE(R) ALL <1946 to September 28, 2021>

Date of search: 30/9/2021

#	Searches	Results
1	(biological adj1 age).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1729
2	Aging/	238838
3	senescenc*.mp.	46228
4	seno*.mp.	3347
5	gero*.mp.	13604
6	geriatric*.mp.	110550
7	frail*.mp.	32200
8	Frail Elderly/	13065
9	Frailty/	5008
10	Geriatric Assessment/	29991
11	Sarcopenia/ or sarcopeni*.mp.	12387
12	Telomere/	16246
13	DNA Methylation/	54316
14	Genomic Instability/	8605
15	(dysregulat* adj3 nutrient sensing).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	20
16	(mitochondr* adj3 dysfunction*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	27541
17	(stem cell* adj3 exhaust*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	283
18	or/1-17	509397
19	funtion*.mp.	282
20	los*.mp.	1382672
21	declin*.mp.	379685

22	reduc*.mp.	3832123
23	or/20-22	5143093
24	19 and 23	51
25	lifespan.mp. or Longevity/	49151
26	short*.mp.	1292776
27	23 or 26	6090528
28	25 and 27	20868
29	18 or 24 or 28	523979
30	Genetic Markers/	57277
31	marker*.mp.	852022
32	biomarker*.mp.	659061
33	Biomarkers/	309154
34	or/30-33	1310877
35	29 and 34	42704
36	nutrition*.mp.	419534
37	diet*.mp.	807802
38	36 or 37	1068245
39	Research/	202699
40	research.mp.	11034578
41	39 or 40	11034578
42	38 and 41	444683
43	35 and 42	2055
44	historical article/	365612
45	letter/	1153532
46	case report.mp. or Case Reports/	2273161
47	or/44-46	3561094
48	43 not 47	2045
49	limit 48 to humans	1322
50	limit 49 to "all aged (65 and over)"	717

EBM Reviews - Cochrane Central Register of Controlled Trials <August 2021>
Date of search: 30/9/2021

#	Searches	Results
1	(biological adj1 age).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	87
2	Aging/	3764
3	senescenc*.mp.	563
4	seno*.mp.	210
5	gero*.mp.	945
6	geriatric*.mp.	9689
7	frail*.mp.	4400
8	Frail Elderly/	756
9	Frailty/	207
10	Geriatric Assessment/	1554
11	Sarcopenia/ or sarcopeni*.mp.	1772
12	Telomere/	67
13	DNA Methylation/	276
14	Genomic Instability/	22
15	(dysregulat* adj3 nutrient sensing).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	0
16	(mitochondr* adj3 dysfunction*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	397
17	(stem cell* adj3 exhaust*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	1
18	or/1-17	19791
19	funtion*.mp.	90
20	los*.mp.	111253
21	declin*.mp.	35674
22	reduc*.mp.	457293
23	or/20-22	543841
24	19 and 23	18
25	lifespan.mp. or Longevity/	1308
26	short*.mp.	149977
27	23 or 26	635196
28	25 and 27	735
29	18 or 24 or 28	20494
30	Genetic Markers/	303
31	marker*.mp.	61818
32	biomarker*.mp.	46553
33	Biomarkers/	15160
34	or/30-33	90803
35	29 and 34	1531
36	nutrition*.mp.	47071

37	diet*.mp.	99377
38	36 or 37	124767
39	Research/	240
40	research.mp.	168809
41	39 or 40	168809
42	38 and 41	14722
43	35 and 42	83
44	historical article/	0
45	letter/	0
46	case report.mp. or Case Reports/	11106
47	or/44-46	11106
48	43 not 47	81

