

REFERENCES

- [1] Beaton, Thomas. "How Preventive Healthcare Services Reduce Spending for Payers." *Health Payer Intelligence*, 29 Aug. 2017, <https://healthpayerintelligence.com/news/how-preventive-healthcare-services-reduce-spending-for-payers>.
- [2] Kamal, Rabah, and Julie Hudman. "What Do We Know about Spending Related to Public Health in the U.S. And Comparable Countries?" *PETERSON-KFF Health System Tracker*, 30 Sept. 2020, www.healthsystemtracker.org/chart-collection/what-do-we-know-about-spending-related-to-public-health-in-the-u-s-and-comparable-countries/#Preventive%20care%20spending%20by%20government/compulsory%20schemes%20as%20a%20share%20of%20total%20national%20health%20expenditures,%202018. Accessed 1 Apr. 2022.
- [3] "Questions and Answers on Dietary Supplements." U.S. Food and Drug Administration, 6 May 2022, www.fda.gov/food/information-consumers-using-dietary-supplements/questions-and-answers-dietary-supplements. Accessed 7 March 2022.
- [4] Shanahan C, De Lorimier R. Smart Prevention-Health Care Cost Savings Resulting from the Targeted Use of Dietary Supplements; 2013. <https://www.crnusa.org/sites/default/files/pdfs-hccs/SmartPrevention-fullreport0913.pdf>
- [5] DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials*. 1986;7(3):177-188. doi:10.1016/0197-2456(86)90046-2
- [6] Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division for Heart Disease and Stroke Prevention. About Heart Disease, Coronary Artery Disease (CAD). Online Database website. Atlanta, GA: Accessed February 1, 2022. https://www.cdc.gov/heartdisease/coronary_ad.htm#:~:text=Coronary%20artery%20disease%20is%20caused,This%20process%20is%20called%20atherosclerosis.
- [7] Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division for Heart Disease and Stroke Prevention. Heart Disease Facts. Online Database website. Atlanta, GA: Accessed February 1, 2022. <https://www.cdc.gov/heartdisease/facts.htm>
- [8] Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2019, Retrieved at <https://wwwn.cdc.gov/nchs/nhanes/default.aspx>
- [9] Agency for Healthcare Research and Quality. Medical Expenditure Panel Survey (MEPS). Retrieved February 2022, from <http://meps.ahrq.gov/mepsweb/>
- [10] Memorial Sloan-Kettering Cancer Center. About Herbs, Botanicals & Other Products - Integrative Medicine. January 2013. <http://www.mskcc.org/cancer-care/integrative-medicine/about-herbs-botanicals-other-products> (accessed January 2022).
- [11] Kris-Etherton PM, Harris WS, Appel LJ; AHA Nutrition Committee. American Heart Association. Omega-3 fatty acids and cardiovascular disease: new recommendations from the American Heart Association. *Arterioscler Thromb Vasc Biol*. 2003 Feb 1;23(2):151-2. doi: 10.1161/01.atv.0000057393.97337.ae. PMID: 12588750.
- [12] Bernasconi AA, Wiest MM, Lavie CJ, Milani RV, Laukkanen JA. Effect of Omega-3 Dosage on Cardiovascular Outcomes: An Updated Meta-Analysis and Meta-Regression of Interventional Trials. *Mayo Clin Proc*. 2021 Feb;96(2):304-313. doi: 10.1016/j.mayocp.2020.08.034. Epub 2020 Sep 17. PMID: 32951855.

- [13] National Institutes of Health (NIH) Office of Dietary Supplements (ODS). Magnesium Fact Sheet for Health Professionals. Online Database website. Atlanta, GA: Accessed February 14, 2022. <https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/>
- [14] Cunha AR, Umbelino B, Correia ML, et al. Magnesium and vascular changes in hypertension. *Int J Hypertens*. 2012; 2012:754250.
- [15] Del Gobbo LC, Imamura F, Wu JH, de Oliveira Otto MC, Chiuve SE, Mozaffarian D. Circulating and dietary magnesium and risk of cardiovascular disease: a systematic review and meta-analysis of prospective studies. *Am J Clin Nutr*. 2013 Jul;98(1):160-73. doi: 10.3945/ajcn.112.053132. Epub 2013 May 29. PMID: 23719551; PMCID: PMC3683817.
- [16] Cook NR, Cohen J, Hebert PR, Taylor JO, Hennekens CH. Implications of Small Reductions in Diastolic Blood Pressure for Primary Prevention. *Arch Intern Med*. 1995;155(7):701–709. doi:10.1001/archinte.1995.00430070053006
- [17] Hardy, Shakia T.; Loehr, Laura R.; Butler, Kenneth R.; Chakladar, Sujatro; Chang, Patricia P.; Folsom, Aaron R.; Heiss, Gerardo; MacLehose, Richard F.; Matsushita, Kunihiro; Avery, Christy L. (2015). Reducing the Blood Pressure–Related Burden of Cardiovascular Disease: Impact of Achievable Improvements in Blood Pressure Prevention and Control. *Journal of the American Heart Association*, 4(10), e002276–. doi:10.1161/JAHA.115.002276
- [18] Zhang, Xi; Li, Yufeng; Del Gobbo, Liana C.; Rosanoff, Andrea; Wang, Jiawei; Zhang, Wen; Song, Yiqing (2016). Effects of Magnesium Supplementation on Blood Pressure, Novelty and Significance. *Hypertension*, 68(2), 324–333. doi:10.1161/HYPERTENSIONAHA.116.07664
- [19] American Heart Association. Atherosclerosis. www.heart.org. Published November 6, 2020. Accessed February 16, 2022. <https://www.heart.org/en/health-topics/cholesterol/about-cholesterol/atherosclerosis>
- [20] Centers for Disease Control and Prevention. Cholesterol Information | cdc.gov. www.cdc.gov. Published September 27, 2021. <https://www.cdc.gov/cholesterol/index.htm#:~:text=About%2038%25%20of%20American%20adults>
- [21] Quagliani D, Felt-Gunderson P. Closing America's Fiber Intake Gap: Communication Strategies from a Food and Fiber Summit. *Am J Lifestyle Med*. 2016;11(1):80-85. Published 2016 Jul 7. doi:10.1177/1559827615588079
- [22] Grundy SM, Cleeman JJ, Merz CNB, et al. Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation*. 2004;110(2):227-239. doi:10.1161/01.cir.0000133317.49796.0e
- [23] Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhalra N, Peto R, Barnes EH, Keech A, Simes J, Collins R. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010 Nov 13;376(9753):1670-81. doi: 10.1016/S0140-6736(10)61350-5. Epub 2010 Nov 8. PMID: 21067804; PMCID: PMC2988224.
- [24] Shanahan, C.J., Gibb, R.D., McRorie, J.W., Brum, J.M. and Ritchey, M.E. (2020), "Economic impact analysis of the coronary heart disease-attributed health care cost savings and productivity gains from the use of Psyllium", *Nutrition & Food Science*, Vol. 50 No. 3, pp. 497-513. <https://doi.org/10.1108/NFS-03-2019-0067>
- [25] Ho HV, Sievenpiper JL, Zurbau A, Blanco Mejia S, Jovanovski E, Au-Yeung F, Jenkins AL, Vuksan V. A systematic review and meta-analysis of randomized controlled trials of the effect of barley β -glucan on LDL-C, non-HDL-C and apoB for cardiovascular disease risk reduction-iv. *Eur J Clin Nutr*. 2016 Nov;70(11):1239-1245. doi: 10.1038/ejcn.2016.89. Epub 2016 Jun 8. Erratum in: *Eur J Clin Nutr*. 2016 Nov;70(11):1340. PMID: 27273067.

