

# پی‌نوشت‌ها

## پیش‌درآمد

1. Yamamoto et al. (2015).

## فصل ۱. یک بازی طولانی

1. Kinsella (1992).
2. Mensah et al. (2017).
3. Siegel et al. (2021).

## فصل ۲. پزشکی ۳/۰

1. Sokol (2013).
2. S. Johnson (2021).
3. Gordon (2016).
4. Manson et al. (2013).
5. New York Times (1985).

### فصل ۳. هدف، راهبرد، تدابیر

1. López-Otín et al. (2013).
2. Benn et al. (2011).
3. Ference (2015).

### فصل ۴. صدساله‌ها

1. Taylor (2009).
2. Spencer (2005).
3. Picard (2018).
4. Rajpathak et al. (2011).
5. United States Census Bureau (2022).
6. Hjelmborg et al. (2006).
7. Sebastiani, Nussbaum, et al. (2016).
8. Xu (2016).
9. Evert et al. (2003).
10. Perls (2017).
11. Hitt et al. (1999).
12. Michaelson (2014).
13. Sebastiani, Gurinovich, et al. (2019).
14. Willcox et al. (2008).
15. Revelas et al. (2018).
16. Serna et al. (2012).
17. Melov et al. (2007).

## فصل ۵. کمتر بخورید، بیشتر عمر کنید؟

1. E.J. Brown et al. (1994); Sabatini et al. (1994).
2. Tatebe and Shiozaki (2017).
3. Liu and Sabatini (2020).
4. Attia (2018a).
5. Attia (2018a).
6. D.E. Harrison, Strong, Sharp, et al. (2009).
7. Selvarani, Mohammed, and Richardson (2021).
8. Baur et al. (2006).
9. Miller et al. (2011); Strong et al. (2013).
10. D.E. Harrison, Strong, Reifsnnyder, et al. (2021).
11. Selvarani, Mohammed, and Richardson (2021).
12. Fontana and Partridge (2015).
13. McDonald and Ramsey (2010).
14. Hardie (2011).
15. Kourtis and Tavernarakis (2009).
16. Karsli-Uzunbas et al. (2014).
17. Mannick et al. (2014).
18. Creevy et al. (2022).
19. Urfer et al. (2017).
20. Attia (2018b).
21. Bannister et al. (2014).

## فصل ۶. بحران وفور نعمت

1. Zelman (1952).
2. Ludwig et al. (1980).
3. S.A. Harrison et al. (2021).
4. Fryar et al. (2018); Ogden et al. (2004).
5. Kwo, Cohen, and Lim (2017).
6. Prati et al. (2002).
7. Fayek et al. (2016).
8. CDC (2022b).
9. Hirode and Wong (2020).
10. Araujo, Cai, and Stevens (2019).
11. Stefan, Schick, and Haring (2017).
12. Gavrilova et al. (2000).
13. Tchernof and Després (2013).
14. Sniderman, Bhopal, et al. (2007).
15. Ahima and Lazar (2013).
16. M.C. Petersen and Shulman (2018).
17. Frayn (2019).
18. Tuchman (2009).
19. Diamond (2003).
20. Joslin (1940).
21. NIDDK (2018).
22. CDC (2022e).
23. CDC (2020).
24. CDC (2020).

25. R.J. Johnson, Stenvinkel, et al. (2020).
26. Attia (2020c).
27. R.J. Johnson and Andrews (2015).
28. R.J. Johnson, Sánchez-Lozada, et al. (2017).
29. Igwe et al. (2015); Matsuzaki et al. (2010); Zethelius and Cederholm (2015).

## فصل ۷. عقربه‌های ساعت

1. Heron (2021); WHO (2019).
2. CDC (2022c).
3. ACS (2022a); Heron (2021).
4. Caselli and Lipsi (2006).
5. Bautch and Caron (2015).
6. McNamara (2015).
7. Mensink and Katan (1992).
8. Lammert and Wang (2005).
9. Jaret (1997).
10. Dietary Guidelines Advisory Committee (2015).
11. Sniderman, Thanassoulis, et al. (2016).
12. Stary (2003).
13. Lawson (2016).
14. Nasir et al. (2022); Uretsky et al. (2011).
15. Marston et al. (2022).
16. Tsimikas et al. (2018).
17. O'Donoghue et al. (2019).
18. Libby (2021).
19. Orphanet (2022).

20. Ritchie and Roser (2018).
21. Dietschy, Turley, and Spady (1993); Ference et al. (2019); Forrester (2010); Jakubowski et al. (2021); Karagiannis et al. (2021); R. Le, Zhao, and Hegele (2022); Libby and Tokgzoğlu (2022); Masana et al. (2018); O’Keefe et al. (2004); Soran, Ho, and Durrington (2018); N. Wang et al. (2020).
22. Haase et al. (2012).
23. Voight et al. (2012).
24. du Souich, Roederer, and Dufour (2017); Stroes et al. (2015).
25. Mach et al. (2018); C.B. Newman et al. (2019).
26. Jose (2016).
27. Thanassoulis, Sniderman, and Pencina (2018).

### فصل ۸. سلول فراری

1. Rosenberg and Barr (1992).
2. NCI (2022b).
3. NCI (2021).
4. NCI (2021).
5. Jamaspishvili et al. (2018).
6. Pollack (2005).
7. Sleeman and Steeg (2010).
8. Hitchens (2014).
9. Hanahan and Weinberg (2011).
10. Warburg (1924, 1956).
11. Liberti and Locasale (2016).
12. Christofferson (2017).
13. J.D. Watson (2009).
14. Vander Heiden, Cantley, and Thompson (2009).

15. Avgerinos et al. (2019).
16. Lega et al. (2019).
17. Bradley (2004); Fruman et al. (2017).
18. Mercken et al. (2013).
19. Mukherjee (2011).
20. Hopkins et al. (2018).
21. de Groot et al. (2020).
22. ACS (2022c).
23. Kochenderfer et al. (2010).
24. D.T. Le et al. (2015).
25. Gay and Prasad (2017).
26. Cavazzoni et al. (2020).
27. Attia (2021b); Rosenberg (2021).
28. Atkins et al. (2000).
29. Taieb et al. (2020).
30. Waks et al. (2019).
31. Hofseth et al. (2020).
32. ACS (2022b).
33. X. Chen et al. (2021).

### فصل ۹. به دنبال خاطرات

1. Reiman, Arboleda-Velasquez, et al. (2020).
2. Belloy et al. (2020).
3. Cacace, Slegers, and Van Broeckhoven (2016); Cruchaga et al. (2012); Cuyvers and Slegers (2016).
4. Cummings et al. (2022).

5. Kolata (2020).
6. Blessed, Tomlinson, and Roth (1968).
7. Rabinovici et al. (2019).
8. Müller, Winter, and Graeber (2013).
9. Kaivola et al. (2022).
10. Attia (2018c).
11. Daviglius et al. (2010).
12. Ngandu et al. (2015).
13. Rosenberg et al. (2020); Andrieu et al. (2017); van Charante et al. (2016).
14. Mosconi et al. (2018); Rahman et al. (2020); Ratnakumar et al. (2019); Zhou et al. (2020).
15. Yan et al. (2022).
16. Cerri et al. (2019).
17. Langa and Levine (2014).
18. Brookmeyer et al. (2018).
19. Attia (2019).
20. Yasuno et al. (2020).
21. Blessed, Tomlinson, and Roth (1968).
22. Raichle and Gusnard (2002).
23. de la Torre (2016).
24. de la Torre (2018).
25. Wolters and Ikram (2019).
26. Cholerton et al. (2016).
27. Neth and Craft (2017).
28. Freiherr et al. (2013).
29. Chapman et al. (2018).



30. Kerrouche et al. (2006).
31. Reiman, Caselli, et al. (1996); Small et al. (2000); Sperling et al. (2011).
32. Kerrouche et al. (2006).
33. Neu et al. (2017).
34. Montagne et al. (2020).
35. Trumble and Finch (2019).
36. Mitter et al. (2012); Oriá et al. (2007).
37. Kloske and Wilcock (2020).
38. Yassine et al. (2017).
39. Grammatikopoulou et al. (2020).
40. Slayday et al. (2021).
41. Maeng and Milad (2015).
42. Esteban-Cornejo et al. (2022).
43. C. Wang and Holtzman (2020).
44. Zheng et al. (2017).
45. Dominy et al. (2019).
46. Laukkanen et al. (2017).
47. Laukkanen et al. (2015).
48. A. Smith et al. (2010).
49. Oulhaj et al. (2016).
50. Maddock et al. (2015).

### فصل ۱۰. تفکر مدیرانه

1. Proctor (1995).
2. NHTSA (2022a).
3. NHTSA (2022b); Attia (2020b)

## فصل ١١. ورزش

1. Blackwell and Clarke (2018).
2. Wen et al. (2011).
3. Reimers, Knapp, and Reimers (2012).
4. Booth and Zwetsloot (2010).
5. I.-M. Lee and Buchner (2008).
6. HHS (2018).
7. Mandsager et al. (2018).
8. Mandsager et al. (2018).
9. Mandsager et al. (2018).
10. Mandsager et al. (2018).
11. Kokkinos et al. (2022).
12. Mandsager et al. (2018).
13. Li et al. (2018).
14. Artero et al. (2011).
15. Naci and Ioannidis (2015).
16. Seifert et al. (2010).
17. Barnes and Corkery (2018).
18. Westerterp et al. (2021).
19. Bunout et al. (2011).
20. Jones et al. (2017).
21. Van Ancum et al. (2018).
22. CDC (2021).
23. H.-S. Lin et al. (2016).
24. Veronese et al. (2022).

25. Nicklas et al. (2015).
26. K.L. Campbell et al. (2019).
27. Zhang et al. (2020).
28. Danneskiold-Samsøe et al. (2009); Hughes et al. (2001); Lindle et al. (1997).

### فصل ۱۰۱.۱۲ تمرین

1. Allen and Coggan (2010).
2. San-Millián and Brooks (2018).
3. Lemasters (2005).
4. Kawada and Ishii (2005).
5. Richter (2021).
6. McMillin et al. (2017).
7. Seifert et al. (2010).
8. Mandsager et al. (2018).
9. C.-H. Kim et al. (2016).
10. Shephard (2009).
11. Trappe et al. (2013).
12. Shephard (2009).
13. Shephard et al. (2009).
14. Booth and Zwetsloot (2010); Mandsager et al. (2018).
15. Billat et al. (2017).
16. Lexell (1995).
17. Kortebein et al. (2007).
18. T.N. Kim and Choi (2013).
19. Xue (2011).
20. Tieland, Dirks, et al. (2012).

21. Easter (2021).
22. Bohannon (2019); Hamer and O'Donovan (2017); Y. Kim et al. (2018); A.B. Newman et al. (2006).
23. Cruz-Jentoft et al. (2019).
24. Fain and Weatherford (2016).

### فصل ١٣. بشارت ثبات

1. Lieberman et al. (2021).
2. Dahlhamer (2018).
3. Shmagel et al. (2018).
4. Gaskin and Richard (2012).
5. Boneti Moreira et al. (2014).
6. Frank, Kobesova, and Kolar (2013).
7. Attia (2021a).
8. Araujo et al. (2022).
9. Tanweer (2021).

### فصل ١٤. تغذية ٣/٥

1. Dye (1988).
2. Naghshi et al. (2020).
3. Bao et al. (2013).
4. Azad et al. (2017).
5. Hill (1965).
6. Schwingshackl, Schwedhelm, et al. (2018).
7. Pesch et al. (2012); Proctor (2001); Sasco, Secretan, and Straif (2004); Youlden, Cramb, and Baade (2008).
8. Moco et al. (2006); Ninonuevo et al. (2006); Wishart et al. (2007).

9. Crowe (2018).
10. Ejima et al. (2016).
11. Naimi et al. (2017).
12. Biddinger et al. (2022).
13. WHI (n.d.).
14. Howard et al. (2006).
15. Estruch et al. (2013).
16. Marttinez-Lapiscina et al. (2013).

### فصل ۱۵. زیست‌شیمی تغذیه در ورطه عمل

1. Colman et al. (2009).
2. Wade (2009).
3. Mattison et al. (2012).
4. Kolata (2012).
5. Cordain, Miller, et al. (2000).
6. Cordain, Eaton, et al. (2002); Pontzer et al. (2018).
7. Gibson et al. (2015); Nymo et al. (2017); Phinney and Volek (2018); Sumithran et al. (2013).
8. Oliveira, Cotrim, and Arrese (2019).
9. Peng et al. (2020).
10. C. Wang and Holtzman (2020).
11. Hines and Rimm (2001); Suzuki et al. (2009).
12. Biddinger et al. (2022).
13. Hanefeld et al. (1999); Kawano et al. (1999); H.-J. Lin et al. (2009); Standl, Schnell, and Ceriello (2011); Watanabe et al. (2011).
14. Pfister et al. (2011).