ESCOhost CINAHL Complete
Date of search: 30/9/2021

#	Searches	Results
1	"biological AND age"	41
2	"senescence"	34532
3	(MH "Frail Elderly") OR (MH "Geriatric Functional Assessment") OR (MH "Geriatric Nutritional Physiology") OR (MH "Aged+") OR "geriatrics or older adults or elderly"	888280
4	(MH "Sarcopenia") OR "sarcopenia"	4679
5	(MH "Telomere") OR "telomere shortening"	1058
6	(MH "DNA Methylation") OR "dna methylation"	4830
7	"genomic instability"	528
8	"mitochondrial dysfunction"	2715
9	"stem cell exhaustion"	18
10	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9	913795
11	"loss of function"	3025
12	(MH "Functional Status") OR "functional decline"	27927
13	S11 OR S12	30888
14	"lifespan"	7865
15	(MH "Life Expectancy") OR (MH "Quality of Life+")	139318
16	S14 OR S15	14641
17	S10 OR S13 OR S16	1026180
18	(MH "Genetic Markers") OR (MH "Biological Markers+") OR "marker"	118276
19	"biomarker"	41800
20	S18 OR S19	134547
21	S17 AND S20	36970
22	(MH "Nutrition+") OR "nutrition"	237468
23	(MH "Diet+") OR "diet"	187168
24	"dietary"	136524
25	"dietetics"	7271
26	S22 OR S23 OR S24 OR S25	362897
27	(MH "Research+") OR "research"	3133156
28	S26 AND S27	186041
29	S21 AND S28	2210
30	S21 AND S28	447
	Limiters - Exclude MEDLINE records; Human; Age Groups: Aged: 65+ years Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	

ii. Supplementary Table 2. Inclusion & Exclusion criteria for selection of studies assessing the effect of nutritional biomarkers on biological ageing in older adults

	Inclusion criteria	Exclusion criteria
Population	Older adults (≥65 years) and mixed populations (mean age ≥65 years, or include only data for ≥65 years population if reported stratified by age)	Children, adolescents and adults <65 years old
Intervention	Research examining the association between nutrition and biological age .	Not research examining the association between nutrition and biological age
Comparator	No restriction	No restriction
Outcomes	Clinical, molecular or (epi-)genetic biomarkers of ageing and biological age, including telomere attrition, DNA methylation, genomic instability, nutrient sensing dysregulation, mitochondrial dysfunction, cognitive function	Mortality/life expectancy, morbidity assessed by admission and length of stay in hospital, sarcopenia, frailty, and clinical markers of disease (HbA1c, blood pressure, lipid profile, weight, BMI, BMD, creatinine, albumin, neurofilament, CRP)
Study design	RCT (including cluster, pilot, crossover, and prospective), observational, cross-sectional	pre/post, case studies, case series, case-control, meta-analyses, small pilot studies (≤10 participants per group)
Language	No restriction	No restriction
Published date	No restriction	No restriction
Publication type	Research article reporting findings of eligible study designs	Reviews, conference abstracts, protocols, commentaries, animal studies, unpublished literature

BMD=bone mineral density; BMI=body mass index; CRP=C-reactive protein; RCT=randomised controlled trials.

iii. Supplementary Table 3. Summary of extracted data from included studies assessing the effect of nutritional biomarkers on biological ageing in older adults

Publication details	Authors' details	Study details	Participants characteristics	Intervention type	Results and conclusion
• Title • Journal • Year	• Names • Affiliations • Funding • Conflict of Interest	• Start date • End date • Country • Design • Purpose • Blinding * • Randomisation method * • Allocation concealment * • Retention rate • Statistical analyses methods	• Condition • Severity of condition • Comorbidities • Sample size • Recruitment process • Inclusion criteria • Exclusion criteria • Demographics (age, sex, race, ethnicity, income, education, remoteness of residence)	• Type * • Duration * • Frequency * • Dietary assessments • Biochemical assessments • Other details • Primary and secondary outcomes • Details of care of comparator group *	• Time point for follow-up • Primary and secondary outcome results and statistical significance • Validated tool for measurement • Authors' conclusion • Limitations

* If a randomised controlled trial.

**If a non-randomised controlled trial.

Supplementary results

i. List of excluded full texts with reasons for exclusion

Ineligible participants

Arai Y, Hirose N, Nakazawa S, et al. Lipoprotein metabolism in Japanese centenarians: effects of apolipoprotein E polymorphism and nutritional status. *J Am Geriatr Soc*. 2001;49(11):1434-1441. doi:10.1046/j.1532-5415.2001.4911234.x

Cassidy A, De Vivo I, Liu Y, et al. Associations between diet, lifestyle factors, and telomere length in women. *Am J Clin Nutr*. 2010;91(5):1273-1280. doi:10.3945/ajcn.2009.28947