- [26] Hartley L, May MD, Loveman E, Colquitt JL, Rees K. Dietary fibre for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev.* 2016 Jan 7;2016(1):CD011472. doi: 10.1002/14651858.CD011472.pub2. PMID: 26758499; PMCID: PMC7032538.
- [27] Gould AL1, Davies GM, Alemao E, Yin DD, Cook JR: Cholesterol reduction yields clinical benefits: meta-analysis including recent trials. *Clin Ther.* 2007 May;29(5):778-94.
- [28] National Institutes of Health Office of Dietary Supplements: Vitamin K Fact Sheet for Health Professionals <https://ods.od.nih.gov/factsheets/VitaminK-HealthProfessional/>. Accessed 3/1/2022.
- [29] Mandatori, D.; Pelusi, L.; Schiavone, V.; Pipino, C.; Di Pietro, N.; Pandolfi, A. The Dual Role of vitamin K2 in “Bone-Vascular Crosstalk”: Opposite Effects on Bone Loss and Vascular Calcification. *Nutrients* 2021, 13, 1222. <https://doi.org/10.3390/nu13041222>
- [30] G.C.M. Gast; N.M. de Roos; I. Sluijs; M.L. Bots; J.W.J. Beulens; J.M. Geleijnse; J.C. Witteman; D.E. Grobbee; P.H.M. Peeters; Y.T. van der Schouw (2009). A high menaquinone intake reduces the incidence of coronary heart disease., 19(7), 0–510. doi: 10.1016/j.numecd.2008.10.004
- [31] Geleijnse JM, Vermeer C, Grobbee DE, Schurgers LJ, Knapen MH, van der Meer IM, Hofman A, Witteman JC. Dietary intake of menaquinone is associated with a reduced risk of coronary heart disease: the Rotterdam Study. *J Nutr.* 2004 Nov;134(11):3100-5. doi: 10.1093/jn/134.11.3100. PMID: 15514282.
- [32] Haugsgjerd TR, Egeland GM, Nygård OK, et al. Association of dietary vitamin K and risk of coronary heart disease in middle-age adults: the Hordaland Health Study Cohort. *BMJ Open* 2020;10: e035953. doi: 10.1136/bmjopen-2019-035953
- [33] Bellinge JW, Dalgaard F, Murray K, Connolly E, Blekkenhorst LC, Bondonno CP, Lewis JR, Sim M, Croft KD, Gislason G, Torp-Pedersen C, Tjønneland A, Overvad K, Hodgson JM, Schultz C, Bondonno NP. Vitamin K Intake and Atherosclerotic Cardiovascular Disease in the Danish Diet Cancer and Health Study. *J Am Heart Assoc.* 2021 Aug 17;10(16): e020551. doi: 10.1161/JAHA.120.020551. Epub 2021 Aug 7. PMID: 34369182; PMCID: PMC8475061.
- [34] Zwakenberg SR et al. Vitamin K intake and all-cause and cause specific mortality. *Clin Nutr.* 2017 Oct;36(5):1294-1300.
- [35] Knapen MH, Braam LA, Drummen NE, Bekers O, Hoeks AP, Vermeer C. Menaquinone-7 supplementation improves arterial stiffness in healthy postmenopausal women. A double-blind randomised clinical trial. *Thromb Haemost.* 2015 May;113(5):1135-44. doi: 10.1160/TH14-08-0675. Epub 2015 Feb 19. PMID: 25694037.
- [36] Vermeer C, Vik H. Effect of Menaquinone-7 (vitamin K2) on vascular elasticity in healthy subjects: results from a one-year study. *Vascular Diseases and Therapeutics.* 2020;5(1). doi:10.15761/vdt.1000179
- [37] DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: An update. *Contemporary Clinical Trials.* 2007;28(2):105-114. doi: 10.1016/j.cct.2006.04.004
- [38] The global burden of osteoporosis: a factsheet. (2014) International Osteoporosis Foundation. <https://www.iofbonehealth.org/sites/default/files/media/PDFs/Fact%20Sheets/2014-factsheet-osteoporosis-A4.pdf>. Accessed February 12, 2019
- [39] Watts, J., Abimanyi-Ochom, J. and Sanders, K (2013) Osteoporosis costing all Australians A new burden of disease analysis – 2012 to 2022. Osteoporosis Australia. www.osteoporosis.org.au

- [40] National Osteoporosis Foundation. (2013). What is Osteoporosis? Retrieved March 2013, from <https://www.nof.org/patients/what-is-osteoporosis/>
- [41] J. A. Kanis, A. Odén, E. V. McCloskey, H. Johansson, D. A. Wahl, C. Cooper, on behalf of the IOF Working Group on Epidemiology and Quality of Life. (2012) A systematic review of hip fracture incidence and probability of fracture worldwide. *Osteoporos Int.* 2012 September; 23(9): 2239–2256.
- [42] Wright NC, Looker AC, Saag KG, et al. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. *J Bone Miner Res.* 2014;29(11):2520-2526. doi:10.1002/jbmr.2269
- [43] NAMS continuing medical education activity: management of osteoporosis in postmenopausal women: 2010 position statement of the North American Menopause Society. (2010) *Menopause* 17:23–24. doi: <https://doi.org/10.1097/gme.0b013e3181cdd4a7>
- [44] Weaver, C.M., Bischoff–Ferrari, H.A. & Shanahan, C.J. *Arch Osteoporos* (2019) 14: 50. <https://doi.org/10.1007/s11657-019-0589-y>
- [45] Adeyemi A, Delhougne G. Incidence and Economic Burden of Intertrochanteric Fracture: A Medicare Claims Database Analysis. *JB JS Open Access.* 2019;4(1): e0045. Published 2019 Feb 27. doi:10.2106/JBJS.OA.18.00045
- [46] Weycker D, Li X, Barron R, Bornheimer R, Chandler D. Hospitalizations for osteoporosis-related fractures: Economic costs and clinical outcomes. *Bone Rep.* 2016; 5:186–191. Published 2016 Jul 30. doi: 10.1016/j.bonr.2016.07.005
- [47] National Institutes of Health (NIH), Office of Dietary Supplements. (2019) Vitamin D - Fact Sheet for Health Professionals. Retrieved at <https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/>. Updated: August 7, 2019. Accessed: December 20, 2019
- [48] Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. Dietary Reference Intakes for Calcium and Vitamin D. Ross AC, Taylor CL, Yaktine AL, Del Valle HB, editors. Washington (DC): National Academies Press (US); 2011. PMID: 21796828.
- [49] European Food Safety Authority. Scientific Opinion in relation to the authorisation procedure for health claims on calcium and vitamin D and the reduction of the risk of osteoporotic fractures by reducing bone loss pursuant to Article 14 of Regulation (EC) No 1924/2006. *EFSA Journal.* 2010;8(5):1609. doi: 10.2903/j.efsa.2010.1609
- [50] Shanahan, C. and de Lorimier, R. (2014). Targeted Use of Complementary Medicines: Potential Health Outcomes & Cost Savings in Australia. Frost & Sullivan. Retrieved at http://www.asmi.com.au/media/14046/final_frost_sullivan_report_photocopy_ready_8_oct_2014.pdf
- [51] Weaver CM, Alexander DD, Boushey CJ, Dawson-Hughes B, Lappe JM, LeBoff MS, Liu S, Looker AC, Wallace TC, Wang DD. (2015) Calcium plus vitamin D supplementation and risk of fractures: an updated meta-analysis from the National Osteoporosis Foundation. *Osteoporos Int.* 2015 Oct 28.
- [52] Weaver CM, Alexander DD, Boushey CJ, Dawson-Hughes B, Lappe JM, LeBoff MS, Liu S, Looker AC, Wallace TC, Wang DD (2016) Calcium plus vitamin D supplementation and risk of fractures: an updated meta-analysis from the National Osteoporosis Foundation. *Osteoporos Int* 27:367-376
- [53] Retina International. Age-related Macular Degeneration (AMD); Frequently Asked Questions (FAQs). Retrieved March 2016. <http://www.retina-international.org/eye-conditions/retinal-degenerative-conditions/amd/>

[54] Facts About Age-Related Macular Degeneration. Department of Health and Human Services. The National Institutes of Health. Retrieved at https://nei.nih.gov/health/maculardegen/armd_facts