15. Echouffo-Tcheugui et al. (2019).
16. Franz (1997).
17. W. Campbell et al. (2001).
18. Wu (2016).
19. Baum, Kim, and Wolfe (2016).
20. Schoenfeld and Aragon (2018).
21. Baum, Kim, and Wolfe (2016).
22. Houston et al. (2008).
23. Rozentryt et al. (2010).
24. Tieland, van de Rest, et al. (2012).
25. Børnheim et al. (2009).
26. Nuttall and Gannon (2006).
27. Boden et al. (2005); Holt et al. (1995); Samra (2010).
28. Blasbalg et al. (2011).
29. Abdelhamid et al. (2018).
30. Hooper et al. (2020).
31. Schwingshackl, Zähringer, et al. (2021).
32. Vendelbo et al. (2014).
33. Bagherniya et al. (2018).
34. Gross, van den Heuvel, and Birnbaum (2008).
35. Hatori et al. (2012).
36. Jensen et al. (2013).
37. Lowe et al. (2020).
38. Jamshed et al. (2019); D. Liu et al. (2022).
39. Varady and Gabel (2019).
40. Templeman et al. (2021).

## فصل ۱۶. بیداری

1. Dawson and Reid (1997); Lamond and Dawson (1999).
2. Mansukhani et al. (2012); Tang et al. (2019).
3. Iftikhar et al. (2015).
4. Shan et al. (2015).
5. Leproult and Van Cauter (2010); Reutrakul and Van Cauter (2018); de Zambotti, Colrain, and Baker (2015).
6. Goldstein and Walker (2014); Killgore (2013); Krause et al. (2017); Kuna et al. (2012); Motomura et al. (2013); Prather, Bogdan, and Hariri (2013); Rupp, Wesensten, and Balkin (2012); Van Dongen, Maislin, et al. (2003); Van Dongen, Baynard, et al. (2004); Yoo et al. (2007).
7. Reddy and van der Werf (2020).
8. C. Wang and Holtzman (2020).
9. Walker (2017).
10. Cirelli and Tononi (2008).
11. Zuccarelli et al. (2019).
12. Cullen et al. (2019); Fullagar et al. (2015).
13. Dewasmes et al. (1993); Kolka and Stephenson (1988); Sawka, Gonzalez, and Pandolf (1984).
14. Milewski et al. (2014).
15. Mah et al. (2011).
16. Ferriss (2018).
17. Jackson et al. (2013).
18. AAA Foundation (2016).
19. Hafner et al. (2017); Killgore (2013); Krause et al. (2017); J. Lim and Dinges (2008); Van Dongen, Maislin, et al. (2003).
20. Oyetakin-White et al. (2015).

21. Broussard, Ehrmann, et al. (2012).
22. Broussard, Ehrmann, et al. (2012); Broussard, Chapotot, et al. (2015); Buxton et al. (2010); Leproult, Holmbück, and Van Cauter (2014); Nedeltcheva et al. (2009); Rao et al. (2015); Spiegel, Leproult, and Van Cauter (1999); Stamatakis and Punjabi (2010); Tasali et al. (2008).
23. Iftikhar et al. (2015); Itani et al. (2017); Shan et al. (2015).
24. Itani et al. (2017).
25. Kuo et al. (2015).
26. Spiegel, Tasali, et al. (2004); Spiegel, Leproult, L'hermite-Balériaux, et al. (2004).
27. Bosity-Westphal et al. (2008); Brondel et al. (2010); Broussard, Kilkus, et al. (2016); Calvin et al. (2013); Spaeth, Dinges, and Goel (2015).
28. Itani et al. (2017); Yin et al. (2017).
29. Dashti et al. (2019).
30. Daghlas et al. (2019).
31. C. Wang and Holtzman (2020).
33. Lendner et al. (2020).
34. Diekelmann and Born (2010); Wilson and McNaughton (1994).
35. Walker (2009).
36. A.K. Patel, Reddy, and Araujo (2022).
37. C. Smith and Lapp (1991); Stickgold et al. (2000).
38. van der Helm and Walker (2009); Hutchison and Rathore (2015).
39. Repantis et al. (2020).
40. Goldstein-Piekarski et al. (2015).
41. Rasking et al. (2007).
42. Yamazaki et al. (2020).
43. Iliff et al. (2013).



44. Lucey, McCullough, et al. (2019).
45. Branger et al. (2016); B. Brown et al. (2016); Ju et al. (2013); Spira et al. (2013); Sprecher et al. (2015).
46. C. Wang and Holtzman (2020).
47. Emamian et al. (2016).
48. Benito-León et al. (2009); Jack et al. (2013); A.S.P. Lim, Kowgier, et al. (2013); A.S.P. Lim, Yu, et al. (2013); Lobo et al. (2008); Osorio et al. (2011).
49. Potvin et al. (2012).
50. A.S.P. Lim, Kowgier, et al. (2013); A.S.P. Lim, Yu, et al. (2013).
51. Ancoli-Israel et al. (2008); Moraes et al. (2006).
52. Winer et al. (2019).
53. Saul (2006).
54. Business Wire (2021).
55. Arbon, Knurowska, and Dijk (2015).
56. Herring et al. (2016).
57. Ziemichód et al. (2022).
58. Picton, Marino, and Nealy (2018).
59. Zheng et al. (2022).
60. Shahid et al. (2011).
- 61 Kalmbach et al. (2017).
62. Hardeland (2013).
63. Gradisar et al. (2013).
64. Gradisar et al. (2013).
65. Harding, Franks, and Wisden (2020).
66. Ebrahim et al. (2013).
67. C. Smith and Smith (2003).

68. Urry and Landolt (2015).
69. IOM (2001).
70. Maurer et al. (2021).
71. Dworak et al. (2007); Youngstedt et al. (2000).
72. D. Kim et al. (2022).

### فصل ۱۷. کار ما هنوز تمام نشده است

1. CDC (2022f).
2. Friend (2003).
3. Spillane et al. (2020).
4. Strobe (2021).
5. CDC (2022a).
6. Case et al. (2015).
7. CDC (2022d).
8. Case and Deaton (2015).
9. Livingston (2019).
10. Real (1998).
11. Wallace (2009).
12. Brooks (2016).
13. Riis (1901).
14. Asarnow et al. (2021); Linehan et al. (2006).
15. Hagerhall (2008).

### شفاف‌سازی

برای مطالعه به‌روزشدهٔ تمامی شفاف‌سازی‌های من، لطفاً به آدرس <https://peterattiamd.com/about> ذیل عنوان "Disclosures" مراجعه کنید.

## منابع

AAA Foundation. (2016). 2015 Traffic Safety Culture Index. <https://aaa-foundation.org/2015-traffic-safety-culture-index/>.

Abbasi, F., Chu, J.W., Lamendola, C., McLaughlin, T., Hayden, J., Reaven, G.M., and Reaven, P.D. (2004). Discrimination between obesity and insulin resistance in the relationship with adiponectin. *Diabetes* 53, 585–590. <https://doi.org/10.2337/diabetes.53.3.585>.

Abdelhamid, A.S., Martin, N., Bridges, C., Brainard, J.S., Wang, X., Brown, T.J., Hanson, S., Jimoh O.F., Ajabnoor S.M., Deane K.H.O., et al. (2018). Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst. Rev.* 11, CD012345. <https://doi.org/10.1002/14651858.CD012345.pub3>.

ACS (American Cancer Society). (2022a). Breast Cancer Statistics | How common is breast cancer? Last revised January 12. <https://www.cancer.org/cancer/breast-cancer/about/how-common-is-breast-cancer.html>.

———. (2022b). Colorectal cancer facts and figures, 2022–2022. <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/colorectal-cancer-facts-and-figures/colorectal-cancer-facts-and-figures-2020-2022.pdf>.

———. (2022c). Eating well during treatment. March 16. <https://www.cancer.org/treatment/survivorship-during-and-after-treatment/coping/nutrition/once-treatment-starts.html>.

ACSM (2017). ACSM's guidelines for exercise testing and prescription. Phil-

adelphia: Lippincott Williams and Wilkins.

Ahima, R.S., and Lazar, M.A. (2013). The health risk of obesity—Better metrics imperative. *Science* 341, 856–858. <https://doi.org/10.1126/science.1241244>.

Alghamdi, B.S. (2018). The neuroprotective role of melatonin in neurological disorders. *J. Neurosci. Res.* 96, 1136–1149. <https://doi.org/10.1002/jnr.24220>.

Allen, H., and Coggan, A. (2010). *Training and racing with a power meter*. Boulder, CO: VeloPress.

Anand, S.S., Tarnopolsky, M.A., Rashid, S., Schulze, K.M., Desai, D., Mente, A., Rao, S., Yusuf, S., Gerstein, H.C., and Sharma, A.M. (2011). Adipocyte hypertrophy, fatty liver and metabolic risk factors in South Asians: The Molecular Study of Health and Risk in Ethnic Groups (mol-SHARE). *PLOS ONE* 6, e22112. <https://doi.org/10.1371/journal.pone.0022112>.

Ancoli-Israel, S., Palmer, B.W., Cooke, J.R., Corey-Bloom, J., Fiorentino, L., Natarajan, L., Liu, L., Ayalon, L., He, F., and Loreda, J.S. (2008). Cognitive effects of treating obstructive sleep apnea in Alzheimer’s disease: A randomized controlled study. *J. Am. Geriatr. Soc.* 56, 2076–2081. <https://doi.org/10.1111/j.1532-5415.2008.01934.x>.

Andersson, C., Blennow, K., Almkvist, O., Andreasen, N., Engfeldt, P., Johansson, S.-E., Lindau, M., and Eriksdotter-Jönghagen, M. (2008). Increasing CSF phospho-tau levels during cognitive decline and progression to dementia. *Neurobiol. Aging* 29, 1466–1473. <https://doi.org/10.1016/j.neurobiolaging.2007.03.027>.

Andreasen, N., Hesse, C., Davidsson, P., Minthon, L., Wallin, A., Winblad, B., Vanderstichele, H., Vanmechelen, E., and Blennow, K. (1999). Cerebrospinal fluid beta-amyloid(1-42) in Alzheimer disease: Differences between early- and late-onset Alzheimer disease and stability during the course of disease. *Arch. Neurol.* 56, 673–680. <https://doi.org/10.1001/archneur.56.6.673>.

Andreasen, N., Vanmechelen, E., Van de Voorde, A., Davidsson, P., Hesse, C., Tarvonen, S., Råihä, I., Sourander, L., Winblad, B., and Blennow, K. (1998). Cerebrospinal fluid tau protein as a biochemical marker for Alzheimer's disease: A community-based follow up study. *J. Neurol. Neurosurg. Psychiatry* 64, 298–305. <https://doi.org/10.1136/jnnp.64.3.298>.

Andrieu, S., Guyonnet, S., Coley, N., Cantet, C., Bonnefoy, M., Bordes, S. (2017). Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): A randomized placebo-controlled trial. *Lancet* 16, 377–389. [https://doi.org/10.1016/S1474-4422\(17\)30040-6](https://doi.org/10.1016/S1474-4422(17)30040-6).

Araujo, C.G., de Souza e Silva, C.G., Laukkanen, J.A., Singh, M.F., Kunutsor, S.K., Myers, J., Franca, J.F., and Castro, C.L. (2022). Successful 10-second one-legged stance performance predicts survival in middle-aged and older individuals. *Br. J. Sports Med.* 56, 975–980. <https://doi.org/10.1136/bjsports-2021-105360>.

Araújo, J., Cai, J., and Stevens, J. (2019). Prevalence of optimal metabolic health in American adults: National Health and Nutrition Examination Survey 2009–2016. *Metab. Syndr. Relat. Disord.* 17, 46–52. <https://doi.org/10.1089/met.2018.0105>.

Arbon, E.L., Knurrowska, M., and Dijk, D.-J. (2015). Randomised clinical trial of the effects of prolonged-release melatonin, temazepam and zolpidem on slow-wave activity during sleep in healthy people. *J. Psychopharmacol.* 29, 764–776. <https://doi.org/10.1177/0269881115581963>.

Artero, E.G., Lee, D.C., Ruiz, J.R. (2011). A prospective study of muscular strength and all-cause mortality in men with hypertension. *J. Am. Coll. Cardiol.* 57(18), 1831–1837. <https://doi:10.1016/j.jacc.2010.12.025>.

Asarnow, J.R., Berk, M.S., Bedics, J., Adrian, M., Gallop, R., Cohen, J., Korslund, K., Hughes, J., Avina, C., Linehan, M.M., et al. (2021). Dialectical Behavior Therapy for suicidal self-harming youth: Emotion regulation, mechanisms, and mediators. *J. Am. Acad. Child Adolesc. Psychiatry* 60, 1105–1115.

e4. <https://doi.org/10.1016/j.jaac.2021.01.016>.

Atkins, M.B., Kunkel, L., Sznol, M., and Rosenberg, S.A. (2000). High-dose recombinant interleukin-2 therapy in patients with metastatic melanoma: Long-term survival update. *Cancer J. Sci. Am.* 6, Suppl 1, S11–14.

Attia, P. (2018a). #09—David Sabatini, M.D., Ph.D.: Rapamycin and the discovery of mTOR—The nexus of aging and longevity? *The Drive* (podcast), episode 9, August 13. <https://peterattiamd.com/davidsabatini/>.

———. (2018b). #10—Matt Kaerberlein, Ph.D.: Rapamycin and dogs—man’s best friends? Living longer, healthier lives and turning back the clock on aging and age-related diseases. *The Drive* (podcast), episode 10, August 20. <https://peterattiamd.com/mattkaerberlein/>.

———. (2018c). #18—Richard Isaacson, M.D.: Alzheimer’s prevention. *The Drive* (podcast), episode 18, October 1. <https://peterattiamd.com/richardisaacson/>.