Crous-Bou M, Fung TT, Prescott J, et al. Mediterranean diet and telomere length in Nurses' Health Study: population based cohort study. *BMJ*. 2014;349:g6674. Published 2014 Dec 2. doi:10.1136/bmj.g6674

Farzaneh-Far R, Lin J, Epel ES, Harris WS, Blackburn EH, Whooley MA. Association of marine omega-3 fatty acid levels with telomeric aging in patients with coronary heart disease. *JAMA*. 2010;303(3):250-257. doi:10.1001/jama.2009.2008

Fitzgerald KN, Hodges R, Hanes D, et al. Potential reversal of epigenetic age using a diet and lifestyle intervention: a pilot randomized clinical trial. *Aging (Albany NY)*. 2021;13(7):9419-9432. doi:10.18632/aging.202913

Kalstad AA, Tveit S, Myhre PL, et al. Leukocyte telomere length and serum polyunsaturated fatty acids, dietary habits, cardiovascular risk factors and features of myocardial infarction in elderly patients. *BMC Geriatr*. 2019;19(1):376. Published 2019 Dec 27. doi:10.1186/s12877-019-1383-9

Kiefer A, Lin J, Blackburn E, Epel E. Dietary restraint and telomere length in pre- and postmenopausal women. *Psychosom Med*. 2008;70(8):845-849. doi:10.1097/PSY.0b013e318187d05e

Le Goallec A, Patel CJ. Age-dependent co-dependency structure of biomarkers in the general population of the United States. *Aging (Albany NY)*. 2019;11(5):1404-1426. doi:10.18632/aging.101842

Liu JJ, Prescott J, Giovannucci E, Hankinson SE, Rosner B, De Vivo I. One-carbon metabolism factors and leukocyte telomere length. *Am J Clin Nutr*. 2013;97(4):794-799. doi:10.3945/ajcn.112.051557

Milte CM, Russell AP, Ball K, Crawford D, Salmon J, McNaughton SA. Diet quality and telomere length in older Australian men and women. *Eur J Nutr*. 2018;57(1):363-372. doi:10.1007/s00394-016-1326-6

Min KB, Min JY. Association between leukocyte telomere length and serum carotenoid in US adults. *Eur J Nutr*. 2017;56(3):1045-1052. doi:10.1007/s00394-016-1152-x

Peng H, Mete M, Desale S, et al. Leukocyte telomere length and ideal cardiovascular health in American Indians: the Strong Heart Family Study. *Eur J Epidemiol*. 2017;32(1):67-75. doi:10.1007/s10654-016-0199-6

Quach A, Levine ME, Tanaka T, et al. Epigenetic clock analysis of diet, exercise, education, and lifestyle factors. *Aging (Albany NY)*. 2017;9(2):419-446. doi:10.18632/aging.101168

Shu Y, Wu M, Yang S, Wang Y, Li H. Association of dietary selenium intake with telomere length in middle-aged and older adults. *Clin Nutr*. 2020;39(10):3086-3091. doi:10.1016/j.clnu.2020.01.014

Stein PK, Soare A, Meyer TE, Cangemi R, Holloszy JO, Fontana L. Caloric restriction may reverse age-related autonomic decline in humans. *Aging Cell*. 2012;11(4):644-650. doi:10.1111/j.1474-9726.2012.00825.x

Uribarri J, Cai W, Peppa M, et al. Circulating glycotoxins and dietary advanced glycation endproducts: two links to inflammatory response, oxidative stress, and aging. *J Gerontol A Biol Sci Med Sci*. 2007;62(4):427-433. doi:10.1093/gerona/62.4.427

Yang Y, Kozloski M. Sex differences in age trajectories of physiological dysregulation: inflammation, metabolic syndrome, and allostatic load. *J Gerontol A Biol Sci Med Sci*. 2011;66(5):493-500. doi:10.1093/gerona/glr003

Ineligible intervention

Franzke B, Schober-Halper B, Hofmann M, et al. Chromosomal stability in buccal cells was linked to age but not affected by exercise and nutrients - Vienna Active Ageing Study (VAAS), a randomized controlled trial. *Redox Biol*. 2020;28:101362. doi:10.1016/j.redox.2019.101362

Gaydosh L, Belsky DW, Glei DA, Goldman N. Testing Proposed Quantifications of Biological Aging in Taiwanese Older Adults. *J Gerontol A Biol Sci Med Sci*. 2020;75(9):1680-1685. doi:10.1093/gerona/glz223