[55] Wong, Wan Ling et al. (2014) Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *The Lancet Global Health*, Volume 2, Issue 2, e106 - e116

[56] Centers for Disease Control and Prevention, Vision Health Initiative (VHI). Basics of Vision and Eye Health. Common Eye Disorders and Diseases. Atlanta, GA: Accessed February 1, 2022, <https://www.cdc.gov/visionhealth/basics/ced/index.html>

[57] Roberts JE and Dennison J. (2015) The Photobiology of Lutein and Zeaxanthin in the Eye. *Journal of Ophthalmology*. Volume 2015, Article ID 687173, 8 pages. <http://dx.doi.org/10.1155/2015/687173>

[58] Defining Visual Impairment. GLOBAL BLINDNESS LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE. Future Learn. Retrieved at <https://www.futurelearn.com/courses/global-blindness/0/steps/5330>

[59] Grassmann F, Fleckenstein M, Chew EY, Strunz T, Schmitz-Valckenberg S, Göbel AP, Klein ML, Ratnapriya R, Swaroop A, Holz FG, Weber BFH (2015) Clinical and Genetic Factors Associated with Progression of Geographic Atrophy Lesions in Age-Related Macular Degeneration. *PLoS ONE* 10(5): e0126636. <https://doi.org/10.1371/journal.pone.0126636>

[60] VISUAL STANDARDS ASPECTS and RANGES of VISION LOSS with Emphasis on Population Surveys. Report prepared for the International Council of Ophthalmology at the 29th International Congress of Ophthalmology Sydney, Australia, April 2002. Retrieved at <http://www.icoph.org/downloads/visualstandardsreport.pdf>

[61] Loughman, J.; Nolan, J.M.; Howard, A.N.; Connolly, E.; Meagher, K.; Beatty, S. The impact of macular pigment augmentation on visual performance using different carotenoid formulations. (2012) *Invest. Ophthalmol. Vis. Sci.* 2012, 53, 7871–7880.

[62] Mari'a C. Puell, Catalina Palomo-Alvarez, Ana R. Barrio, Fernando J. Go' mez-Sanz² and Mari'a Jesu's Pe'rez-Carrasco. Relationship between macular pigment and visual acuity in eyes with early age-related macular degeneration. *Acta Ophthalmol.* 2013; 91: e298–e303

[63] Obana A, Tanito M, Gohto Y, Okazaki S, Gellermann W, Bernstein PS. Changes in Macular Pigment Optical Density and Serum Lutein Concentration in Japanese Subjects Taking Two Different Lutein Supplements. *PLoS One.* 2015 Oct 9;10(10): e0139257. doi: 10.1371/journal.pone.0139257.

[64] Weigert G, Kaya S, Pemp B, Sacu S, Lasta M, Werkmeister RM, Dragostinoff N, Simader C, Garhöfer G, Schmidt-Erfurth U, Schmetterer L. Effects of lutein supplementation on macular pigment optical density and visual acuity in patients with age-related macular degeneration. *Invest Ophthalmol Vis Sci.* 2011 Oct 17;52(11): 8174-8. doi: 10.1167/iovs.11-7522.

[65] Yao Y, Qiu QH, Wu XW, Cai ZY, Xu S, Liang XQ. Lutein supplementation improves visual performance in Chinese drivers: 1-year randomized, double-blind, placebo-controlled study. *Nutrition.* 2013 Jul-Aug;29(7-8): 958-64. doi

[66] Huang YM, Dou HL, Huang FF, Xu XR, Zou ZY, Lin XM. Effect of supplemental lutein and zeaxanthin on serum, macular pigmentation, and visual performance in patients with early age-related macular degeneration. *Biomed Res Int.* 2015;2015: 564738. doi: 10.1155/2015/564738.

- [67] Murray IJ, Makridaki M, van der Veen RL, Carden D, Parry NR, Berendschot TT. Lutein supplementation over a one-year period in early AMD might have a mild beneficial effect on visual acuity: the CLEAR study. *Invest Ophthalmol Vis Sci.* 2013 Mar 11;54(3): 1781-8. doi
- [68] Bovier ER, Hammond BR. A randomized placebo-controlled study on the effects of lutein and zeaxanthin on visual processing speed in young healthy subjects. *Arch Biochem Biophys.* 2015 Apr 15;572: 54-7. doi: 10.1016/j.abb.2014.11.012.
- [69] Loughman J, Nolan JM, Howard AN, Connolly E, Meagher K, Beatty S. The impact of macular pigment augmentation on visual performance using different carotenoid formulations. *Invest Ophthalmol Vis Sci.* 2012 Nov 29;53(12): 7871-80. doi: 10.1167/iovs.12-10690.
- [70] Dawczynski J, Jentsch S, Schweitzer D, Hammer M, Lang GE, Strobel J. Long term effects of lutein, zeaxanthin and omega-3-LCPUFAs supplementation on optical density of macular pigment in AMD patients: the LUTEGA study. *Graefes Arch Clin Exp Ophthalmol.* 2013 Dec;251(12): 2711-23. doi
- [71] Ma L, Yan SF, Huang YM, Lu XR, Qian F, Pang HL, Xu XR, Zou ZY, Dong PC, Xiao X, Wang X, Sun TT, Dou HL, Lin XM. Effect of lutein and zeaxanthin on macular pigment and visual function in patients with early age-related macular degeneration. *Ophthalmology.* 2012 Nov;119(11): 2290-7. doi: 10.1016/j.ophtha.2012.06.014.
- [72] Siah WF, Loughman J, O'Brien C. Lower Macular Pigment Optical Density in Foveal-Involved Glaucoma. *Ophthalmology.* 2015 Oct;122(10): 2029-37. doi: 10.1016/j.ophtha.2015.06.028.
- [73] Richer SP, Stiles W, Graham-Hoffman K, Levin M, Ruskin D, Wrobel J, Park DW, Thomas C. Randomized, double-blind, placebo-controlled study of zeaxanthin and visual function in patients with atrophic age-related macular degeneration: the Zeaxanthin and Visual Function Study (ZVF) FDA IND #78, 973. *Optometry.* 2011 Nov;82(11): 667-680.e6. doi
- [74] Tanito M, Obana A, Gohto Y, Okazaki S, Gellermann W, Ohira A. Macular pigment density changes in Japanese individuals supplemented with lutein or zeaxanthin: quantification via resonance Raman spectrophotometry and autofluorescence imaging. *Jpn J Ophthalmol.* 2012 Sep;56(5): 488-96. doi
- [75] Hammond BR, Fletcher LM, Roos F, Wittwer J, Schalch W. A double-blind, placebo-controlled study on the effects of lutein and zeaxanthin on photostress recovery, glare disability, and chromatic contrast. *Invest Ophthalmol Vis Sci.* 2014 Dec 2;55(12): 8583-9. doi: 10.1167/iovs.14-15573.
- [76] Sasamoto Y, Gomi F, Sawa M, Tsujikawa M, Nishida K. Effect of 1-year lutein supplementation on macular pigment optical density and visual function. *Graefes Arch Clin Exp Ophthalmol.* 2011 Dec;249(12): 1847-54. doi: 10.1007/s00417-011-1780-z.
- [77] García-Layana A, Recalde S, Alamán AS, Robredo PF. Effects of lutein and docosahexaenoic Acid supplementation on macular pigment optical density in a randomized controlled trial. *Nutrients.* 2013 Feb 15;5(2): 543-51. doi: 10.3390/nu5020543.
- [78] Wolf-Schnurrbusch UE, Zinkernagel MS, Munk MR, Ebnetter A, Wolf S. Oral Lutein Supplementation Enhances Macular Pigment Density and Contrast Sensitivity but Not in Combination with Polyunsaturated Fatty Acids. *Invest Ophthalmol Vis Sci.* 2015 Dec;56(13): 8069-74. doi: 10.1167/iovs.15-17586.
- [79] Berrow EJ, Bartlett HE, Eperjesi F. The effect of nutritional supplementation on the multifocal electroretinogram in healthy eyes. *Doc Ophthalmol.* 2016 Apr;132(2): 123-35. doi: 10.1007/s10633-016-9532-3.