———. (2019). #38—Francisco Gonzalez-Lima, Ph.D.: Advancing Alzheimer’s disease treatment and prevention: Is AD actually a vascular and metabolic disease? *The Drive* (podcast), episode 38, January 28. <https://peterattiamd.com/franciscogonzalezlima/>.

———. (2020a). Colorectal cancer screening. *peterattiamd.com* (blog), September 27. <https://peterattiamd.com/colorectal-cancer-screening/>.

———. (2020b). The killer(s) on the road: Reducing your risk of automotive death. *peterattiamd.com* (blog), February 9. <https://peterattiamd.com/the-killers-on-the-road-reducing-your-risk-of-automotive-death/>.

———. (2020c). Rick Johnson, M.D.: Metabolic effects of fructose. *The Drive* (podcast), episode 87, January 6. <https://peterattiamd.com/rickjohnson/>.

———. (2021a). Michael Rintala, D.C.: Principles of Dynamic Neuromuscular Stabilization (DNS). *The Drive* (podcast), episode 152, March 8. <https://>

[peterattiamd.com/michaelrintala/](http://peterattiamd.com/michaelrintala/).

———. (2021b). Steven Rosenberg, M.D., Ph.D.: The development of cancer immunotherapy and its promise for treating advanced cancers. *The Drive* (podcast), episode 177, September 27.

Avgerinos, K.I., Spyrou, N., Mantzoros, C.S., and Dalamaga, M. (2019). Obesity and cancer risk: Emerging biological mechanisms and perspectives. *Metabolism* 91, 121–135. <https://doi.org/10.1016/j.metabol.2018.11.001>.

Azad, M.B., Abou-Setta, A.M., Chauhan, B.F., Rabbani, R., Lys, J., Copstein, L., Mann, A., Jeyaraman, M.M., Reid, A.E., Fiander, M., et al. (2017). Nonnutritive sweeteners and cardiometabolic health: A systematic review and meta-analysis of randomized controlled trials and prospective cohort studies. *CMAJ* 189, E929–E939. <https://doi.org/10.1503/cmaj.161390>.

Bagherniya, M., Butler, A.E., Barreto, G.E., and Sahebkar, A. (2018). The effect of fasting or calorie restriction on autophagy induction: A review of the literature. *Ageing Res. Rev.* 47, 183–197. <https://doi.org/10.1016/j.arr.2018.08.004>.

Bannister, C.A., Holden, S.E., Jenkins-Jones, S., Morgan, C.L., Halcox, J.P., Scherthaner, G., Mukherjee, J., and Currie, C.J. (2014). Can people with type 2 diabetes live longer than those without? A comparison of mortality in people initiated with metformin or sulphonylurea monotherapy and matched, non-diabetic controls. *Diabetes Obes. Metab.* 16, 1165–1173. <https://doi.org/10.1111/dom.12354>.

Bao, Y., Han, J., Hu, F.B., Giovannucci, E.L., Stampfer, M.J., Willett, W.C., and Fuchs, C.S. (2013). Association of nut consumption with total and cause-specific mortality. *N. Engl. J. Med.* 369, 2001–2011. <https://doi.org/10.1056/NEJMoa1307352>.

Barnes, J.N., and Corkery, A.T. (2018). Exercise improves vascular function, but does this translate to the brain? *Brain Plast.* 4, 65–79. <https://doi.org/10.3233/BPL-180075>.

Baum, J.I., Kim, I.-Y., and Wolfe, R.R. (2016). Protein consumption and the elderly: What is the optimal level of intake? *Nutrients* 8, 359. <https://doi.org/10.3390/nu8060359>.

Baur, J.A., Pearson, K.J., Price, N.L., Jamieson, H.A., Lerin, C., Kalra, A., Prabhu, V.V., Allard, J.S., Lopez-Lluch, G., Lewis, K., et al. (2006). Resveratrol improves health and survival of mice on a high-calorie diet. *Nature* 444, 337–342. <https://doi.org/10.1038/nature05354>.

Bautch, V.L., and Caron, K.M. (2015). Blood and lymphatic vessel formation. *Cold Spring Harb. Perspect. Biol.* 7, a008268. <https://doi.org/10.1101/cshperspect.a008268>.

Beckett, L.A., Harvey, D.J., Gamst, A., Donohue, M., Kornak, J., Zhang, H., Kuo, J.H., and Alzheimer's Disease Neuroimaging Initiative (2010). The Alzheimer's Disease Neuroimaging Initiative: Annual change in biomarkers and clinical outcomes. *Alzheimers Dement.* 6, 257–264. <https://doi.org/10.1016/j.jalz.2010.03.002>.

Belloy, M.E., Napolioni, V., Han, S.S., Le Guen, Y., and Greicius, M.D. (2020). Association of Klotho-VS heterozygosity with risk of Alzheimer disease in individuals who carry APOE4. *JAMA Neurol.* 77, 849–862. <https://doi.org/10.1001/jamaneurol.2020.0414>.

Benito-León, J., Bermejo-Pareja, F., Vega, S., and Louis, E.D. (2009). Total daily sleep duration and the risk of dementia: A prospective population-based study. *Eur. J. Neurol.* 16, 990–997. <https://doi.org/10.1111/j.1468-1331.2009.02618.x>.

Benn, M., Tybjærg-Hansen, A., Stender, S., Frikke-Schmidt, R., and Nordestgaard, B.G. (2011). Low-density lipoprotein cholesterol and the risk of cancer: A Mendelian randomization study. *J. Natl. Cancer Inst.* 103, 508–519. <https://doi.org/10.1093/jnci/djr008>.

Biddinger, K.J., Emdin, C.A., Haas, M.E., Wang, M., Hindy, G., Ellinor, P.T., Kathiresan, S., Khera, A.V., and Aragam, K.G. (2022). Association of habitual al-



cohol intake with risk of cardiovascular disease. *JAMA Netw. Open* 5, e223849. <https://doi.org/10.1001/jamanetworkopen.2022.3849>.

Billat, V., Dhonneur, G., Mille-Hamard, L., Le Moyec, L., Momken, I., Launay, T., Koralsztejn, J.P., and Besse, S. (2017). Case studies in physiology: Maximal oxygen consumption and performance in a centenarian cyclist. *J. Appl. Physiol.* 122, 430–434. <https://doi.org/10.1152/jappphysiol.00569.2016>.

Blackwell, D.L., and Clarke, T.C. (2018). State variation in meeting the 2008 federal guidelines for both aerobic and muscle-strengthening activities through leisure-time physical activity among adults aged 18–64: United States, 2010–2015. *Natl. Health Stat. Rep.* 112 (June), 1–22.

Blasbalg, T.L., Hibbeln, J.R., Ramsden, C.E., Majchrzak, S.F., and Rawlings, R.R. (2011). Changes in consumption of omega-3 and omega-6 fatty acids in the United States during the 20th century. *Am. J. Clin. Nutr.* 93, 950–962. <https://doi.org/10.3945/ajcn.110.006643>.

Blessed, G., Tomlinson, B.E., and Roth, M. (1968). The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *Br. J. Psychiatry J. Ment. Sci.* 114, 797–811. <https://doi.org/10.1192/bjp.114.512.797>.

Boden, G., Sargrad, K., Homko, C., Mozzoli, M., and Stein, T.P. (2005). Effect of a low-carbohydrate diet on appetite, blood glucose levels, and insulin resistance in obese patients with type 2 diabetes. *Ann. Intern. Med.* 142, 403–411. <https://doi.org/10.7326/0003-4819-142-6-200503150-00006>.

Bohannon, R.W. (2019). Grip strength: An indispensable biomarker for older adults. *Clin. Interv. Aging* 14, 1681–1691. <https://doi.org/10.2147/CIA.S194543>.

Boneti Moreira, N., Vagetti, G.C., de Oliveira, V., and de Campos, W. (2014). Association between injury and quality of life in athletes: A systematic review, 1980–2013. *Apunts Sports Med.* 49, 123–138.

Booth, F.W., and Zwetsloot, K.A. (2010). Basic concepts about genes, inac-

tivity and aging. *Scand. J. Med. Sci. Sports* 20, 1–4. <https://doi.org/10.1111/j.1600-0838.2009.00972.x>.

Børshiem, E., Bui, Q.-U.T., Tissier, S., Cree, M.G., Rønsen, O., Morio, B., Ferrando, A.A., Kobayashi, H., Newcomer, B.R., and Wolfe, R.R. (2009). Amino acid supplementation decreases plasma and liver triglycerides in elderly. *Nutr. Burbank Los Angel. Cty. Calif.* 25, 281–288. <https://doi.org/10.1016/j.nut.2008.09.001>.

Bosy-Westphal, A., Hinrichs, S., Jauch-Chara, K., Hitze, B., Later, W., Wilms, B., Settler, U., Peters, A., Kiosz, D., and Müller, M.J. (2008). Influence of partial sleep deprivation on energy balance and insulin sensitivity in healthy women. *Obes. Facts* 1, 266–273. <https://doi.org/10.1159/000158874>.

Bouwman, F.H., van der Flier, W.M., Schoonenboom, N.S.M., van Elk, E.J., Kok, A., Rijmen, F., Blankenstein, M.A., and Scheltens, P. (2007). Longitudinal changes of CSF biomarkers in memory clinic patients. *Neurology* 69, 1006–1011. <https://doi.org/10.1212/01.wnl.0000271375.37131.04>.

Bradley, D. (2004). Biography of Lewis C. Cantley. *Proc. Natl. Acad. Sci.* 101, 3327–3328. <https://doi.org/10.1073/pnas.0400872101>.

Branger, P., Arenaza-Urquijo, E.M., Tomadesso, C., Mézence, F., André, C., de Flores, R., Mutlu, J., de La Sayette, V., Eustache, F., Chételat, G., et al. (2016). Relationships between sleep quality and brain volume, metabolism, and amyloid deposition in late adulthood. *Neurobiol. Aging* 41, 107–114. <https://doi.org/10.1016/j.neurobiolaging.2016.02.009>.

Brondel, L., Romer, M.A., Nougues, P.M., Touyarou, P., and Davenne, D. (2010). Acute partial sleep deprivation increases food intake in healthy men. *Am. J. Clin. Nutr.* 91, 1550–1559. <https://doi.org/10.3945/ajcn.2009.28523>.

Brookmeyer, R., Abdalla, N., Kawas, C.H., and Corrada, M.M. (2018). Forecasting the prevalence of preclinical and clinical Alzheimer’s disease in the United States. *Alzheimers Dement.* 14, 121–129. <https://doi.org/10.1016/j.jalz.2017.10.009>.

Brooks, D. (2016). *The road to character*. Farmington Hills, MI: Large Print Press.

Broussard, J.L., Chapotot, F., Abraham, V., Day, A., Delebecque, F., Whitmore, H.R., and Tasali, E. (2015). Sleep restriction increases free fatty acids in healthy men. *Diabetologia* 58, 791–798. <https://doi.org/10.1007/s00125-015-3500-4>.

Broussard, J.L., Ehrmann, D.A., Van Cauter, E., Tasali, E., and Brady, M.J. (2012). Impaired insulin signaling in human adipocytes after experimental sleep restriction. *Ann. Intern. Med.* 157, 549–557. <https://doi.org/10.7326/0003-4819-157-8-201210160-00005>.

Broussard, J.L., Kilkus, J.M., Delebecque, F., Abraham, V., Day, A., Whitmore, H.R., and Tasali, E. (2016). Elevated ghrelin predicts food intake during experimental sleep restriction. *Obesity* 24, 132–138. <https://doi.org/10.1002/oby.21321>.

Brown, B.M., Rainey-Smith, S.R., Villemagne, V.L., Weinborn, M., Bucks, R.S., Sohrabi, H.R., Laws, S.M., Taddei, K., Macaulay, S.L., Ames, D., et al. (2016). The relationship between sleep quality and brain amyloid burden. *Sleep* 39, 1063–1068. <https://doi.org/10.5665/sleep.5756>.

Brown, E.J., Albers, M.W., Shin, T.B., Ichikawa, K., Keith, C.T., Lane, W.S., and Schreiber, S.L. (1994). A mammalian protein targeted by G1-arresting rapamycin-receptor complex. *Nature* 369, 756–758. <https://doi.org/10.1038/369756a0>.

Brys, M., Pirraglia, E., Rich, K., Rolstad, S., Mosconi, L., Switalski, R., Glodzik-Sobanska, L., De Santi, S., Zinkowski, R., Mehta, P., et al. (2009). Prediction and longitudinal study of CSF biomarkers in mild cognitive impairment. *Neurobiol. Aging* 30, 682–690. <https://doi.org/10.1016/j.neurobiolaging.2007.08.010>.

Bunout, D., de la Maza, M.P., Barrera, G., Leiva, L., and Hirsch, S. (2011). Association between sarcopenia and mortality in healthy older people. *Austral-*

as. *J. Ageing* 30, 89–92. <https://doi.org/10.1111/j.1741-6612.2010.00448.x>.

Business Wire (2021). U.S. sleep aids market worth \$30 billion as Americans battle insomnia, sleep disorders—ResearchAndMarkets.com, June 30. <https://www.businesswire.com/news/home/20210630005428/en/U.S.-Sleep-Aids-Market-Worth-30-Billion-as-Americans-Battle-Insomnia-Sleep-Disorders---ResearchAndMarkets.com>.