Hastings WJ, Shalev I, Belsky DW. Comparability of biological aging measures in the National Health and Nutrition Examination Study, 1999-2002. *Psychoneuroendocrinology*. 2019;106:171-178. doi:10.1016/j.psyneuen.2019.03.012

Liu B, Sun Y, Xu G, et al. Association between Body Iron Status and Leukocyte Telomere Length, a Biomarker of Biological Aging, in a Nationally Representative Sample of US Adults. *J Acad Nutr Diet*. 2019;119(4):617-625. doi:10.1016/j.jand.2018.09.007

Liu D, Zhu Z, Zhou L, Yang M. The joint effects of frailty and telomere length for predicting mortality in older adults: the National Health and Nutrition Examination Survey 1999-2002. *Aging Clin Exp Res*. 2020;32(9):1839-1847. doi:10.1007/s40520-019-01376-3

Parker DC, Bartlett BN, Cohen HJ, et al. Association of Blood Chemistry Quantifications of Biological Aging With Disability and Mortality in Older Adults. *J Gerontol A Biol Sci Med Sci*. 2020;75(9):1671-1679. doi:10.1093/gerona/glz219

Ineligible outcomes

Brouwer-Brolsma EM, van de Rest O, Tieland M, et al. Serum 25-hydroxyvitamin D is associated with cognitive executive function in Dutch prefrail and frail elderly: a cross-sectional study exploring the associations of 25-hydroxyvitamin D with glucose metabolism, cognitive performance and depression. *J Am Med Dir Assoc*. 2013;14(11):852.e9-852.e8.52E17. doi:10.1016/j.jamda.2013.06.010

de Leeuw FA, van de Rest O, Doorduijn AS, et al. Associations Between Nutrient Intake and Corresponding Nutritional Biomarker Levels in Blood in a Memory Clinic Cohort: The NUDAD Project. *J Am Med Dir Assoc*. 2020;21(10):1436-1438. doi:10.1016/j.jamda.2020.04.031

García-Calzón S, Gea A, Razquin C, et al. Longitudinal association of telomere length and obesity indices in an intervention study with a Mediterranean diet: the PREDIMED-NAVARRA trial. *Int J Obes (Lond)*. 2014;38(2):177-182. doi:10.1038/ijo.2013.68

Gardener SL, Rainey-Smith SR, Barnes MB, et al. Dietary patterns and cognitive decline in an Australian study of ageing. *Mol Psychiatry*. 2015;20(7):860-866. doi:10.1038/mp.2014.79

Ghosh TS, Rampelli S, Jeffery IB, et al. Mediterranean diet intervention alters the gut microbiome in older people reducing frailty and improving health status: the NU-AGE 1-year dietary intervention across five European countries. *Gut*. 2020;69(7):1218-1228. doi:10.1136/gutjnl-2019-319654

Levine ME. Modeling the rate of senescence: can estimated biological age predict mortality more accurately than chronological age?. *J Gerontol A Biol Sci Med Sci*. 2013;68(6):667-674. doi:10.1093/gerona/gls233

Lindberg M, Saltvedt I, Sletvold O, Bjerve KS. Long-chain n-3 fatty acids and mortality in elderly patients. *Am J Clin Nutr*. 2008;88(3):722-729. doi:10.1093/ajcn/88.3.722

Liu Z, Kuo PL, Horvath S, Crimmins E, Ferrucci L, Levine M. A new aging measure captures morbidity and mortality risk across diverse subpopulations from NHANES IV: A cohort study [published correction appears in PLoS Med. 2019 Feb 25;16(2):e1002760]. *PLoS Med*. 2018;15(12):e1002718. Published 2018 Dec 31. doi:10.1371/journal.pmed.1002718

Talukdar T, Zamroziewicz MK, Zwilling CE, Barbey AK. Nutrient biomarkers shape individual differences in functional brain connectivity: Evidence from omega-3 PUFAs. *Hum Brain Mapp*. 2019;40(6):1887-1897. doi:10.1002/hbm.24498

Ineligible study design

de Jong N. Nutrition and senescence: healthy aging for all in the new millennium?. *Nutrition*. 2000;16(7-8):537-541. doi:10.1016/s0899-9007(00)00317-8