- [80] Nolan JM, O'Reilly P, Loughman J, Stack J, Loane E, Connolly E, Beatty S. Augmentation of macular pigment following implantation of blue light-filtering intraocular lenses at the time of cataract surgery. *Invest Ophthalmol Vis Sci.* 2009 Oct;50(10): 4777-85. doi: 10.1167/iovs.08-3277.
- [81] Stringham JM, Stringham NT. Serum and retinal responses to three different doses of macular carotenoids over 12 weeks of supplementation. *Exp Eye Res.* 2016 Oct;151: 1-8. doi: 10.1016/j.exer.2016.07.005.
- [82] Ma L, Dou HL, Huang YM, Lu XR, Xu XR, Qian F, Zou ZY, Pang HL, Dong PC, Xiao X, Wang X, Sun TT, Lin XM. Improvement of retinal function in early age-related macular degeneration after lutein and zeaxanthin supplementation: a randomized, double-masked, placebo-controlled trial. *Am J Ophthalmol.* 2012 Oct;154(4): 625-634.e1. doi
- [83] Connolly EE, Beatty S, Loughman J, Howard AN, Louw MS, Nolan JM. Supplementation with all three macular carotenoids: response, stability, and safety. *Invest Ophthalmol Vis Sci.* 2011 Nov 29;52(12): 9207-17. doi
- [84] Stringham JM, O'Brien KJ, Stringham NT. Contrast Sensitivity and Lateral Inhibition Are Enhanced with Macular Carotenoid Supplementation. *Invest Ophthalmol Vis Sci.* 2017 Apr 1;58(4): 2291-2295. doi: 10.1167/iovs.16-21087.
- [85] Azar G, Quaranta-El Maftouhi M, Masella JJ, Mauget-Faÿsse M. Macular pigment density variation after supplementation of lutein and zeaxanthin using the Visucam (®) 200 pigment module: Impact of age-related macular degeneration and lens status. *J Fr Ophtalmol.* 2017 Apr;40(4): 303-313. doi
- [86] Merle BMJ, Buaud B, Korobelnik JF, Bron A, Delyfer MN, Rougier MB, Savel H, Vaysse C, Creuzot-Garcher C, Delcourt C. Plasma long-chain omega-3 polyunsaturated fatty acids and macular pigment in subjects with family history of age-related macular degeneration: the Limpia Study. *Acta Ophthalmol.* 2017 Dec;95(8): e763-e769. doi
- [87] Forte R, Panzella L, Cesarano I, Cennamo G, Eidenberger T, Napolitano A. Epilutein for Early-Stage Age-Related Macular Degeneration: A Randomized and Prospective Study. *Ophthalmic Res.* 2017;58(4): 231-241. doi
- [88] Korobelnik JF, Rougier MB, Delyfer MN, Bron A, Merle BMJ, Savel H, Chêne G, Delcourt C, Creuzot-Garcher C. Effect of Dietary Supplementation with Lutein, Zeaxanthin, and ω -3 on Macular Pigment: A Randomized Clinical Trial. *JAMA Ophthalmol.* 2017 Nov 1;135(11): 1259-1266.
- [89] Wittenborn JS, Zhang X, Feagan CW, et al. The Economic Burden of Vision Loss and Eye Disorders among the United States Population Younger than 40 Years. *Ophthalmology.* 2013;120(9):1728-1735. doi: 10.1016/j.ophtha.2013.01.068
- [90] Mozaffarieh, M., Sacu, S., and Wedrich, A., (2003) The role of the carotenoids, lutein, and zeaxanthin, in protecting against age-related macular degeneration: A review based on controversial evidence. *Nutrition Journal*, 2:20, Retrieved at <https://nutritionj.biomedcentral.com/articles/10.1186/1475-2891-2-20>
- [91] American Optometric Association. Lutein, zeaxanthin reaffirmed over beta-carotene in AREDS2. www.aoa.org. Accessed July 13, 2022. <https://www.aoa.org/news/clinical-eye-care/health-and-wellness/lutein-zeaxanthin-reaffirmed-over-beta-carotene-in-areds2?sso=y>
- [92] Chew, E., et al., (2013). Age-Related Eye Disease Study 2 Research Group. Lutein + Zeaxanthin and Omega-3 Fatty Acids for Age-Related Macular Degeneration. *J Am. Med. Assoc.*, 309(19).
- [93] The Age-related Eye Disease Study 2 (AREDS2) Research Group. (2013) Secondary Analyses of the Effects of Lutein/Zeaxanthin on Age-Related Macular Degeneration Progression. AREDS2 Report No. 3, *JAMA Ophthalmol* Dec 5

- [94] R. Liu, T. Wang, B. Zhang et al., "Lutein and zeaxanthin supplementation and association with visual function in age-related macular degeneration," *Investigative Ophthalmology & Visual Science*, vol. 56, no. 1, pp. 252–258, 2015.
- [95] Lisa M Wilson, Saraniya Tharmarajah, Yuanxi Jia, Richard D Semba, Debra A Schaumberg, Karen A Robinson, The Effect of Lutein/Zeaxanthin Intake on Human Macular Pigment Optical Density: A Systematic Review and Meta-Analysis, *Advances in Nutrition*, Volume 12, Issue 6, November 2021, Pages 2244–2254, <https://doi.org/10.1093/advances/nmab071>
- [96] Arnold C, Jentsch S, Dawczynski J. Age-related macular degeneration: Effects of a short-term intervention with an oleaginous kale extract--a pilot study. (2013) *Nutrition*. 2013 Nov-Dec;29(11-12):1412-7. doi: 10.1016/j.nut.2013.05.012.
- [97] Bone, R.A.; Landrum, J.T.; Cao, Y.; Howard, A.N.; Alvarez-Calderon, F. Macular pigment response to a supplement containing meso-zeaxanthin, lutein, and zeaxanthin. (2007) *Nutr. Metab. (Lond.)* 2007, 4, 12.
- [98] Bone, R.A.; Landrum, J.T. Dose-dependent response of serum lutein and macular pigment optical density to supplementation with lutein esters. (2010) *Arch. Biochem. Biophys.* 2010, 504, 50–55.
- [99] Bovier, E.R.; Hammond, B.R. A randomized placebo-controlled study on the effects of lutein and zeaxanthin on visual processing speed in young healthy subjects. (2015) *Arch. Biochem. Biophys.* 2015, 572, 54–57.
- [100] Connolly, E.E.; Beatty, S.; Loughman, J.; Howard, A.N.; Louw, M.S.; Nolan, J.M. Supplementation with all three macular carotenoids: Response, stability, and safety. (2011) *Invest. Ophthalmol. Vis. Sci.* 2011, 52, 9207–9217.
- [101] Curran-Celentano J, Hammond BR Jr, Ciulla TA, Cooper DA, Pratt LM, Danis RB. Relation between dietary intake, serum concentrations, and retinal concentrations of lutein and zeaxanthin in adults in a Midwest population. (2001) *Am J Clin Nutr.* 2001 Dec;74(6):796-802.
- [102] Dawczynski J, Jentsch S, Schweitzer D, Hammer M, Lang GE, Strobel J. (2013) Long term effects of lutein, zeaxanthin and omega-3-LCPUFAs supplementation on optical density of macular pigment in AMD patients: the LUTEGA study. *Graefes Arch Clin Exp Ophthalmol.* 2013; 251:2711–2723
- [103] García-Layana, A.; Recalde, S.; Alamán, A.S.; Robredo, P.F. Effects of lutein and docosahexaenoic acid supplementation on macular pigment optical density in a randomized controlled trial. (2013) *Nutrients* 2013, 5, 543–551.
- [104] Huang, Y.M.; Dou, H.L.; Huang, F.F.; Xu, X.R.; Zou, Z.Y.; Lu, X.R.; Lin, X.M. Changes following supplementation with lutein and zeaxanthin in retinal function in eyes with early age-related macular degeneration: A randomised, double-blind, placebo-controlled trial. (2015) *Br. J. Ophthalmol.* 2015, 99, 371–375.
- [105] Johnson, E.J.; Chung, H.Y.; Caldarella, S.M.; Snodderly, D.M. The influence of supplemental lutein and docosahexaenoic acid on serum, lipoproteins, and macular pigmentation. (2008) *Am. J. Clin. Nutr.* 2008, 87, 1521–1529.
- [106] Kvangsakul, J.; Rodriguez-Carmona, M.; Edgar, D.F.; Barker, F.M.; Köpcke, W.; Schalch, W.; Barbur, J.L. Supplementation with the carotenoids lutein or zeaxanthin improves human visual performance. (2006) *Ophthalmic. Physiol. Opt.* 2006, 26, 362–371.
- [107] Landrum, J.; Bone, R.; Mendez, V.; Valenciaga, A.; Babino, D. Comparison of dietary supplementation with lutein diacetate and lutein: A pilot study of the effects on serum and macular pigment. (2012) *Acta Biochim. Pol.* 2012, 59, 167–169. [