Buxton, O.M., Pavlova, M., Reid, E.W., Wang, W., Simonson, D.C., and Adler, G.K. (2010). Sleep restriction for 1 week reduces insulin sensitivity in healthy men. *Diabetes* 59, 2126–2133. <https://doi.org/10.2337/db09-0699>.

Buysse, D.J., Reynolds, C.F., Charles, F., Monk, T.H., Berman, S.R., and Kupfer, D.J. (1989). The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiat. Res.* 28(2), 193–213.

Cacace, R., Slegers, K., and Van Broeckhoven, C. (2016). Molecular genetics of early-onset Alzheimer's disease revisited. *Alzheimers Dement.* 12, 733–748. <https://doi.org/10.1016/j.jalz.2016.01.012>.

Calle, E.E., Rodriguez, C., Walker-Thurmond, K., and Thun, M.J. (2003). Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N. Engl. J. Med.* 348, 1625. <https://doi.org/10.1056/NEJMoa021423>.

Calvin, A.D., Carter, R.E., Adachi, T., Macedo, P.G., Albuquerque, F.N., van der Walt, C., Bukartyk, J., Davison, D.E., Levine, J.A., and Somers, V.K. (2013). Effects of experimental sleep restriction on caloric intake and activity energy expenditure. *Chest* 144, 79–86. <https://doi.org/10.1378/chest.12-2829>.

Campbell, K.L., Winters-Stone, K., Wiskemann, J., May, A.M., Schwartz, A.L., Courneya, K.S., Zucker, D., Matthews, C., Ligibel, J., Gerber, L., et al. (2019). Exercise guidelines for cancer survivors: Consensus statement from International Multidisciplinary Roundtable. *Med. Sci. Sports Exerc.* 51, 2375–2390. <https://doi.org/10.1249/MSS.0000000000002116>.

Campbell, W.W., Trappe, T.A., Wolfe, R.R., and Evans, W.J. (2001). The

recommended dietary allowance for protein may not be adequate for older people to maintain skeletal muscle. *J. Gerontol. A. Biol. Sci. Med. Sci.* 56, M373–380. <https://doi.org/10.1093/gerona/56.6.m373>.

Case, A., and Deaton, A. (2015). Rising morbidity and mortality in mid-life among white non-Hispanic Americans in the 21st century. *Proc. Natl. Acad. Sci.* 112(49), 15078–15083. <https://www.pnas.org/doi/full/10.1073/pnas.1518393112>.

Caselli, G., and Lipsi, R.M. (2006). Survival differences among the oldest old in Sardinia: Who, what, where, and why? *Demogr. Res.* 14, 267–294.

Cavazzoni, A., Digiacomo, G., Alfieri, R., La Monica, S., Fumarola, C., Galetti, M., Bonelli, M., Cretella, D., Barili, V., Zecca, A., et al. (2020). Pemetrexed enhances membrane PD-L1 expression and potentiates T cell-mediated cytotoxicity by anti-PD-L1 antibody therapy in non-small-cell lung cancer. *Cancers* 12, E666. <https://doi.org/10.3390/cancers12030666>.

Cerri, S., Mus, L., and Blandini, F. (2019). Parkinson's disease in women and men: What's the difference? *J. Parkinson's Dis.* 9(3), 501–515. <https://doi.org/10.3233/JPD-191683>.

CDC (Centers for Disease Control). (2020a). The influence of metabolic syndrome in predicting mortality risk among US adults: Importance of metabolic syndrome even in adults with normal weight. [https://www.cdc.gov/pcd/issues/2020/20\\_0020.htm](https://www.cdc.gov/pcd/issues/2020/20_0020.htm).

———. (2020b). Diabetes. FastStats. <https://www.cdc.gov/nchs/fastats/diabetes.htm>.

———. (2021). Facts about falls. Injury Center. <https://www.cdc.gov/falls/facts.html>.

———. (2022a). Accidents or unintentional injuries. FastStats. <https://www.cdc.gov/nchs/fastats/accidental-injury.htm>.

———. (2022b) Adult obesity facts. <https://www.cdc.gov/obesity/data/>

adult.html.

———. (2022c). Heart disease facts. <https://www.cdc.gov/heartdisease/facts.htm>.

———. (2022d). Life expectancy in the U.S. dropped for the second year in a row in 2021. Press release, August 31. [https://www.cdc.gov/nchs/press-room/nchs\\_press\\_releases/2022/20220831.htm](https://www.cdc.gov/nchs/press-room/nchs_press_releases/2022/20220831.htm).

———. (2022e). National diabetes statistics report. <https://www.cdc.gov/diabetes/data/statistics-report/index.html?ACSTrackingID=DM72996&ACSTrackingLabel=New%20Report%20Shares%20Latest%20Diabetes%20Stats%20&deliveryName=DM72996>.

———. (2022f). Ten leading causes of death and injury. [https://www.cdc.gov/injury/wisqars/LeadingCauses\\_images.html](https://www.cdc.gov/injury/wisqars/LeadingCauses_images.html).

Chan, J.M., Rimm, E.B., Colditz, G.A., Stampfer, M.J., and Willett, W.C. (1994). Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care* 17, 961–969. <https://doi.org/10.2337/diacare.17.9.961>.

Chapman, C.D., Schiöth, H.B., Grillo, C.A., and Benedict, C. (2018). Intranasal insulin in Alzheimer’s disease: Food for thought. *Neuropharmacology* 136, 196–201. <https://doi.org/10.1016/j.neuropharm.2017.11.037>.

Chen, D.L., Liess, C., Poljak, A., Xu, A., Zhang, J., Thoma, C., Trenell, M., Milner, B., Jenkins, A.B., Chisholm, D.J., et al. (2015). Phenotypic characterization of insulin-resistant and insulin-sensitive obesity. *J. Clin. Endocrinol. Metab.* 100, 4082–4091. <https://doi.org/10.1210/jc.2015-2712>.

Chen, X., Dong, Z., Hubbell, E., Kurtzman, K.N., Oxnard, G.R., Venn, O., Melton, C., Clarke, C.A., Shaknovich, R., Ma, T., et al. (2021). Prognostic significance of blood-based multi-cancer detection in plasma cell-free DNA. *Clin. Cancer Res.* 27, 4221–4229. <https://doi.org/10.1158/1078-0432.CCR-21-0417>.

Cholerton, B., Baker, L.D., Montine, T.J., and Craft, S. (2016). Type 2 diabetes, cognition, and dementia in older adults: Toward a precision health approach. *Diabetes Spectr.* 29, 210–219. <https://doi.org/10.2337/ds16-0041>.

Christofferson, Travis. *Tripping Over the Truth: How the Metabolic Theory of Cancer Is Overturning One of Medicine's Most Entrenched Paradigms*. Chelsea Green Publishing, 2017.

Cirelli, C., and Tononi, G. (2008). Is sleep essential? *PLOS Biol.* 6, e216. <https://doi.org/10.1371/journal.pbio.0060216>.

Colman, R.J., Anderson, R.M., Johnson, S.C., Kastman, E.K., Kosmatka, K.J., Beasley, T.M., Allison, D.B., Cruzen, C., Simmons, H.A., Kemnitz, J.W., et al. (2009). Caloric restriction delays disease onset and mortality in rhesus monkeys. *Science* 325, 201–204. <https://doi.org/10.1126/science.1173635>.

Copinschi, G., and Caufriez, A. (2013). Sleep and hormonal changes in aging. *Endocrinol. Metab. Clin. North Am.* 42, 371–389. <https://doi.org/10.1016/j.ecl.2013.02.009>.

Cordain, L., Eaton, S.B., Miller, J.B., Mann, N., and Hill, K. (2002). The paradoxical nature of hunter-gatherer diets: Meat-based, yet non-atherogenic. *Eur. J. Clin. Nutr.* 56, S42–S52. <https://doi.org/10.1038/sj.ejcn.1601353>.

Cordain, L., Miller, J.B., Eaton, S.B., Mann, N., Holt, S.H., and Speth, J.D. (2000). Plant-animal subsistence ratios and macronutrient energy estimations in worldwide hunter-gatherer diets. *Am. J. Clin. Nutr.* 71, 682–692. <https://doi.org/10.1093/ajcn/71.3.682>.

Creevy, K.E., Akey, J.M., Kaerberlein, M., and Promislow, D.E.L. (2022). An open science study of ageing in companion dogs. *Nature* 602, 51–57. <https://doi.org/10.1038/s41586-021-04282-9>.

Crispim, C.A., Zimberg, I.Z., dos Reis, B.G., Diniz, R.M., Tufik, S., and de Mello, M.T. (2011). Relationship between food intake and sleep pattern in healthy individuals. *J. Clin. Sleep Med.* 7, 659–664. <https://doi.org/10.5664/jcsm.1476>.

Crowe, K. (2018). University of Twitter? Scientists give impromptu lecture critiquing nutrition research. *CBC Health*, May 5. <https://www.cbc.ca/news/health/second-opinion-alcohol180505-1.4648331>.

Cruchaga, C., Haller, G., Chakraverty, S., Mayo, K., Vallania, F.L.M., Mitra, R.D., Faber, K., Williamson, J., Bird, T., Diaz-Arrastia, R., et al. (2012). Rare variants in APP, PSEN1 and PSEN2 increase risk for AD in late-onset Alzheimer's disease families. *PLOS ONE* 7, e31039. <https://doi.org/10.1371/journal.pone.0031039>.

Cruz-Jentoft, A.J., Bahat, G., Bauer, J., Boirie, Y., Bruyère, O., Cederholm, T., Cooper, C., Landi, F., Rolland, Y., Sayer, A.A., et al. (2019). Sarcopenia: Revised European consensus on definition and diagnosis. *Age Ageing* 48, 16–31. <https://doi.org/10.1093/ageing/afy169>.

Cullen, T., Thomas, G., Wadley, A.J., and Myers, T. (2019). The effects of a single night of complete and partial sleep deprivation on physical and cognitive performance: A Bayesian analysis. *J. Sports Sci.* 37, 2726–2734. <https://doi.org/10.1080/02640414.2019.1662539>.

Cummings, J.L., Goldman, D.P., Simmons-Stern, N.R., and Ponton, E. (2022). The costs of developing treatments for Alzheimer's disease: A retrospective exploration. *Alzheimers Dement.* 18, 469–477. <https://doi.org/10.1002/alz.12450>.

Cuyvers, E., and Sleegers, K. (2016). Genetic variations underlying Alzheimer's disease: Evidence from genome-wide association studies and beyond. *Lancet Neurol.* 15, 857–868. [https://doi.org/10.1016/S1474-4422\(16\)00127-7](https://doi.org/10.1016/S1474-4422(16)00127-7).

Daghlas, I., Dashti, H.S., Lane, J., Aragam, K.G., Rutter, M.K., Saxena, R., and Vetter, C. (2019). Sleep duration and myocardial infarction. *J. Am. Coll. Cardiol.* 74, 1304–1314. <https://doi.org/10.1016/j.jacc.2019.07.022>.

Dahlhamer, J. (2018). Prevalence of chronic pain and high-impact chronic pain among adults—United States, 2016. *MMWR* 67. <https://doi.org/>



10.15585/ mmwr.mm6736a2.

Danneskiold-Samsøe, B., Bartels, E.M., Bülow, P.M., Lund, H., Stockmarr, A., Holm, C.C., Wätjen, I., Appleyard, M., and Bliddal, H. (2009). Isokinetic and isometric muscle strength in a healthy population with special reference to age and gender. *Acta Physiol.* 197, 1–68. <https://doi.org/10.1111/j.1748-1716.2009.02022.x>.

Dashti, H.S., Jones, S.E., Wood, A.R., Lane, J.M., van Hees, V.T., Wang, H., Rhodes, J.A., Song, Y., Patel, K., Anderson, S.G., et al. (2019). Genome-wide association study identifies genetic loci for self-reported habitual sleep duration supported by accelerometer-derived estimates. *Nat. Commun.* 10, 1100. <https://doi.org/10.1038/s41467-019-08917-4>.

Daviglus, M.L., Bell, C.C., Berrettini, W., Bowen, P.E., Connolly, E.S., Cox, N.J., Dunbar-Jacob, J.M., Granieri, E.C., Hunt, G., McGarry, K., et al. (2010). NIH state-of-the-science conference statement: Preventing Alzheimer's disease and cognitive decline. *NIH Consens. State Sci. Statements* 27, 1–30.

Dawson, D., and Reid, K. (1997). Fatigue, alcohol and performance impairment. *Nature* 388, 235–235. <https://doi.org/10.1038/40775>.

de Groot, S., Lugtenberg, R.T., Cohen, D., Welters, M.J.P., Ehsan, I., Vreeswijk, M.P.G., Smit, V.T.H.B.M., de Graaf, H., Heijns, J.B., Portielje, J.E.A., et al. (2020). Fasting mimicking diet as an adjunct to neoadjuvant chemotherapy for breast cancer in the multicentre randomized phase 2 DIRECT trial. *Nat. Commun.* 11, 3083. <https://doi.org/10.1038/s41467-020-16138-3>.

de la Torre, J. (2016). *Alzheimer's turning point: A vascular approach to clinical prevention*. Cham, Switzerland: Springer International, 169–183.