González-Guardia L, Yubero-Serrano EM, Delgado-Lista J, et al. Effects of the Mediterranean diet supplemented with coenzyme q10 on metabolomic profiles in elderly men and women. *J Gerontol A Biol Sci Med Sci*. 2015;70(1):78-84. doi:10.1093/gerona/glu098

ii. Supplementary Figure 1: Map of included studies assessing the effect of nutritional biomarkers on biological ageing in older adults

The map displays thirteen studies with a sum of 5043 participants from eight countries. The name of the first author is shown; the number denotes participants in the study. The locations of the studies were:

Author	Country	Sample
Alonso-Pedrero L.	Spain	886
Atzmon G.	USA	139
Bowman G.L.	USA	104
Chang K.V.	Taiwan	72
Freitas-Simoes T.M.	Spain	344
Garcia-Calzon S.	Spain	520
Gensous N.	Italy & Poland	120
Handing E.P.	USA	1308
Nettleton J.A.	USA	840
O' Callachan N.	Australia	44
Praveen G.	India	428
Seesen M.	Thailand	122
Zwilling C.E.	USA	116

Below the number of participants per each country, and the classification of the income economy of the country according to World Bank:[1]

Country	Income economy	Sample
Australia	High	44
India	Lower-Middle	428
Italy	High	60
Poland	High	60
Spain	High	1750
Taiwan	High	72
Thailand	Upper-Middle	122
USA	High	2507

1. The World Bank. World Bank Country and Lending Groups – Country Classification. Available from https://datahelpdesk.worldbank.org/knowledgebase/articles/906519. Accessed on January 16, 2022.

iii. Supplementary Table 4: Summary of baseline demographic characteristics of older adults from included studies assessing the effect of nutritional biomarkers on biological ageing

Baseline mean age, years (SD)	71·7 (±8·8)
Gender, n (%)	
Men	2218 (44·0%)
Women	2825 (56·0%)
Ethnic background (race), n (%)	
European White	2483 (49·2%)
Hispanic	468 (9·3%)
African	354 (7·0%)
Indian	428 (8·5%)
Multiracial or unspecified	1310 (26·0%) *
Education, years (SD)	
Mean number of years completed at baseline	13.2 (±3·2) †
Marital status, mean % (range)	
Married	70 (65-75) ‡

SD=standard deviation. *Six studies did not report on the race of participants. †Three studies reported the percentage of participants that completed high-school or college, therefore the mean number of years of education is not known for these studies and has not been included in the calculations. ‡Only two studies reported on the marital status of participants.

iv. Supplementary Table 5: Summary of baseline lifestyle & clinical characteristics of older adults from included studies assessing the effect of nutritional biomarkers on biological ageing

Baseline mean BMI, kg/m^2 (SD)	26·6 (±1·8) *
Smokers, % (SD)	18·7 (±17·7) †
Drinkers, % (SD)	28·2 (±13·9) ‡
Participants with, %	
Hypertension	63.6 §
Dyslipidaemia	54.1 §
Diabetes	16.2 ¶

BMI=body mass index. SD=standard deviation. *One study reported the percentage of overweight or obese participants instead of the value for BMI, and therefore this study has not been included in the calculation. †Seven studies did not report on smoking. ‡Only three studies reported on drinking. §Only two studies reported percentage of participants with high blood pressure or dyslipidaemia. ¶ Only four studies reported percentage of participants with diabetes.

v. Supplementary Table 6: Summary of reported conflicts of interest and funding sources and assessment of conflict of interest of included studies assessing the effect of nutritional biomarkers on biological ageing in older adults

Authors, year	Conflict of Interest Statement	Conflict of Interest Exists	Funding Source
Alonso-Pedrero L., 2020 (28)	Yes	Possible	Both industry and non-industry
Atzmon G., 2002 (29)	No	Not known	Non-industry
Bowman G.L., 2012 (30)	Yes	Possible	Non-industry
Chang K.V., 2020 (31)	Yes	No	Non-industry
Freitas-Simoes T.M., 2019 (32)	Yes	Yes	Industry
Garcia-Calzon S.Z., 2015 (33)	Yes	Possible	Non-industry
Gensous N., 2020 (34)	Yes	No	Non-industry
Handing E.P., 2019 (35)	Yes	No	None
Nettleton J.A., 2008 (36)	Yes	No	Non-industry
O'Callaghan N., 2014 (37)	No	Not known	Non-industry
Praveen G., 2020 (38)	No	Not known	Non-industry
Seeseen M., 2020 (39)	Yes	No	Non-industry
Zwilling C.E., 2019 (40)	Yes	Yes	Industry

i. Supplementary Table 7: Detailed reported conflicts of interest and funding sources and assessment of conflict of interest of included studies assessing the effect of nutritional biomarkers on biological ageing in older adults