- [108] Loughman, J.; Nolan, J.M.; Howard, A.N.; Connolly, E.; Meagher, K.; Beatty, S. The impact of macular pigment augmentation on visual performance using different carotenoid formulations. (2012) *Invest. Ophthalmol. Vis. Sci.* 2012, 53, 7871–7880.
- [109] Murray IJ, Makridaki M, van der Veen RL, Carden D, Parry NR, Berendschot TT. (2013) Lutein supplementation over a one-year period in early AMD might have a mild beneficial effect on visual acuity: the CLEAR study. *Invest Ophthalmol Vis Sci.* 2013; 54:1781–1788.
- [110] Nolan JM, Stack J, O'connell E, Beatty S. The relationships between macular pigment optical density and its constituent carotenoids in diet and serum. (2007) *Invest Ophthalmol Vis Sci.* 2007 Feb;48(2):571-82.
- [111] Nolan, J.M.; Loughman, J.; Akkali, M.C.; Stack, J.; Scanlon, G.; Davison, P.; Beatty, S. The impact of macular pigment augmentation on visual performance in normal subjects: COMPASS. (2011) *Vis. Res.* 2011, 51, 459–469.
- [112] Nolan, J.M.; Power, R.; Stringham, J.; Dennison, J.; Stack, J.; Kelly, D.; Moran, R.; Akuffo, K.; Corcoran, L.; Beatty, S. Enrichment of Macular Pigment Enhances Contrast Sensitivity in Subjects Free of Retinal Disease: okCentral Retinal Enrichment Supplementation Trials—Report 1. (2016) *Invest. Ophthalmol. Vis. Sci.* 2016, 57,3429–3439. [
- [113] Richer, S.; Devenport, J.; Lang, J.C. LAST II: Differential temporal responses of macular pigment optical density in patients with atrophic age-related macular degeneration to dietary supplementation with xanthophylls. (2007) *Optometry* 2007, 78, 213–219.
- [114] Trieschmann et al. Changes in macular pigment optical density and serum concentrations of its constituent carotenoids following supplemental lutein and zeaxanthin: the LUNA study. (2007) *Exp. Eye Res.* 2007, 84, 718–728.
- [115] van der Made SM1, Kelly ER2, Kijlstra A2, Plat J1, Berendschot TT2. Consuming a buttermilk drink containing lutein-enriched egg yolk daily for 1-year increased plasma lutein but did not affect serum lipid or lipoprotein concentrations in adults with early signs of age-related macular degeneration. (2016) *J Ophthalmol.* 2016; 2016:9035745. doi: 10.1155/2016/9035745. Epub 2016 Mar 14.
- [116] Weigert G, Kaya S, Pemp B, et al. (2011) Effects of lutein supplementation on macular pigment optical density and visual acuity in patients with age-related macular degeneration. *Invest Ophthalmol Vis Sci.* 2011; 52:8174–8178.
- [117] Wolf-Schnurrbusch UE, Zinkernagel MS, Munk MR, Ebnetter A, Wolf S. Oral Lutein Supplementation Enhances Macular Pigment Density and Contrast Sensitivity but Not in Combination with Polyunsaturated Fatty Acids. (2015) *Invest Ophthalmol Vis Sci.* 2015 Dec;56(13):8069-74. doi: 10.1167/iops.15-17586.
- [118] Yao, Y.; Qiu, Q.H.; Wu, X.W.; Cai, Z.Y.; Xu, S.; Liang, X.Q. Lutein supplementation improves visual performance in Chinese drivers: 1-year randomized, double-blind, placebo-controlled study. (2013) *Nutrition* 2013, 29, 958–964.
- [119] Mayo Clinic. Mild cognitive impairment - Symptoms and causes. Mayo Clinic. Published 2018. <https://www.mayoclinic.org/diseases-conditions/mild-cognitive-impairment/symptoms-causes/syc-20354578>
- [120] Mayo Clinic. Dementia - Symptoms and causes. Mayo Clinic. Published June 17, 2021. <https://www.mayoclinic.org/diseases-conditions/dementia/symptoms-causes/syc-20352013>
- [121] Hale JM, Schneider DC, Mehta NK, Myrskylä M. Cognitive impairment in the U.S.: Lifetime risk, age at onset, and years impaired. *SSM - Population Health.* 2020;11. doi:10.1016/j.ssmph.2020.100577
- [122] Owens DK, Davidson KW, Krist AH, et al. Screening for Cognitive Impairment in Older Adults. *JAMA.* 2020;323(8):757. doi:10.1001/jama.2020.0435

- [123] Pharmaceutical Research and Manufacturers of America. Medicines in Development for Alzheimer's Disease 2017 Report. phrma.org. Published September 20, 2018. Accessed May 17, 2022. <https://www.phrma.org/medicines-in-development/medicines-in-development-for-alzheimer-s-disease>
- [124] Alzheimer's Association. Mild Cognitive Impairment (MCI). Alzheimer's Disease and Dementia. Published 2022. Accessed May 17, 2022. https://www.alz.org/alzheimers-dementia/what-is-dementia/related_conditions/mild-cognitive-impairment#:~:text=An%20estimated%2010%25%20to%2015
- [125] Pangman, V. C., Sloan, J., & Guse, L. (2000). An examination of psychometric properties of the Mini-Mental State Examination and the standardized Mini-Mental State Examination: Implications for clinical practice. *Applied Nursing Research*, 13(4), 209-213.
- [126] Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H (2005). "The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment". *J Am Geriatr Soc*. 53 (4): 695–9. doi:10.1111/j.1532-5415.2005.53221.x [2] Eurostat (2017) Retrieved at http://ec.europa.eu/eurostat/statistics-explained/index.php/Population_and_population_change_statistics
- [127] Katz, S.; Downs, T.D.; Cash, H.R.; Grotz, R.C. (1970). "Progress in development of the index of ADL". *The Gerontologist*. 10 (1 Part 1): 20–30. doi:10.1093/geront/10.1_Part_1.20.
- [128] Katz, S.; Ford, A. B.; Moskowitz, R. W.; Jackson, B. A.; Jaffe, M. W. (1963). "Studies of illness in the aged. The index of adl: A standardized measure of biological and psychosocial function". *Journal of the American Medical Association*. 185 (12): 914–19. doi:10.1001/jama.1963.0
- [129] Wechsler, D. (1955). *Manual for the Wechsler Adult Intelligence Scale*. Psychological Corp. Retrieved at <https://psycnet.apa.org/record/1955-07334-000>
- [130] Sahakian, Barbara J.; Morris, Robin G.; Evenden, John L.; Heald, Andrew; Levy, Raymond; Philpot, Michael; Robbins, Trevor W. (1988). "A Comparative Study of Visuospatial Memory and Learning in Alzheimer-Type Dementia and Parkinson's Disease". *Brain*. 111 (3): 695–718. doi:10.1093/
- [131] Lezak, Muriel Deutsch (1995). *Neuropsychological assessment*. Oxford [Oxfordshire]: Oxford University Press. ISBN 0-19-509031-4.
- [132] Brandt J. (1991) The Hopkins Verbal Learning Test: Development of a new memory test with six equivalent forms. *The Clinical Neuropsychologist*
- [133] Benedict R.H.B.; Schretlen D; Groninger L; Brandt J. Hopkins Verbal Learning Test – Revised: Normative Data and Analysis of Inter-Form and Test-Retest Reliability. *The Clinical Neuropsychologist (Neuropsychology, Development and Cognition: Sec, Volume 12, Number 1, February 1998,*
- [134] Kaplan; Goodglass, Harold; Weintraub, Sandra (1983). *Boston Naming Test*. Philadelphia: Lea & Febiger. OCLC 10450471
- [135] Kim, H., Kim, G., Jang, W., Kim, S. Y., & Chang, N. (2014). Association between intake of B vitamins and cognitive function in elderly Koreans with cognitive impairment. *Nutrition journal*, 13(1), 118. <https://doi.org/10.1186/1475-2891-13-118>
- [136] Tardy, A. L., Pouteau, E., Marquez, D., Yilmaz, C., & Scholey, A. (2020). Vitamins and Minerals for Energy, Fatigue and Cognition: A Narrative Review of the Biochemical and Clinical Evidence. *Nutrients*, 12(1), 228. <https://doi.org/10.3390/nu12010228>