———. (2018). The vascular hypothesis of Alzheimer's disease: A key to preclinical prediction of dementia using neuroimaging. *J. Alzheimers Dis.* 63, 35–52. <https://doi.org/10.3233/JAD-180004>.

de Leon, M.J., DeSanti, S., Zinkowski, R., Mehta, P.D., Pratico, D., Segal, S., Rusinek, H., Li, J., Tsui, W., Saint Louis, L.A., et al. (2006). Longitudinal CSF and

MRI biomarkers improve the diagnosis of mild cognitive impairment. *Neurobiol. Aging* 27, 394–401. <https://doi.org/10.1016/j.neurobiolaging.2005.07.003>.

Dewasmes, G., Bothorel, B., Hoeft, A., and Candas, V. (1993). Regulation of local sweating in sleep-deprived exercising humans. *Eur. J. Appl. Physiol.* 66, 542–546. <https://doi.org/10.1007/BF00634307>.

de Zambotti, M., Colrain, I.M., and Baker, F.C. (2015). Interaction between reproductive hormones and physiological sleep in women. *J. Clin. Endocrinol. Metab.* 100, 1426–1433. <https://doi.org/10.1210/jc.2014-3892>.

Diamond, J. (2003). The double puzzle of diabetes. *Nature* 423, 599–602. <https://doi.org/10.1038/423599a>.

Diekelmann, S., and Born, J. (2010). The memory function of sleep. *Nat. Rev. Neurosci.* 11, 114–126. <https://doi.org/10.1038/nrn2762>.

Dietary Guidelines Advisory Committee. (2015). Scientific report of the 2015 Dietary Guidelines Advisory Committee: Advisory report to the Secretary of Health and Human Services and the Secretary of Agriculture. Washington, D.C.: U.S. Department of Agriculture, Agricultural Research Service. <https://health.gov/sites/default/files/2019-09/Scientific-Report-of-the-2015-Dietary-Guidelines-Advisory-Committee.pdf>.

Dietschy, J.M., Turley, S.D., and Spady, D.K. (1993). Role of liver in the maintenance of cholesterol and low density lipoprotein homeostasis in different animal species, including humans. *J. Lipid Res.* 34, 1637–1659.

Dominy, S.S., Lynch, C., Ermini, F., Benedyk, M., Marczyk, A., Konradi, A., Nguyen, M., Haditsch, U., Raha, D., Griffin, C., et al. (2019). *Porphyromonas gingivalis* in Alzheimer’s disease brains: Evidence for disease causation and treatment with small-molecule inhibitors. *Sci. Adv.* 5, eaau3333. <https://doi.org/10.1126/sciadv.aau3333>.

du Souich, P., Roederer, G., and Dufour, R. (2017). Myotoxicity of statins: Mechanism of action. *Pharmacol. Ther.* 175, 1–16. <https://doi.org/10.1016/j.pharmthera.2017.02.029>.

Dworak, M., Diel, P., Voss, S., Hollmann, W., and Strüder, H.K. (2007). Intense exercise increases adenosine concentrations in rat brain: Implications for a homeostatic sleep drive. *Neuroscience* 150, 789–795. <https://doi.org/10.1016/j.neuroscience.2007.09.062>.

Dye, L. (1988). Nobel physicist R. P. Feynman of Caltech dies. *Los Angeles Times*, February 16. <https://www.latimes.com/archives/la-xpm-1988-02-16-mn-42968-story.html>.

Easter, M. (2021). *The comfort crisis: Embrace discomfort to reclaim your wild, happy, healthy self*. New York: Rodale Books.

Ebrahim, I.O., Shapiro, C.M., Williams, A.J., and Fenwick, P.B. (2013). Alcohol and sleep I: Effects on normal sleep. *Alcohol. Clin. Exp. Res.* 37, 539–549. <https://doi.org/10.1111/acer.12006>.

Echouffo-Tcheugui, J.B., Zhao, S., Brock, G., Matsouaka, R.A., Kline, D., and Joseph, J.J. (2019). Visit-to-visit glycemic variability and risks of cardiovascular events and all-cause mortality: The ALLHAT study. *Diabetes Care* 42, 486–493. <https://doi.org/10.2337/dc18-1430>.

Ejima, K., Li, P., Smith, D.L., Nagy, T.R., Kadish, I., van Groen, T., Dawson, J.A., Yang, Y., Patki, A., and Allison, D.B. (2016). Observational research rigor alone does not justify causal inference. *Eur. J. Clin. Invest.* 46, 985–993. <https://doi.org/10.1111/eci.12681>.

Emamian, F., Khazaie, H., Tahmasian, M., Leschziner, G.D., Morrell, M.J., Hsiung, G.-Y.R., Rosenzweig, I., and Sepehry, A.A. (2016). The association between obstructive sleep apnea and Alzheimer's disease: A meta-analysis perspective. *Front. Aging Neurosci.* 8, 78. <https://doi.org/10.3389/fnagi.2016.00078>.

Esteban-Cornejo, I., Ho, F.K., Petermann-Rocha, F., Lyall, D.M., Martinez-Gomez, D., Cabanas-Sánchez, V., Ortega, F.B., Hillman, C.H., Gill, J.M.R., Quinn, T.J., et al. (2022). Handgrip strength and all-cause dementia incidence and mortality: Findings from the UK Biobank prospective cohort study.

J. Cachexia Sarcopenia Muscle 13, 1514–1525. [https://doi.org/ 10.1002/jcsm.12857](https://doi.org/10.1002/jcsm.12857).

Estruch, R., Ros, E., Salas-Salvadó, J., Covas, M.-I., Corella, D., Arós, F., Gómez-Gracia, E., Ruiz-Gutiérrez, V., Fiol, M., Lapetra, J., et al. (2013). Primary prevention of cardiovascular disease with a Mediterranean diet. *N. Engl. J. Med.* 368, 1279–1290. [https://doi.org/ 10.1056/NEJMoa1200303](https://doi.org/10.1056/NEJMoa1200303).

Evert, J., Lawler, E., Bogan, H., and Perls, T. (2003). Morbidity profiles of centenarians: Survivors, delayers, and escapers. *J. Gerontol. Ser. A* 58, M232–M237. <https://doi.org/10.1093/gerona/58.3.M232>.

Fagan, A.M., Mintun, M.A., Mach, R.H., Lee, S.-Y., Dence, C.S., Shah, A.R., LaRossa, G.N., Spinner, M.L., Klunk, W.E., Mathis, C.A., et al. (2006). Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid Abeta42 in humans. *Ann. Neurol.* 59, 512–519. <https://doi.org/10.1002/ana.20730>.

Fain, E., and Weatherford, C. (2016). Comparative study of millennials' (age 20–34 years) grip and lateral pinch with the norms. *J. Hand Ther.* 29, 483–488. [https://doi.org/ 10.1016/j.jht.2015.12.006](https://doi.org/10.1016/j.jht.2015.12.006).

Fayek, S.A., Quintini, C., Chavin, K.D., and Marsh, C.L. (2016). The current state of liver transplantation in the United States. *Am. J. Transplant.* 16, 3093–3104. <https://doi.org/10.1111/ajt.14017>.

Ference, B.A. (2015). Mendelian randomization studies: Using naturally randomized genetic data to fill evidence gaps. *Curr. Opin. Lipidol.* 26, 566–571. <https://doi.org/10.1097/MOL.0000000000000247>.

Ference, B.A., Bhatt, D.L., Catapano, A.L., Packard, C.J., Graham, I., Kaptoge, S., Ference, T.B., Guo, Q., Laufs, U., Ruff, C.T., et al. (2019). Association of genetic variants related to combined exposure to lower low-density lipoproteins and lower systolic blood pressure with lifetime risk of cardiovascular disease. *JAMA* 322, 1381–1391. <https://doi.org/10.1001/jama.2019.14120>.

Ferriss, T. (2018). LeBron James and his top-secret trainer, Mike Mancias (#349). *Tim Ferriss Show* (podcast), episode 349, November 27.

Fontana, L., and Partridge, L. (2015). Promoting health and longevity through diet: From model organisms to humans. *Cell* 161, 106–118. <https://doi.org/10.1016/j.cell.2015.02.020>.

Forrester, J.S. (2010). Redefining normal low-density lipoprotein cholesterol: A strategy to unseat coronary disease as the nation's leading killer. *J. Am. Coll. Cardiol.* 56, 630–636. <https://doi.org/10.1016/j.jacc.2009.11.090>.

Frank, C., Kobesova, A., and Kolar, P. (2013). Dynamic neuromuscular stabilization and sports rehabilitation. *Int. J. Sports Phys. Ther.* 8, 62–73.

Franz, M.J. (1997). Protein: Metabolism and effect on blood glucose levels. *Diabetes Educ.* 23, 643–646, 648, 650–651. <https://doi.org/10.1177/014572179702300603>.

Frayn, K. (2019). *Human metabolism: A regulatory perspective*. 4th ed. New York: Wiley.

Freiherr, J., Hallschmid, M., Frey, W.H., Brünner, Y.F., Chapman, C.D., Hölscher, C., Craft, S., De Felice, F.G., and Benedict, C. (2013). Intranasal insulin as a treatment for Alzheimer's disease: A review of basic research and clinical evidence. *CNS Drugs* 27, 505–514. <https://doi.org/10.1007/s40263-013-0076-8>.

Friend, T. (2003). Jumpers. *New Yorker*, October 13. <https://www.newyorker.com/magazine/2003/10/13/jumpers>.

Fruman, D.A., Chiu, H., Hopkins, B.D., Bagrodia, S., Cantley, L.C., and Abraham, R.T. (2017). The PI3K pathway in human disease. *Cell* 170, 605–635. <https://doi.org/10.1016/j.cell.2017.07.029>.

Fryar, C.D., Kruszon-Moran, D., Gu, Q., and Ogden, C.L. (2018). Mean body weight, height, waist circumference, and body mass index among adults: United States, 1999–2000 through 2015–2016. *Natl. Health Stat. Rep.* 1–16.

Fullagar, H.H.K., Skorski, S., Duffield, R., Hammes, D., Coutts, A.J., and Meyer, T. (2015). Sleep and athletic performance: The effects of sleep loss on

exercise performance, and physiological and cognitive responses to exercise. *Sports Med. Auckl. NZ* 45, 161–186. <https://doi.org/10.1007/s40279-014-0260-0>.

Gaskin, D.J., and Richard, P. (2012). The economic costs of pain in the United States. *J. Pain* 13, 715–724. <https://doi.org/10.1016/j.jpain.2012.03.009>.

Gavrilova, O., Marcus-Samuels, B., Graham, D., Kim, J.K., Shulman, G.I., Castle, A.L., Vinson, C., Eckhaus, M., and Reitman, M.L. (2000). Surgical implantation of adipose tissue reverses diabetes in lipoatrophic mice. *J. Clin. Invest.* 105, 271–278.

Gay, N., and Prasad, V. (2017). Few people actually benefit from “breakthrough” cancer immunotherapy. *Stat News*, March 8. <https://www.statnews.com/2017/03/08/immunotherapy-cancer-breakthrough/>.

Gibala, M.J., Little, J.P., van Essen, M., Wilkin, G.P., Burgomaster, K.A., Safdar, A., Raha, S., and Tarnopolsky, M.A. (2006). Short-term sprint interval versus traditional endurance training: Similar initial adaptations in human skeletal muscle and exercise performance. *J. Physiol.* 575, 901–911. <https://doi.org/10.1113/jphysiol.2006.112094>.

Gibson, A.A., Seimon, R.V., Lee, C.M.Y., Ayre, J., Franklin, J., Markovic, T.P., Caterson, I.D., and Sainsbury, A. (2015). Do ketogenic diets really suppress appetite? A systematic review and meta-analysis. *Obes. Rev.* 16, 64–76. <https://doi.org/10.1111/obr.12230>.

Gillen, J.B., Percival, M.E., Skelly, L.E., Martin, B.J., Tan, R.B., Tarnopolsky, M.A., and Gibala, M.J. (2014). Three minutes of all-out intermittent exercise per week increases skeletal muscle oxidative capacity and improves cardiometabolic health. *PLOS ONE* 9, e111489. <https://doi.org/10.1371/journal.pone.0111489>.

Goldin, A., Beckman, J.A., Schmidt, A.M., and Creager, M.A. (2006). Advanced glycation end products. *Circulation* 114, 597–605. <https://doi.org/10.1161/CIRCULATIONAHA.106.621854>.

Goldstein, A.N., and Walker, M.P. (2014). The role of sleep in emotional brain function. *Annu. Rev. Clin. Psychol.* 10, 679–708. <https://doi.org/10.1146/annurev-clinpsy-032813-153716>.

Goldstein-Piekarski, A.N., Greer, S.M., Saletin, J.M., and Walker, M.P. (2015). Sleep deprivation impairs the human central and peripheral nervous system discrimination of social threat. *J. Neurosci.* 35, 10135–10145. <https://doi.org/10.1523/JNEUROSCI.5254-14.2015>.

Gordon, R.J. (2016). *The rise and fall of American growth: The U.S. standard of living since the Civil War*. Princeton, NJ: Princeton University Press.

Gradisar, M., Wolfson, A.R., Harvey, A.G., Hale, L., Rosenberg, R., and Czeisler, C.A. (2013). The sleep and technology use of Americans: Findings from the National Sleep Foundation's 2011 Sleep in America Poll. *J. Clin. Sleep Med.* 9, 1291–1299. <https://doi.org/10.5664/jcsm.3272>.

Graeber, C. (2018). *The breakthrough: Immunotherapy and the race to cure cancer*. New York: Twelve.