First author, year	Affiliations	Funding Declaration	Funding Categorisation	Conflict of Interest Declaration	COI assessment
Alonso-Pedrero L., 2020 (28)	Academic	Supported by Spanish National Institute of Health Carlos III (CIBEROBN) and European Regional Development Fund (FEDER) grant PI17/01795 (to MB-R) and the University of Navarra. Two researchers (LA-P and AO-R) leading to these results have received funding from "La Caixa" Banking Foundation.	Both	The authors report no conflicts of interest.	Possible COI
Atzmon G., 2002 (29)	Academic	This work was supported by grants from the Paul Beeson Physician Faculty Scholar in Aging Award, the Ellison Medical Foundation Senior Scholar Award (RO1-AG-18728-01A1), the General Clinical Research Center (MO1-RR12248-05), and the Diabetes Research and Training Center (DK 20541) at the Albert Einstein College of Medicine.	Non-Industry	No statement	Cannot be assessed

Bowman G.L., 2012 (30)	Academic	Supported by NIH/NCCAM AT004777 (G.L.B.), NIH/NIA P30 AG008017 (J.A.K.), NIH/NCRR UL1 RR024140 Oregon Clinical and Translational Research Institute, and Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development.	Non-Industry	Dr. Bowman serves on the editorial board of the Journal of Alzheimer's Disease, receives salary and research support from the NIH, and insurance reimbursement for patient care. Dr. Silbert receives research support from the NIH; receives reimbursement through Medicare or commercial insurance plans for providing clinical assessment and care for patients and for intraoperative neurophysiological monitoring; and is salaried to see patients at the Portland VA Medical Center. Dr. Howieson receives salary support from the NIH/NIA and insurance reimbursement from Medicare and other sources for providing patient care. Dr. Dodge receives research support from the NIH and serves on the Scientific Review Board of the National Alzheimer's Coordinating Center. Dr. Traber receives research support from the NIH and USDA National Institute for Food and Agriculture. Dr. Frei currently serves on the Scientific Advisory Board for Unilever, Englewood Cliffs, NJ; the Almond Board Nutrition & Health Advisory Council of the Almond Board of California, Modesto, CA; the Neutrogena Naturals Advisory Board, Los Angeles, CA; and is a consultant for Bayer Consumer Care Ltd., Basel, Switzerland. He receives research funding from NIH grants P01 AT002034 and T32 AT002688, and USANA Health Sciences, Inc., Salt Lake City, UT. Dr. Kaye receives research support from the Department of Veterans Affairs (Merit Review grant) and the NIH; directs a center that receives research support from the NIH, Elan Corporation, Intel Corporation; receives reimbursement through Medicare and commercial insurance plans for providing patient care; is salaried to see patients at the Portland VA Medical Center; serves as an unpaid Chair for the Work Group on Technology and for the National Alzheimer's Association and as an unpaid Commissioner for the Center for Aging Services and Technologies; receives an annual royalty from sales of the book, Evidence-based Dementia Practice; and serves on the editorial advisory board of Alzheimer's & Dementia. Dr. Shannon reports no disclosures. Dr. Quinn has received honoraria for speaking from Pfizer Inc, Novartis, and Forest Laboratories, Inc. and for consulting from Phylogeny, Inc.; is a co-inventor on a patent for the use of DHA for the treatment of Alzheimer's disease; receives compensation for conducting clinical trials from Elan Corporation, Bristol-Myers Squibb, and Baxter International Inc.; and receives funding from the NIH and Department of Veterans Affairs.	Possible COI
Chang K.V., 2020 (31)	Academic	The study was made possible by the National Taiwan University Hospital, Bei-Hu Branch, and the Ministry of Science and Technology (107-2314-B-002 -047 -MY3, 108-2321-B-001 -028 -MY2, 108-2321-B-001 -005, 107-2321-B-001-020, 106-2321-B-001-044).	Non-Industry	The authors declare no conflict of interest.	No COI exists