- [137] Meng, H., Li, Y., Zhang, W., Zhao, Y., Niu, X., & Guo, J. (2019). The relationship between cognitive impairment and homocysteine in a B12 and folate deficient population in China: A cross-sectional study. *Medicine*, 98(47), e17970. <https://doi.org/10.1097/MD.00000000000017970>
- [138] Zhang, D.-M., Ye, J.-X., Mu, J.-S., & Cui, X.-P. (2016). Efficacy of Vitamin B Supplementation on Cognition in Elderly Patients with Cognitive-Related Diseases. *Journal of Geriatric Psychiatry and Neurology*, 30(1), 50–59. doi:10.1177/0891988716673466
- [139] Hooshmand, B., Refsum, H., Smith, A. D., Kalpouzos, G., Mangialasche, F., von Arnim, C. A. F., Fratiglioni, L. (2019). Association of Methionine to Homocysteine Status with Brain Magnetic Resonance Imaging Measures and Risk of Dementia. *JAMA Psychiatry*.
- [140] Harvard T.H. Chan School of Public Health. Folate (Folic Acid) – Vitamin B9. The Nutrition Source. Published September 18, 2012. Accessed May 17, 2022. <https://www.hsph.harvard.edu/nutritionsource/folic-acid/#:~:text=Recommended%20Amounts>
- [141] Mayo Clinic. Vitamin B-6. Mayo Clinic. Published February 3, 2021. <https://www.mayoclinic.org/drugs-supplements-vitamin-b6/art-20363468#:~:text=The%20recommended%20daily%20amount%20of>
- [142] National Institutes of Health. Office of Dietary Supplements - Vitamin B12. Nih.gov. Published 2016. <https://ods.od.nih.gov/factsheets/VitaminB12-HealthProfessional/>
- [143] Shanahan, C. Cognitive Health and Economic Benefits of Using Vitamin B Food Supplements Among the European Union's Aging Population, *International Journal of Nutrition and Food Sciences*. Volume 10, Issue 6, November 2021, pp. 117-125. doi: 10.11648/j.ijnfs.20211006.11
- [144] Ma F, Li Q, Zhou X, Zhao J, Song A, Li W, Liu H, Xu W, Huang G. (2019) *Eur J Nutr*. 2019 Feb;58(1):345-356. doi: 10.1007/s00394-017-1598-5. Epub 2017 Dec 18.
- [145] Kwok T, Lee J, Ma RC, Wong SY, Kung K, Lam A, Ho CS, Lee V, Harrison J, Lam L. (2017) *Clin Nutr*. 2017 Dec;36(6):1509-1515. doi: 10.1016/j.clnu.2016.10.018. Epub 2016 Oct 27.
- [146] Dangour AD, Allen E, Clarke R, Elbourne D, Fletcher AE, Letley L, Richards M, Whyte K, Uauy R, Mills K. (2015) *Am J Clin Nutr*. 2015 Sep;102(3):639-47. doi: 10.3945/ajcn.115.110775. Epub 2015 Jul 1.
- [147] van der Zwaluw NL, Dhonukshe-Rutten RA, van Wijngaarden JP, Brouwer-Brolsma EM, van de Rest O, In 't Veld PH, Enneman AW, van Dijk SC, Ham AC, Swart KM, van der Velde N, van Schoor NM, van der Cammen TJ, Uitterlinden AG, Lips P, Kessels RP, de Groot LC. (2014) *Neurology*. 2014 Dec 2;83(23):2158-66. doi: 10.1212/WNL.0000000000001050. Epub 2014 Nov 12.
- [148] Cheng D, Kong H, Pang W, Yang H, Lu H, Huang C, Jiang Y. (2016) *Nutr Neurosci*. 2016 Dec;19(10):461-466. Epub 2016 Mar 2.
- [149] Walker JG, Batterham PJ, Mackinnon AJ, Jorm AF, Hickie I, Fenech M, Kljakovic M, Crisp D, Christensen H. (2012) *Am J Clin Nutr*. 2012 Jan;95(1):194-203. doi: 10.3945/ajcn.110.007799. Epub 2011 Dec 14. Erratum in: *Am J Clin Nutr*. 2012 Aug;96(2):448. Dosage error in article text.
- [150] Ford AH, Flicker L, Alfonso H, Thomas J, Clarnette R, Martins R, Almeida OP. (2010) *Neurology*. 2010 Oct 26;75(17):1540-7. doi: 10.1212/WNL.0b013e3181f962c4. Epub 2010 Sep 22. Erratum in: *Neurology*. 2011 Aug 23;77((8):804. Dosage error in published abstract; MEDLINE/PubMed abstract corrected; Dosage error in article text.