Grammatikopoulou, M.G., Goulis, D.G., Gkiouras, K., Theodoridis, X., Gkouskou, K.K., Evangeliou, A., Dardiotis, E., and Bogdanos, D.P. (2020). To keto or not to keto? A systematic review of randomized controlled trials assessing the effects of ketogenic therapy on Alzheimer disease. *Adv. Nutr.* 11, 1583–1602. <https://doi.org/10.1093/advances/nmaa073>.

Grandner, M.A., Sean, P.A., Drummond. (2007). Who are the long sleepers? Towards an understanding of the mortality relationship. *Sleep Medicine Reviews*, 11: 5, 341–360. <https://doi.org/10.1016/j.smrv.2007.03.010>.

Grimmer, T., Riemenschneider, M., Förstl, H., Henriksen, G., Klunk, W.E., Mathis, C.A., Shiga, T., Wester, H.-J., Kurz, A., and Drzezga, A. (2009). Beta amyloid in Alzheimer's disease: Increased deposition in brain is reflected in reduced concentration in cerebrospinal fluid. *Biol. Psychiatry* 65, 927–934. <https://doi.org/10.1016/j.biopsych.2009.01.027>.

Gross, D.N., van den Heuvel, A.P.J., and Birnbaum, M.J. (2008). The role of

FoxO in the regulation of metabolism. *Oncogene* 27, 2320–2336. <https://doi.org/10.1038/onc.2008.25>.

Guyenet, S.J., and Carlson, S.E. (2015). Increase in adipose tissue linoleic acid of US adults in the last half century. *Adv. Nutr.* 6, 660–664. <https://doi.org/10.3945/an.115.009944>.

Haase, C.L., Tybjærg-Hansen, A., Ali Qayyum, A., Schou, J., Nordestgaard, B.G., and Frikke-Schmidt, R. (2012). LCAT, HDL cholesterol and ischemic cardiovascular disease: A Mendelian randomization study of HDL cholesterol in 54,500 Individuals. *J. Clin. Endocrinol. Metab.* 97, E248–E256. <https://doi.org/10.1210/jc.2011-1846>.

Hafner, M., Stepanek, M., Taylor, J., Troxel, W.M., and van Stolk, C. (2017). Why sleep matters: The economic costs of insufficient sleep. *Rand Health Q.* 6, 11.

Hagerhall, C.M., et al. 2008. Investigations of human EEG response to viewing fractal patterns. *Perception* 37, 1488–1494. <https://doi.org/10.1068/p5918>.

Hamer, M., and O’Donovan, G. (2017). Sarcopenic obesity, weight loss, and mortality: The English Longitudinal Study of Ageing. *Am. J. Clin. Nutr.* 106, 125–129. <https://doi.org/10.3945/ajcn.117.152488>.

Hanahan, D., and Weinberg, R.A. (2011). Hallmarks of cancer: The next generation. *Cell* 144, 646–674. <https://doi.org/10.1016/j.cell.2011.02.013>.

Hanefeld, M., Koehler, C., Schaper, F., Fuecker, K., Henkel, E., and Temelkova-Kurtschiev, T. (1999). Postprandial plasma glucose is an independent risk factor for increased carotid intima-media thickness in non-diabetic individuals. *Atherosclerosis* 144, 229–235. [https://doi.org/10.1016/S0021-9150\(99\)00059-3](https://doi.org/10.1016/S0021-9150(99)00059-3).

Hardeland, R. (2013). Chronobiology of melatonin beyond the feedback to the suprachiasmatic nucleus: Consequences to melatonin dysfunction. *Int. J. Mol. Sci.* 14, 5817–5841. <https://doi.org/10.3390/ijms14035817>.



Hardie, D.G. (2011). AMP-activated protein kinase: An energy sensor that regulates all aspects of cell function. *Genes Dev.* 25, 1895–1908. <https://doi.org/10.1101/gad.17420111>.

Harding, E.C., Franks, N.P., and Wisden, W. (2020). Sleep and thermoregulation. *Curr. Opin. Physiol.* 15, 7–13. <https://doi.org/10.1016/j.cophys.2019.11.008>.

Harrison, D.E., Strong, R., Reifsnnyder, P., Kumar, N., Fernandez, E., Flurkey, K., Javors, M.A., Lopez-Cruzan, M., Macchiarini, F., Nelson, J.F., et al. (2021). 17- $\alpha$ -estradiol late in life extends lifespan in aging UM-HET3 male mice; nicotinamide riboside and three other drugs do not affect lifespan in either sex. *Aging Cell* 20, e13328. <https://doi.org/10.1111/accel.13328>.

Harrison, D.E., Strong, R., Sharp, Z.D., Nelson, J.F., Astle, C.M., Flurkey, K., Nadon, N.L., Wilkinson, J.E., Frenkel, K., Carter, C.S., et al. (2009). Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. *Nature* 460, 392–395. <https://doi.org/10.1038/nature08221>.

Harrison, S.A., Gawrieh, S., Roberts, K., Lisanti, C.J., Schwobe, R.B., Cebe, K.M., Paradis, V., Bedossa, P., Aldridge Whitehead, J.M., Labourdette, A., et al. (2021). Prospective evaluation of the prevalence of non-alcoholic fatty liver disease and steatohepatitis in a large middle-aged US cohort. *J. Hepatol.* 75, 284–291. <https://doi.org/10.1016/j.jhep.2021.02.034>.

Hatori, M., Vollmers, C., Zarrinpar, A., DiTacchio, L., Bushong, E.A., Gill, S., Leblanc, M., Chaix, A., Joens, M., Fitzpatrick, J.A.J., et al. (2012). Time restricted feeding without reducing caloric intake prevents metabolic diseases in mice fed a high fat diet. *Cell Metab.* 15, 848–860. <https://doi.org/10.1016/j.cmet.2012.04.019>.

Heron, M. (2021). Deaths: Leading causes for 2018. *Natl. Vital Stat. Rep.* 70(4), 1–115.

Herring, W.J., Connor, K.M., Ivgy-May, N., Snyder, E., Liu, K., Snavelly, D.B., Krystal, A.D., Walsh, J.K., Benca, R.M., Rosenberg, R., et al. (2016). Suvorexant

in patients with insomnia: Results from two 3-month randomized controlled clinical trials. *Biol. Psychiatry* 79, 136–148. <https://doi.org/10.1016/j.biopsych.2014.10.003>.

HHS (US Department of Health and Human Services). (2018). Physical activity guidelines for Americans. 2nd ed. [https://health.gov/sites/default/files/2019-09/Physical\\_Activity\\_Guidelines\\_2nd\\_edition.pdf](https://health.gov/sites/default/files/2019-09/Physical_Activity_Guidelines_2nd_edition.pdf).

Hill, A.B. (1965). The environment and disease: Association or causation? *Proc. R. Soc. Med.* 58, 295–300.

Hines, L., and Rimm, E. (2001). Moderate alcohol consumption and coronary heart disease: A review. *Postgrad. Med. J.* 77, 747–752. <https://doi.org/10.1136/pmj.77.914.747>.

Hirode, G., and Wong, R.J. (2020). Trends in the prevalence of metabolic syndrome in the United States, 2011–2016. *JAMA* 323, 2526–2528. <https://doi.org/10.1001/jama.2020.4501>.

Hitchens, C. (2014). *Mortality*. New York: Twelve.

Hitt, R., Young-Xu, Y., Silver, M., and Perls, T. (1999). Centenarians: The older you get, the healthier you have been. *Lancet* 354, 652.

Hjelmborg, J., Iachine, I., Skytthe, A., Vaupel, J.W., McGue, M., Koskenvuo, M., Kaprio, J., Pedersen, N.L., and Christensen, K. (2006). Genetic influence on human lifespan and longevity. *Hum. Genet.* 119, 312–321. <https://doi.org/10.1007/s00439-006-0144-y>.

Hofseth, L.J., Hebert, J.R., Chanda, A., Chen, H., Love, B.L., Pena, M.M., Murphy, E.A., Sajish, M., Sheth, A., Buckhaults, P.J., et al. (2020). Early-onset colorectal cancer: Initial clues and current views. *Nat. Rev. Gastroenterol. Hepatol.* 17, 352–364. <https://doi.org/10.1038/s41575-019-0253-4>.

Hoglund, K., Thelen, K.M., Syversen, S., Sjogren, M., von Bergmann, K., Wallin, A., Vanmechelen, E., Vanderstichele, H., Lutjohann, D., and Blennow, K. (2005). The effect of simvastatin treatment on the amyloid precursor

protein and brain cholesterol metabolism in patients with Alzheimer's disease. *Dement. Geriatr. Cogn. Disord.* 19, 256–265. <https://doi.org/10.1159/000084550>.

Holt, S.H., Miller, J.C., Petocz, P., and Farmakalidis, E. (1995). A satiety index of common foods. *Eur. J. Clin. Nutr.* 49, 675–690.

Hooper, L., Martin, N., Jimoh, O.F., Kirk, C., Foster, E., and Abdelhamid, A.S. (2020). Reduction in saturated fat intake for cardiovascular disease. *Cochrane Database Syst. Rev.* <https://doi.org/10.1002/14651858.CD011737.pub3>.

Hopkins, B.D., Pauli, C., Du, X., Wang, D.G., Li, X., Wu, D., Amadiume, S.C., Goncalves, M.D., Hodakoski, C., Lundquist, M.R., et al. (2018). Suppression of insulin feedback enhances the efficacy of PI3K inhibitors. *Nature* 560, 499–503. <https://doi.org/10.1038/s41586-018-0343-4>.

Houston, D.K., Nicklas, B.J., Ding, J., Harris, T.B., Tylavsky, F.A., Newman, A.B., Lee, J.S., Sahyoun, N.R., Visser, M., Kritchevsky, S.B., et al. (2008). Dietary protein intake is associated with lean mass change in older, community-dwelling adults: The Health, Aging, and Body Composition (Health ABC) Study. *Am. J. Clin. Nutr.* 87, 150–155. <https://doi.org/10.1093/ajcn/87.1.150>.

Howard, B.V., Van Horn, L., Hsia, J., Manson, J.E., Stefanick, M.L., Wassertheil-Smoller, S., Kuller, L.H., LaCroix, A.Z., Langer, R.D., Lasser, N.L., et al. (2006). Low-fat dietary pattern and risk of cardiovascular disease: The Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA* 295, 655–666. <https://doi.org/10.1001/jama.295.6.655>.

Hughes, V.A., Frontera, W.R., Wood, M., Evans, W.J., Dallal, G.E., Roubenoff, R., and Singh, M.A.F. (2001). Longitudinal muscle strength changes in older adults: Influence of muscle mass, physical activity, and health. *J. Gerontol. Ser. A* 56, B209–B217. <https://doi.org/10.1093/gerona/56.5.B209>.

Hutchison, I.C., and Rathore, S. (2015). The role of REM sleep theta activity in emotional memory. *Front. Psychol.* 6, 1439. <https://doi.org/10.3389/fpsyg.2015.01439>.

Iftikhar, I.H., Donley, M.A., Mindel, J., Pleister, A., Soriano, S., and Malgalang, U.J. (2015). Sleep duration and metabolic syndrome: An updated dose-risk metaanalysis. *Ann. Am. Thorac. Soc.* 12, 1364–1372. <https://doi.org/10.1513/AnnalsATS.201504-1900C>.

Igwe, E., Azman, A.Z.F., Nordin, A.J., and Mohtarrudin, N. (2015). Association between HOMA-IR and cancer. *Int. J. Public Health Clin. Sci.* 2, 21.

Iliff, J.J., Lee, H., Yu, M., Feng, T., Logan, J., Nedergaard, M., and Benveniste, H. (2013). Brain-wide pathway for waste clearance captured by contrast-enhanced MRI. *J. Clin. Invest.* 123, 1299–1309. <https://doi.org/10.1172/JCI67677>.

IOM (Institute of Medicine). Committee on Military Nutrition Research. (2001). Caffeine for the sustainment of mental task performance: Formulations for military operations. Washington, DC: National Academies Press.

Ioannidis, J.P.A. (2018). The challenge of reforming nutritional epidemiologic research. *JAMA* 320, 969–970. <https://doi.org/10.1001/jama.2018.11025>.

Itani, O., Jike, M., Watanabe, N., and Kaneita, Y. (2017). Short sleep duration and health outcomes: A systematic review, meta-analysis, and meta-regression. *Sleep Med.* 32, 246–256. <https://doi.org/10.1016/j.sleep.2016.08.006>.

Jack, C.R., Knopman, D.S., Jagust, W.J., Petersen, R.C., Weiner, M.W., Aisen, P.S., Shaw, L.M., Vemuri, P., Wiste, H.J., Weigand, S.D., et al. (2013). Update on hypothetical model of Alzheimer’s disease biomarkers. *Lancet Neurol.* 12, 207–216. [https://doi.org/10.1016/S1474-4422\(12\)70291-0](https://doi.org/10.1016/S1474-4422(12)70291-0).

Jackson, M.L., Croft, R.J., Kennedy, G.A., Owens, K., and Howard, M.E. (2013). Cognitive components of simulated driving performance: Sleep loss effects and predictors. *Accid. Anal. Prev.* 50, 438–444. <https://doi.org/10.1016/j.aap.2012.05.020>.