Freitas-Simoes T.M., 2019 (32)	Academic	This work was supported by a grant from the California Walnut Commission, Sacramento, CA. The funding agency had no input in the study design, data collection, analyses or writing and submission of the manuscript. AS-V is recipient of the Instituto de Salud Carlos III Miguel Servet fellowship (CP12/03299) and Fondo de Investigaci on Sanitaria grant - FEDER funds (PI15/01014).	Industry	JS, ER and AS-V have received research funding from the California Walnut Commission, Sacramento, CA. JS and ER are nonpaid members of its Scientific Advisory Committee. The other authors report no conflicts.	COI exists
Garcia-Calzon S.Z., 2015 (33)	Academic	Research relating to this work was supported by grants from Línea Especial, Nutrición, Obesidad y Salud of the University of Navarra (LE/97), the Spanish Government (FIS-ISCIII: PI050976, PI070240, PI081943, PI1002293, RTIC 06/0045, CIBERobn, and CNIC/06, SAF-2010-20367), and the Government of Navarra (PI41/2005, PI79/2006, PI36/2008, PI54/2009, and IDISNA). JRH and NS were supported by grant no. R44DK103377 from the US National Institute of Diabetes and Digestive and Kidney Diseases. The supplemental foods used	Non-Industry	JRH owns a controlling interest in Connecting Health Innovations LLC, a company planning to license the right to his invention of the DII from the University of South Carolina to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. NS is an employee of Connecting Health Innovations LLC. None of the other authors had a financial or other conflict of interest to disclose.	Possible COI

		in the study were donated by Patrimonio Comunal Olivarero and Hojiblanca, the California Walnut Commission, Borges S. A., and La Morella Nuts.			
Gensous N., 2020 (34)	Academic	This study was supported by the European Union's Seventh Framework Program under grant agreement n°266486 ("NU-AGE: New dietary strategies addressing the specific needs of the elderly population for healthy aging in Europe") and by the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement n°675003 ("PANINI: Physical Activity and Nutrition Influences In ageing"). We acknowledge support by the grant of the Ministry of Education and Science of the Russian Federation Agreement No. 075-15-2019-871.	Non-Industry	The authors declare that they have no competing interests.	No COI exists

Handing E.P., 2019 (35)	Academic	No funding was received for the current study.	None	Authors have no conflicts of interest.	No COI exists
Nettleton J.A., 2008 (36)	Academic	Supported by the National Heart, Lung, and Blood Institute (contracts N01-HC-95159 through N01-HC-95166 and N01-HC-95169) and the General Clinical Research Center (grant M01-RR00645) from the National Center for Research Resources and by funding from the MacArthur Foundation.	Non-Industry	None of the authors had a personal or financial conflict of interest.	No COI exists
O'Callaghan N., 2014 (37)	Academic	This work was funded, in part, by Mason Foundation. PH and NS are recipients of an ARC-Linkage project Grant (LP0776922) in partnership with Novasel Australia entitled "Cognitive and behavioral benefits of omega-3 fatty acids across the lifespan." NP is supported by NHMRC Program Grant funding (# 320860 and 631947).	Non-Industry	No statement	Cannot be assessed
Praveen G., 2020 (38)	Academic	GP, TS and MS received a research fellowship from the Indian Council of Medical Research, Government of India.	Non-Industry	No statement	Cannot be assessed
Seesen M., 2020 (39)	Academic	This research was funded by The Agricultural Research Development Agency (Public Organization) (ARDA) (Grant No. PRP6005021700).	Non-Industry	The authors declare no conflict of interest.	No COI exists

Zwilling C.E., 2019 (40)	Academic	This work was supported by a grant from Abbott Nutrition through the Center for Nutrition, Learning, and Memory at the University of Illinois (ANGC1205; PI: Barbey).	Industry	Dr. Barbey is a member of the Center for Nutrition Learning and Memory, and serves on the Scientific Advisory Board for the Institute of Inflammation and Ageing at the University of Birmingham, UK, and at Natrol, a vitamin and supplement producer.	COI exists