- [151] Eussen SJ, de Groot LC, Joosten LW, Bloo RJ, Clarke R, Ueland PM, Schneede J, Blom HJ, Hoefnagels WH, van Staveren WA. (2006) *Am J Clin Nutr.* 2006 Aug;84(2):361-70.
- [152] Ipsos. 2021 CRN Consumer Survey on Dietary Supplements. Available at <https://www.crnusa.org/resources/type/consumer-data>
- [153] Juanola-Falgarona, M.; Salas-Salvado, J.; Martinez-Gonzalez, M. A.; Corella, D.; Estruch, R.; Ros, E.; Fito, M.; Aros, F.; Gomez-Gracia, E.; Fiol, M.; Lapetra, J.; Basora, J.; Lamuela-Raventos, R. M.; Serra-Majem, L.; Pinto, X.; Munoz, M. A.; Ruiz-Gutierrez, V.; Fernandez-Ballart, J.; Bullo, M. (2014). Dietary Intake of Vitamin K Is Inversely Associated with Mortality Risk. *Journal of Nutrition*, 144(5), 743–750. doi:10.3945/jn.113.187740
- [154] U.S. Census Bureau (June 2020). Annual Estimates of the Resident Population for Selected Age Groups by Sex for the United States: April 1, 2010, to July 1, 2019 (NC-EST2019-AGESEX). Retrieved from [<https://www2.census.gov/programs-surveys/popest/tables/2010-2019/national/asrh/nc-est2019-agesex.xlsx>]
- [155] Christopher J. Shanahan & Robert de Lorimier (2016) From Science to Finance—A Tool for Deriving Economic Implications from the Results of Dietary Supplement Clinical Studies, *Journal of Dietary Supplements*, 13:1, 16-34, DOI: 10.3109/19390211.2014.952866
- [156] Doshi JA, Cai Q, Buono JL, Spalding WM, Sarocco P, Tan H, Stephenson JJ, Carson RT. Economic burden of irritable bowel syndrome with constipation: a retrospective analysis of health care costs in a commercially insured population. *J Manag Care Spec Pharm.* 2014. doi: 10.18553/jmcp.2014.20.4.382. PMID: 24684643.
- [157] Palsson, Olafur S.; Whitehead, William; Törnblom, Hans; Sperber, Ami D.; Simren, Magnus (2020). Prevalence of Rome IV Functional Bowel Disorders Among Adults in the United States, Canada, and the United Kingdom. *Gastroenterology*, (), S0016508520300019–. doi: 1
- [158] Kajander K, Hatakka K, Poussa T, Farkkila M, Korpela R. A probiotic mixture alleviates symptoms in irritable bowel syndrome patients: a controlled 6-month intervention. *Alimentary Pharmacology and Therapeutics.* 2005;22(5):387-394. doi:10.1111/j.1365-2036.2005.
- [159] Lyra A, Hillilä M, Huttunen T, et al. irritable bowel syndrome symptom severity improves equally with probiotic and placebo. *World Journal of Gastroenterology.* 2016;22(48):10631-10642. doi:10.3748/wjg.v22.i48.10631
- [160] Mekonnen TH, Lamessa SK, Wami SD. Sickness-related absenteeism and risk factors associated among flower farm industry workers in Bishoftu town, Southeast Ethiopia, 2018: a cross-sectional study. *BMC Research Notes.* 2019;12(1). doi:10.1186/s13104-019-4223-2
- [161] Ballou S, McMahon C, Lee HN, et al. Effects of Irritable Bowel Syndrome on Daily Activities Vary Among Subtypes Based on Results from the IBS in America Survey. *Clinical Gastroenterology and Hepatology.* 2019;17(12):2471-2478.e3. doi: 10.1016/j.cgh.2019.08.016
- [162] U.S. Bureau of Labor Statistics. Current Employment Statistics - CES (National): U.S. Bureau of Labor Statistics. [Bls.gov.](https://www.bls.gov/ces/) <https://www.bls.gov/ces/>
- [163] Hill, C., Guarner, F., Reid, G. et al. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol* 11, 506–514 (2014).
- [164] Frost & Sullivan. 2021. Global Probiotic Ingredients in Human Nutrition Growth Opportunities. Future Growth Potential Due to Consumer Cognizance and New Product Development. Global Chemicals, Materials & Nutrition Research Team at Frost & Sullivan. PC19

- [165] Fleishman C. Probiotic Supplements: What is an Adequate Dosage? International Probiotics Association. Published May 25, 2021. <https://internationalprobiotics.org/probiotic-dosage-what-is-adequate/>
- [166] Ford AC, Quigley EM, Lacy BE, Lembo AJ, Saito YA, Schiller LR, Soffer EE, Spiegel BM, Moayyedi P. Efficacy of prebiotics, probiotics, and synbiotics in irritable bowel syndrome and chronic idiopathic constipation: systematic review and meta-analysis. *Am J Gastroe*
- [167] Bernasconi AA, Wiest MM, Lavie CJ, Milani RV, Laukkanen JA. Effect of Omega-3 Dosage on Cardiovascular Outcomes: An Updated Meta-Analysis and Meta-Regression of Interventional Trials. *Mayo Clin Proc*. 2021 Feb;96(2):304-313. doi: 10.1016/j.mayocp.2020.08.034. Epub
- [168] Skrzydło-Radomańska B, Prozorow-Król B, Cichoż-Lach H, Majsiaik E, Bierła JB, Kanarek E, Sowińska A, Cukrowska B. *Nutrients*. 2021 Feb 26;13(3):756. doi: 10.3390/nu13030756.
- [169] Lewis ED, Antony JM, Crowley DC, Piano A, Bhardwaj R, Tompkins TA, Evans M. *Nutrients*. 2020 Apr 21;12(4):1159. doi: 10.3390/nu12041159.
- [170] Martoni CJ, Srivastava S, Leyer GJ. *Nutrients*. 2020 Jan 30;12(2):363. doi: 10.3390/nu12020363.
- [171] Sadrin S, Sennoune S, Gout B, Marque S, Moreau J, Zinoune K, Grillasca JP, Pons O, Maixent JM. *Dig Liver Dis*. 2020 May;52(5):534-540. doi: 10.1016/j.dld.2019.12.009. Epub 2020 Jan 15.
- [172] Oh JH, Jang YS, Kang D, Chang DK, Min YW. *Nutrients*. 2019 Nov 27;11(12):2887. doi: 10.3390/nu11122887.
- [173] Preston K, Krumian R, Hattner J, de Montigny D, Stewart M, Gaddam S. *Benef Microbes*. 2018 Sep 18;9(5):697-706. doi: 10.3920/BM2017.0105. Epub 2018 Jun 11.
- [174] Stevenson C, Blaauw R, Fredericks E, Visser J, Roux S. *Nutrition*. 2014 Oct;30(10):1151-7. doi: 10.1016/j.nut.2014.02.010. Epub 2014 Feb 27.
- [175] Lorenzo-Zúñiga V, Llop E, Suárez C, Alvarez B, Abreu L, Espadaler J, Serra J. *World J Gastroenterol*. 2014 Jul 14;20(26):8709-16. doi: 10.3748/wjg.v20.i26.8709.
- [176] Yoon JS, Sohn W, Lee OY, Lee SP, Lee KN, Jun DW, Lee HL, Yoon BC, Choi HS, Chung WS, Seo JG. *J Gastroenterol Hepatol*. 2014 Jan;29(1):52-9. doi: 10.1111/jgh.12322.
- [177] Ducrotté P, Sawant P, Jayanthi V. *World J Gastroenterol*. 2012 Aug 14;18(30):4012-8. doi: 10.3748/wjg.v18.i30.4012.
- [178] Ki Cha B, Mun Jung S, Hwan Choi C, Song ID, Woong Lee H, Joon Kim H, Hyuk J, Kyung Chang S, Kim K, Chung WS, Seo JG. *J Clin Gastroenterol*. 2012 Mar;46(3):220-7. doi: 10.1097/MCG.0b013e31823712b1.
- [179] Williams EA, Stimpson J, Wang D, Plummer S, Garaiova I, Barker ME, Corfe BM. *Aliment Pharmacol Ther*. 2009 Jan;29(1):97-103. doi: 10.1111/j.1365-2036.2008.03848.x. Epub 2008 Sep 9.
- [180] Sinn DH, Song JH, Kim HJ, Lee JH, Son HJ, Chang DK, Kim YH, Kim JJ, Rhee JC, Rhee PL. *Dig Dis Sci*. 2008 Oct;53(10):2714-8. doi: 10.1007/s10620-007-0196-4. Epub 2008 Feb 15.
- [181] Kajander K, Myllyluoma E, Rajilić-Stojanović M, Kyrönpalo S, Rasmussen M, Järvenpää S, Zoetendal EG, de Vos WM, Vapaatalo H, Korpela R. *Aliment Pharmacol Ther*. 2008 Jan 1;27(1):48-57. doi: 10.1111/j.1365-2036.2007.03542.x. Epub 2007 Oct 5.