Jakubowski, B., Shao, Y., McNeal, C., Xing, C., and Ahmad, Z. (2021). Monogenic and polygenic causes of low and extremely low LDL-C levels in patients referred to specialty lipid clinics: Genetics of low LDL-C. *J. Clin. Lipidol.* 15,

658–664. <https://doi.org/10.1016/j.jacl.2021.07.003>.

Jamaspishvili, T., Berman, D.M., Ross, A.E., Scher, H.I., De Marzo, A.M., Squire, J.A., and Lotan, T.L. (2018). Clinical implications of PTEN loss in prostate cancer. *Nat. Rev. Urol.* 15, 222–234. <https://doi.org/10.1038/nrurol.2018.9>.

Jamshed, H., Beyl, R.A., Della Manna, D.L., Yang, E.S., Ravussin, E., and Peterson, C.M. (2019). Early time-restricted feeding improves 24-hour glucose levels and affects markers of the circadian clock, aging, and autophagy in humans. *Nutrients* 11, 1234. <https://doi.org/10.3390/nu11061234>.

Jensen, T.L., Kiersgaard, M.K., Sørensen, D.B., and Mikkelsen, L.F. (2013). Fasting of mice: A review. *Lab. Anim.* 47, 225–240. <https://doi.org/10.1177/0023677213501659>.

Johnson, R.J., and Andrews, P. (2015). Ancient mutation in apes may explain human obesity and diabetes. *Scientific American*, October 1.

Johnson, R.J., Sánchez-Lozada, L.G., Andrews, P., and Lanaspa, M.A. (2017). Perspective: A historical and scientific perspective of sugar and its relation with obesity and diabetes. *Adv. Nutr.* 8, 412–422. <https://doi.org/10.3945/an.116.014654>.

Johnson, R.J., Stenvinkel, P., Andrews, P., Sánchez-Lozada, L.G., Nakagawa, T., Gaucher, E., Andres-Hernando, A., Rodriguez-Iturbe, B., Jimenez, C.R., Garcia, G., et al. (2020). Fructose metabolism as a common evolutionary pathway of survival associated with climate change, food shortage and droughts. *J. Intern. Med.* 287, 252–262. <https://doi.org/10.1111/joim.12993>.

Johnson, S. (2021). *Extra life: A short history of living longer*. New York: Riverhead Books.

Jones, K., Gordon-Weeks, A., Coleman, C., and Silva, M. (2017). Radiologically determined sarcopenia predicts morbidity and mortality following abdominal surgery: A systematic review and meta-analysis. *World J. Surg.* 41, 2266–2279. <https://doi.org/10.1007/s00268-017-3999-2>.

Jose, J. (2016). Statins and its hepatic effects: Newer data, implications, and changing recommendations. *J. Pharm. Bioallied Sci.* 8, 23–28. <https://doi.org/10.4103/0975-7406.171699>.

Joslin, E.P. (1940). The universality of diabetes: A survey of diabetic morbidity in Arizona. The Frank Billings Lecture. *JAMA* 115, 2033–2038. <https://doi.org/10.1001/jama.1940.02810500001001>.

Ju, Y.-E.S., McLeland, J.S., Toedebusch, C.D., Xiong, C., Fagan, A.M., Duntley, S.P., Morris, J.C., and Holtzman, D.M. (2013). Sleep quality and preclinical Alzheimer disease. *JAMA Neurol.* 70, 587–593. <https://doi.org/10.1001/jamaneurol.2013.2334>.

Kalmbach, D.A., Schneider, L.D., Cheung, J., Bertrand, S.J., Kariharan, T., Pack, A.I., and Gehrman, P.R. (2017). Genetic basis of chronotype in humans: Insights from three landmark GWAS. *Sleep* 40, zsw048. <https://doi.org/10.1093/sleep/zsw048>.

Kanai, M., Matsubara, E., Isoe, K., Urakami, K., Nakashima, K., Arai, H., Sasaki, H., Abe, K., Iwatsubo, T., Kosaka, T., et al. (1998). Longitudinal study of cerebrospinal fluid levels of tau, A beta1-40, and A beta1-42(43) in Alzheimer's disease: A study in Japan. *Ann. Neurol.* 44, 17–26. <https://doi.org/10.1002/ana.410440108>.

Karagiannis, A.D., Mehta, A., Dhindsa, D.S., Virani, S.S., Orringer, C.E., Blumenthal, R.S., Stone, N.J., and Sperling, L.S. (2021). How low is safe? The frontier of very low (<30 mg/dL) LDL cholesterol. *Eur. Heart J.* 42, 2154–2169. <https://doi.org/10.1093/eurheartj/ehaa1080>.

Karsli-Uzunbas, G., Guo, J.Y., Price, S., Teng, X., Laddha, S.V., Khor, S., Kaiaany, N.Y., Jacks, T., Chan, C.S., Rabinowitz, J.D., et al. (2014). Autophagy is required for glucose homeostasis and lung tumor maintenance. *Cancer Discov.* 4, 914–927. <https://doi.org/10.1158/2159-8290.CD-14-0363>.

Kaivola, K., Shah, Z., Chia, R., International LBD Genomics Consortium, and Scholz, S.W. (2022). Genetic evaluation of dementia with Lewy bodies impli-

cates distinct disease subgroups. *Brain* 145(5), 1757–1762. <https://doi.org/10.1093/brain/awab402>.

Kawada, S., and Ishii, N. (2005). Skeletal muscle hypertrophy after chronic restriction of venous blood flow in rats. *Med. Sci. Sports Exerc.* 37, 1144–1150. <https://doi.org/10.1249/01.mss.0000170097.59514.bb>.

Kawano, H., Motoyama, T., Hirashima, O., Hirai, N., Miyao, Y., Sakamoto, T., Kugiyama, K., Ogawa, H., and Yasue, H. (1999). Hyperglycemia rapidly suppresses flow-mediated endothelium-dependent vasodilation of brachial artery. *J. Am. Coll. Cardiol.* 34, 146–154. [https://doi.org/10.1016/S0735-1097\(99\)00168-0](https://doi.org/10.1016/S0735-1097(99)00168-0).

Keramidas, M.E., and Botonis, P.G. (2021). Short-term sleep deprivation and human thermoregulatory function during thermal challenges. *Exp. Physiol.* 106, 1139–1148. <https://doi.org/10.1113/EP089467>.

Kerrouche, N., Herholz, K., Mielke, R., Holthoff, V., and Baron, J.-C. (2006). 18FDG PET in vascular dementia: Differentiation from Alzheimer's disease using voxel-based multivariate analysis. *J. Cereb. Blood Flow Metab.* 26, 1213–1221. <https://doi.org/10.1038/sj.jcbfm.9600296>.

Killgore, W.D.S. (2013). Self-reported sleep correlates with prefrontal-amygdala functional connectivity and emotional functioning. *Sleep* 36, 1597–1608. <https://doi.org/10.5665/sleep.3106>.

Kim, C.-H., Wheatley, C.M., Behnia, M., and Johnson, B.D. (2016). The effect of aging on relationships between lean body mass and VO<sub>2</sub>max in rowers. *PLOS ONE* 11, e0160275. <https://doi.org/10.1371/journal.pone.0160275>.

Kim, D.-Y., Hong, S.-H., Jang, S.-H., Park, S.-H., Noh, J.-H., Seok, J.-M., Jo, H.-J., Son, C.-G., and Lee, E.-J. (2022). Systematic review for the medical applications of meditation in randomized controlled trials. *Int. J. Environ. Res. Public Health* 19, 1244. <https://doi.org/10.3390/ijerph19031244>.

Kim, T.N., and Choi, K.M. (2013). Sarcopenia: Definition, epidemiology, and pathophysiology. *J. Bone Metab.* 20, 1–10. <https://doi.org/10.11005/>

jbm.2013.20.1.1.

Kim, Y., White, T., Wijndaele, K., Westgate, K., Sharp, S.J., Helge, J.W., Wareham, N.J., and Brage, S. (2018). The combination of cardiorespiratory fitness and muscle strength, and mortality risk. *Eur. J. Epidemiol.* 33, 953–964. <https://doi.org/10.1007/s10654-018-0384-x>.

Kinsella, K.G. (1992). Changes in life expectancy, 1900–1990. *Am. J. Clin. Nutr.* 55, 1196S–1202S. <https://doi.org/10.1093/ajcn/55.6.1196S>.

Kloske, C.M., and Wilcock, D.M. (2020). The important interface between apolipoprotein E and neuroinflammation in Alzheimer’s disease. *Front. Immunol.* 11, 754. <https://doi.org/10.3389/fimmu.2020.00754>.

Kochenderfer, J.N., Wilson, W.H., Janik, J.E., Dudley, M.E., Stetler-Stevenson, M., Feldman, S.A., Maric, I., Raffeld, M., Nathan, D.-A.N., Lanier, B.J., et al. (2010). Eradication of B-lineage cells and regression of lymphoma in a patient treated with autologous T cells genetically engineered to recognize CD19. *Blood* 116, 4099–4102. <https://doi.org/10.1182/blood-2010-04-281931>.

Kokkinos, P., Faselis, C., Babu, H.S.I., Pittaras, A., Doulas, M., Murphy, R., Heimal, M.S., Sui, X., Zhang, J., and Myers, J. (2022). Cardiorespiratory fitness and mortality risk across the spectra of age, race, and sex. *J. Am. Coll. Cardiol.* 80, 598–609.

Kolata, G. (2012). Severe diet doesn’t prolong life, at least in monkeys. *New York Times*, August 29, 2012. <https://www.nytimes.com/2012/08/30/science/low-calorie-diet-doesnt-prolong-life-study-of-monkeys-finds.html?action=click&module=RelatedCoverage&pgtype=Article&region=Footer>.

———. (2020). An Alzheimer’s treatment fails: “We don’t have anything now.” *New York Times*, February 10. <https://www.nytimes.com/2020/02/10/health/alzheimers-amyloid-drug.html>.

Kolka, M.A., and Stephenson, L.A. (1988). Exercise thermoregulation after prolonged wakefulness. *J. Appl. Physiol.* 64, 1575–1579. <https://doi.org/10.1152/jappl.1988.64.4.1575>.



Konstantinos, I., Avgerinos, N.S., Mantzoros, C.S., Dalamaga, M. (2019). Obesity and cancer risk: Emerging biological mechanisms and perspectives, *Metabolism* 92, 121–135. <https://doi.org/10.1016/j.metabol.2018.11.001>.

Kortebein, P., Ferrando, A., Lombeida, J., Wolfe, R., and Evans, W.J. (2007). Effect of 10 days of bed rest on skeletal muscle in healthy older adults. *JAMA* 297, 1769–1774. <https://doi.org/10.1001/jama.297.16.1772-b>.

Kourtis, N., and Tavernarakis, N. (2009). Autophagy and cell death in model organisms. *Cell Death Differ.* 16, 21–30. <https://doi.org/10.1038/cdd.2008.120>.

Krause, A.J., Simon, E.B., Mander, B.A., Greer, S.M., Saletin, J.M., Goldstein-Piekarski, A.N., and Walker, M.P. (2017). The sleep-deprived human brain. *Nat. Rev. Neurosci.* 18, 404–418. <https://doi.org/10.1038/nrn.2017.55>.

Kuna, S.T., Maislin, G., Pack, F.M., Staley, B., Hachadoorian, R., Coccaro, E.F., and Pack, A.I. (2012). Heritability of performance deficit accumulation during acute sleep deprivation in twins. *Sleep* 35, 1223–1233. <https://doi.org/10.5665/sleep.2074>.

Kuo, T., McQueen, A., Chen, T.-C., and Wang, J.-C. (2015). Regulation of glucose homeostasis by glucocorticoids. *Adv. Exp. Med. Biol.* 872, 99–126. [https://doi.org/10.1007/978-1-4939-2895-8\\_5](https://doi.org/10.1007/978-1-4939-2895-8_5).

Kwo, P.Y., Cohen, S.M., and Lim, J.K. (2017). ACG clinical guideline: Evaluation of abnormal liver chemistries. *Am. J. Gastroenterol.* 112, 18–35. <https://doi.org/10.1038/ajg.2016.517>.

Kwok, C.S., Kontopantelis, E., Kuligowski, G., Gray, M., Muhyaldeen, A., Gale, C.P., Peat, G.M., Cleator, J., Chew-Graham, C., Loke, Y.K., Mamas, M.A. (2018). Self-reported sleep duration and quality and cardiovascular disease and mortality. *JAHA*, 7:15. <https://doi.org/10.1161/JAHA.118.008552>.

Lammert, F., and Wang, D.Q.-H. (2005). New insights into the genetic regulation of intestinal cholesterol absorption. *Gastroenterology* 129, 718–734. <https://doi.org/10.1053/j.gastro.2004.11.017>.

Lamond, N., and Dawson, D. (1999). Quantifying the performance impairment associated with fatigue. *J. Sleep Res.* 8, 255–262. <https://doi.org/10.1046/j.1365-2869.1999.00167.x>.

Langa, K.M., and Levine, D.A. (2014). The diagnosis and management of mild cognitive impairment: A clinical review. *JAMA* 312, 2551–2561. <https://doi.org/10.1001/jama.2014.13806>.

Laukkanen, T., Khan, H., Zaccardi, F., and Laukkanen, J.A. (2015). Association between sauna bathing and fatal cardiovascular and all-cause mortality events. *JAMA Intern. Med.* 175, 542–548. <https://doi.org/10.1001/jamainternmed.2014.8187>.