- [182] Whorwell, Peter J.; Altringer, Linda; Morel, Jorge; Bond, Yvonne; Charbonneau, Duane; O'Mahony, Liam; Kiely, Barry; Shanahan, Fergus; Quigley, Eamonn M. M. (2006). Efficacy of an Encapsulated Probiotic *Bifidobacterium infantis* 35624 in Women with Irritable Bowel
- [183] Liam O'Mahony; Jane McCarthy; Peter Kelly; George Hurley; Fangyi Luo; Kersang Chen; Gerald C. O'Sullivan; Barry Kiely; J. Kevin Collins; Fergus Shanahan; Eamonn M.M. Quigley (2005). *Lactobacillus* and *bifidobacterium* in irritable bowel syndrome: Symptom responses
- [184] Lakens D. Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. *Frontiers in Psychology*. 2013;4(863). doi:10.3389/fpsyg.2013.00863
- [185] Wallace TC, Fulgoni VL. Usual Choline Intakes Are Associated with Egg and Protein Food Consumption in the United States. *Nutrients*. 2017 Aug 5;9(8):839. doi: 10.3390/nu9080839. PMID: 28783055; PMCID: PMC5579632.
- [186] AMA Wire. AMA Backs Global Health Experts in Calling Infertility a Disease. Available online: <https://wire.ama-assn.org/ama-news/ama-backs-global-health-experts-calling-infertility-disease> (accessed on 10 June 2019).
- [187] Korsmo HW, Jiang X, Caudill MA. Choline: Exploring the Growing Science on Its Benefits for Moms and Babies. *Nutrients*. 2019 Aug 7;11(8):1823. doi: 10.3390/nu11081823. PMID: 31394787; PMCID: PMC6722688.
- [188] Derbyshire E, Obeid R. Choline, Neurological Development and Brain Function: A Systematic Review Focusing on the First 1000 Days. *Nutrients*. 2020;12(6):1731. Published 2020 Jun 10. doi:10.3390/nu12061731
- [189] CDC. Child Development Specific Conditions | CDC. Centers for Disease Control and Prevention. Published June 3, 2020. <https://www.cdc.gov/ncbddd/childdevelopment/conditions.html>
- [190] Suryavanshi MS, Yang Y. Clinical and Economic Burden of Mental Disorders Among Children with Chronic Physical Conditions, United States, 2008–2013. *Preventing Chronic Disease*. 2016;13. doi:10.5888/pcd13.150535
- [191] Davis KE. Expenditures for treatment of mental health disorders among children, ages 5–17, 2009–2011: estimates for the US civilian noninstitutionalized population. Statistical brief no. 440; Medical Expenditure Panel Survey. Rockville (MD): Agency for Healthcare Research and Quality; June 2014.
- [192] Tkacz J, Brady B. PMH28 The Increasing Rate of Childhood Mental Illnesses and Associated Healthcare Costs in the United States: Trends over the Past Decade. *Value in Health*. 2019;22:S231. doi:10.1016/j.jval.2019.04.1073
- [193] National Institutes of Health. Office of Dietary Supplements. Choline Fact Sheet for Health Professionals. ods.od.nih.gov. Published March 29, 2021. Accessed May 17, 2022. <https://ods.od.nih.gov/factsheets/Choline-HealthProfessional/#:~:text=>
- [194] Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2019, Retrieved at <https://wwwn.cdc.gov/nchs/nhanes/default.aspx>
- [195] Caudill MA, Strupp BJ, Muscalu L, Nevins JEH, Canfield RL. Maternal choline supplementation during the third trimester of pregnancy improves infant information processing speed: a randomized, double-blind, controlled feeding study. *The FASEB Journal*. 2018;32(4):2172-2180. doi:10.1096/fj.201700692rr
- [196] Bahnfleth CL, Strupp BJ, Caudill MA, Canfield RL. Prenatal choline supplementation improves child sustained attention: A 7-year follow-up of a randomized controlled feeding trial. *The FASEB Journal*. 2021;36(1). doi:10.1096/fj.202101217r

- [197] Cheatham CL, Goldman BD, Fischer LM, da Costa KA, Reznick JS, Zeisel SH. Phosphatidylcholine supplementation in pregnant women consuming moderate-choline diets does not enhance infant cognitive function: a randomized, double-blind, placebo-controlled trial. *The American Journal of Clinical Nutrition*. 2012;96(6):1465-1472. doi:10.3945/ajcn.112.037184
- [198] Boeke CE, Gillman MW, Hughes MD, Rifas-Shiman SL, Villamor E, Oken E. Choline intake during pregnancy and child cognition at age 7 years. *Am J Epidemiol*. 2013 Jun 15;177(12):1338-47. doi: 10.1093/aje/kws395. Epub 2013 Feb 20. PMID: 23425631; PMCID: PMC3676149.
- [199] Ross RG, Hunter SK, Hoffman MC, McCarthy L, Chambers BM, Law AJ, Leonard S, Zerbe GO, Freedman R. Perinatal Phosphatidylcholine Supplementation and Early Childhood Behavior Problems: Evidence for CHRNA7 Moderation. *Am J Psychiatry*. 2016 May 1;173(5):509-16. doi: 10.1176/appi.ajp.2015.15091188. Epub 2015 Dec 7. Erratum in: *Am J Psychiatry*. 2016 Jul 1;173(7):735. PMID: 26651393; PMCID: PMC5892450.
- [200] Wu BT, Dyer RA, King DJ, Richardson KJ, Innis SM. Early second trimester maternal plasma choline and betaine are related to measures of early cognitive development in term infants. *PLoS One*. 2012;7(8): e43448. doi: 10.1371/journal.pone.0043448. Epub 2012 Aug 20. PMID: 22916264; PMCID: PMC3423345.
- [201] Lakens D. Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. *Frontiers in Psychology*. 2013;4(863). doi:10.3389/fpsyg.2013.00863
- [202] Nilsson, T. K.; Hurtig-Wennlo f, A.; Sjo stro m, M.; Herrmann, W.; Obeid, R.; Owen, J. R.; Zeisel, S. (2016). Plasma 1-carbon metabolites and academic achievement in 15-yr-old adolescents. *The FASEB Journal*, (), fj.15-281097-. doi:10.1096/fj.15-281097
- [203] Taesuwan S, McDougall MQ, Malysheva OV, Bender E, Nevins JEH, Devapatla S, Vidavalur R, Caudill MA, Klatt KC. Choline metabolome response to prenatal choline supplementation across pregnancy: A randomized controlled trial. *FASEB J*. 2021 Dec;35(12): e22063. doi: 10.1096/fj.202101401RR. Erratum in: *FASEB J*. 2022 May;36(5): e22299. PMID: 34820909.
- [204] FDA Announces New Qualified Health Claims for EPA and DHA Omega-3 Consumption and the Risk of Hypertension and Coronary Heart Disease. Constituent Update. June 19, 2019. Retrieved on July 15, 2022, at <https://www.fda.gov/food/cfsan-constituent-updates/fda-announces-new-qualified-health-claims-epa-and-dha-omega-3-consumption-and-risk-hypertension-and#:~:text=The%20U.S.%20Food%20and%20Drug,of%20hypertension%20and%20coronary%20heart>
- [205] 101.72 Health claims: calcium, vitamin D, and osteoporosis. 21 CFR Part 101. Retrieved on July 18, 2022, at <https://www.ecfr.gov/current/title-21/chapter-I/subchapter-B/part-101>
- [206] Mansour AG, Hariri E, Daaboul Y, Korjian S, El Alam A, Protogerou AD, Kilany H, Karam A, Stephan A, Bahous SA. Vitamin K2 supplementation and arterial stiffness among renal transplant recipients-a single-arm, single-center clinical trial. *J Am Soc Hypertens*. 2017 Sep;11(9):589-597. doi: 10.1016/j.jash.2017.07.001. Epub 2017 Jul 13. PMID: 28756183.
- [207] Khalil Z, Alam B, Akbari AR, Sharma H. The Medical Benefits of Vitamin K2 on Calcium-Related Disorders. *Nutrients*. 2021 Feb 21;13(2):691. doi: 10.3390/nu13020691. PMID: 33670005; PMCID: PMC7926526.
- [208] 101.77 Health claims: fruits, vegetables, and grain products that contain fiber, particularly soluble fiber, and risk of coronary heart disease. 21 CFR Part 101. Retrieved on July 18, 2022, at <https://www.ecfr.gov/current/title-21/chapter-I/subchapter-B/part-101>



Council for Responsible Nutrition

The Science Behind the Supplements