Laukkanen, T., Kunutsor, S., Kauhanen, J., and Laukkanen, J.A. (2017). Sauna bathing is inversely associated with dementia and Alzheimer’s disease in middle-aged Finnish men. *Age Ageing* 46, 245–249. <https://doi.org/10.1093/ageing/afw212>.

Lawson, J.S. (2016). Multiple infectious agents and the origins of atherosclerotic coronary artery disease. *Front. Cardiovasc. Med.* 3, 30. <https://doi.org/10.3389/fcvm.2016.00030>.

Le, D.T., Uram, J.N., Wang, H., Bartlett, B.R., Kemberling, H., Eyring, A.D., Skora, A.D., Luber, B.S., Azad, N.S., Laheru, D., et al. (2015). PD-1 blockade in tumors with mismatch-repair deficiency. *N. Engl. J. Med.* 372, 2509–2520. <https://doi.org/10.1056/NEJMoa1500596>.

Le, R., Zhao, L., and Hegele, R.A. (2022). Forty year follow-up of three patients with complete absence of apolipoprotein B-containing lipoproteins. *J. Clin. Lipidol.* 16, 155–159. <https://doi.org/10.1016/j.jacl.2022.02.003>.

Lee, I.-M., and Buchner, D.M. (2008). The importance of walking to public health. *Med. Sci. Sports Exerc.* 40, S512–518. <https://doi.org/10.1249/MSS.0b013e31817c65d0>.

Lee, J.C., Kim, S.J., Hong, S., and Kim, Y. (2019). Diagnosis of Alzheimer’s disease utilizing amyloid and tau as fluid biomarkers. *Exp. Mol. Med.* 51, 1–10.

<https://doi.org/10.1038/s12276-019-0250-2>.

Lega, I.C., and Lipscombe, L.L. (2019). Review: diabetes, obesity, and cancer—pathophysiology and clinical implications. *Endocr. Rev.* 41(1), 33–52. [https://doi.org/ 10.1210/ endrev/ bnz014](https://doi.org/10.1210/ endrev/ bnz014).

Lemasters, J.J. (2005). Selective mitochondrial autophagy, or mitophagy, as a targeted defense against oxidative stress, mitochondrial dysfunction, and aging. *Rejuvenation Res.* 8, 3–5. <https://doi.org/10.1089/rej.2005.8.3>.

Lendner, J.D., Helfrich, R.F., Mander, B.A., Romundstad, L., Lin, J.J., Walker, M.P., Larsson, P.G., and Knight, R.T. (2020). An electrophysiological marker of arousal level in humans. *ELife* 9, e55092. <https://doi.org/10.7554/eLife.55092>.

Leproult, R., Holmbäck, U., and Van Cauter, E. (2014). Circadian misalignment augments markers of insulin resistance and inflammation, independently of sleep loss. *Diabetes* 63, 1860–1869. <https://doi.org/10.2337/db13-1546>.

Leproult, R., and Van Cauter, E. (2010). Role of sleep and sleep loss in hormonal release and metabolism. *Endocr. Dev.* 17, 11–21. <https://doi.org/10.1159/000262524>.

Lexell, J. (1995). Human aging, muscle mass, and fiber type composition. *J. Gerontol. A. Biol. Sci. Med. Sci.* 50 Spec No, 11–16. [https://doi.org/10.1093/gerona/50a.special\\_issue.11](https://doi.org/10.1093/gerona/50a.special_issue.11).

Li, R., Xia, J., Zhang, X., Gathirua-Mwangi, W.G., Guo, J., Li, Y., McKenzie, S., and Song, Y. (2018). Associations of muscle mass and strength with all-cause mortality among US older adults. *Med. Sci. Sports Exerc.* 50, 458–467. <https://doi.org/10.1249/MSS.0000000000001448>.

Libby, P. (2021). The changing landscape of atherosclerosis. *Nature* 592, 524–533. <https://doi.org/10.1038/s41586-021-03392-8>.

Libby, P., and Tokgözoğlu, L. (2022). Chasing LDL cholesterol to the bottom: PCSK9 in perspective. *Nat. Cardiovasc. Res.* 1, 554–561. <https://doi.org/10.1038/s44161-022-00085-x>.

Liberti, M.V., and Locasale, J.W. (2016). The Warburg effect: How does it benefit cancer cells? *Trends Biochem. Sci.* 41, 211–218. <https://doi.org/10.1016/j.tibs.2015.12.001>.

Lieberman, D.E., Kistner, T.M., Richard, D., Lee, I.-M., and Baggish, A.L. (2021). The active grandparent hypothesis: Physical activity and the evolution of extended human healthspans and lifespans. *Proc. Natl. Acad. Sci.* 118, e2107621118. <https://doi.org/10.1073/pnas.2107621118>.

Liguori, G., ed. (2020). *ACSM's guidelines for exercise testing and prescription*. 10th ed. Philadelphia: Wolters Kluwer Health.

Lim, A.S.P., Kowgier, M., Yu, L., Buchman, A.S., and Bennett, D.A. (2013a). Sleep fragmentation and the risk of incident Alzheimer's disease and cognitive decline in older persons. *Sleep* 36, 1027–1032. <https://doi.org/10.5665/sleep.2802>.

Lim, A.S.P., Yu, L., Kowgier, M., Schneider, J.A., Buchman, A.S., and Bennett, D.A. (2013b). Sleep modifies the relation of APOE to the risk of Alzheimer disease and neurofibrillary tangle pathology. *JAMA Neurol.* 70, 10.1001/jamaneurol.2013.4215. <https://doi.org/10.1001/jamaneurol.2013.4215>.

Lim, J., and Dinges, D.F. (2008). Sleep deprivation and vigilant attention. *Ann. N.Y. Acad. Sci.* 1129, 305–322. <https://doi.org/10.1196/annals.1417.002>.

Lin, H.-J., Lee, B.-C., Ho, Y.-L., Lin, Y.-H., Chen, C.-Y., Hsu, H.-C., Lin, M.-S., Chien, K.-L., and Chen, M.-F. (2009). Postprandial glucose improves the risk prediction of cardiovascular death beyond the metabolic syndrome in the non-diabetic population. *Diabetes Care* 32, 1721–1726. <https://doi.org/10.2337/dc08-2337>.

Lin, H.-S., Watts, J.N., Peel, N.M., and Hubbard, R.E. (2016). Frailty and post-operative outcomes in older surgical patients: A systematic review. *BMC Geriatr.* 16, 157. <https://doi.org/10.1186/s12877-016-0329-8>.

Lindle, R.S., Metter, E.J., Lynch, N.A., Fleg, J.L., Fozard, J.L., Tobin, J., Roy, T.A., and Hurley, B.F. (1997). Age and gender comparisons of muscle strength

in 654 women and men aged 20–93 yr. *J. Appl. Physiol.* 83, 1581–1587. <https://doi.org/10.1152/jappl.1997.83.5.1581>.

Linehan, M.M., Comtois, K.A., Murray, A.M., Brown, M.Z., Gallop, R.J., Heard, H.L., Korslund, K.E., Tutek, D.A., Reynolds, S.K., and Lindenboim, N. (2006). Two-year randomized controlled trial and follow-up of dialectical behavior therapy vs therapy by experts for suicidal behaviors and borderline personality disorder. *Arch. Gen. Psychiatry* 63, 757–766. <https://doi.org/10.1001/archpsyc.63.7.757>.

Little, J.P., Gillen, J.B., Percival, M.E., Safdar, A., Tarnopolsky, M.A., Punthakee, Z., Jung, M.E., and Gibala, M.J. (2011). Low-volume high-intensity interval training reduces hyperglycemia and increases muscle mitochondrial capacity in patients with type 2 diabetes. *J. Appl. Physiol.* 111, 1554–1560. <https://doi.org/10.1152/jappphysiol.00921.2011>.

Liu, D., Huang, Y., Huang, C., Yang, S., Wei, X., Zhang, P., Guo, D., Lin, J., Xu, B., Li, C., et al. (2022). Calorie restriction with or without time-restricted eating in weight loss. *N. Engl. J. Med.* 386, 1495–1504. <https://doi.org/10.1056/NEJMoa2114833>.

Liu, G.Y., and Sabatini, D.M. (2020). mTOR at the nexus of nutrition, growth, ageing and disease. *Nat. Rev. Mol. Cell Biol.* 21, 183–203. <https://doi.org/10.1038/s41580-019-0199-y>.

Livingston, G. (2019). On average, older adults spend over half their waking hours alone. *Grius*, July 19. <https://qrius.com/on-average-older-adults-spend-over-half-their-waking-hours-alone/>.

Lobo, A., López-Antón, R., de-la-Cámara, C., Quintanilla, M.A., Campayo, A., Saz, P., and ZARADEMP Workgroup (2008). Non-cognitive psychopathological symptoms associated with incident mild cognitive impairment and dementia, Alzheimer's type. *Neurotox. Res.* 14, 263–272. <https://doi.org/10.1007/BF03033815>.

López-Otín, C., Blasco, M.A., Partridge, L., Serrano, M., and Kroemer, G.

(2013). The hallmarks of aging. *Cell* 153, 1194–1217. <https://doi.org/10.1016/j.cell.2013.05.039>.

Lowe, D.A., Wu, N., Rohdin-Bibby, L., Moore, A.H., Kelly, N., Liu, Y.E., Philip, E., Vittinghoff, E., Heymsfield, S.B., Olgin, J.E., et al. (2020). Effects of time-restricted eating on weight loss and other metabolic parameters in women and men with overweight and obesity: The TREAT randomized clinical trial. *JAMA Intern. Med.* 180, 1491–1499. <https://doi.org/10.1001/jamainternmed.2020.4153>.

Lucey, B.P., McCullough, A., Landsness, E.C., Toedebusch, C.D., McLeland, J.S., Zaza, A.M., Fagan, A.M., McCue, L., Xiong, C., Morris, J.C., et al. (2019). Reduced non-rapid eye movement sleep is associated with tau pathology in early Alzheimer’s disease. *Sci. Transl. Med.* 11, eaau6550. <https://doi.org/10.1126/scitranslmed.aau6550>.

Ludwig, J., Viggiano, T.R., McGill, D.B., and Oh, B.J. (1980). Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. *Mayo Clinic proceedings*, 55(7), 434–438.

Lüth, H.-J., Ogunlade, V., Kuhla, B., Kientsch-Engel, R., Stahl, P., Webster, J., Arendt, T., and Münch, G. (2005). Age- and stage-dependent accumulation of advanced glycation end products in intracellular deposits in normal and Alzheimer’s disease brains. *Cereb. Cortex* 15, 211–220. <https://doi.org/10.1093/cercor/bhh123>.

Mach, F., Ray, K.K., Wiklund, O., Corsini, A., Catapano, A.L., Bruckert, E., De Backer, G., Hegele, R.A., Hovingh, G.K., Jacobson, T.A., et al. (2018). Adverse effects of statin therapy: perception vs. the evidence: Focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract. *Eur. Heart J.* 39, 2526–2539. <https://doi.org/10.1093/eurheartj/ehy182>.

Maddock, J., Cavadino, A., Power, C., and Hyppönen, E. (2015). 25-hydroxyvitamin D, APOE ε4 genotype and cognitive function: Findings from the 1958 British birth cohort. *Eur. J. Clin. Nutr.* 69, 505–508. <https://doi.org/10.1038/ejcn.2014.201>.

Maeng, L.Y., and Milad, M.R. (2015). Sex differences in anxiety disorders: Interactions between fear, stress, and gonadal hormones. *Horm. Behav.* 76, 106–117. <https://doi.org/10.1016/j.yhbeh.2015.04.002>.

Mah, C.D., Mah, K.E., Kezirian, E.J., and Dement, W.C. (2011). The effects of sleep extension on the athletic performance of collegiate basketball players. *Sleep* 34, 943–950. <https://doi.org/10.5665/SLEEP.1132>.

Mandsager, K., Harb, S., Cremer, P., Phelan, D., Nissen, S.E., and Jaber, W. (2018). Association of cardiorespiratory fitness with long-term mortality among adults undergoing exercise treadmill testing. *JAMA Netw. Open* 1, e183605. <https://doi.org/10.1001/jamanetworkopen.2018.3605>.

Mannick, J.B., Del Giudice, G., Lattanzi, M., Valiante, N.M., Praestgaard, J., Huang, B., Lonetto, M.A., Maecker, H.T., Kovarik, J., Carson, S., et al. (2014). mTOR inhibition improves immune function in the elderly. *Sci. Transl. Med.* 6, 268ra179. <https://doi.org/10.1126/scitranslmed.3009892>.

Manson, J.E., Chlebowski, R.T., Stefanick, M.L., Aragaki, A.K., Rossouw, J.E., Prentice, R.L., Anderson, G., Howard, B.V., Thomson, C.A., LaCroix, A.Z., et al. (2013). The Women's Health Initiative hormone therapy trials: Update and overview of health outcomes during the intervention and post-stopping phases. *JAMA* 310, 1353–1368.

Mansukhani, M.P., Kolla, B.P., Surani, S., Varon, J., and Ramar, K. (2012). Sleep deprivation in resident physicians, work hour limitations, and related outcomes: A systematic review of the literature. *Postgrad. Med.* 124, 241–249. <https://doi.org/10.3810/pgm.2012.07.2583>.

Marston, N.A., Giugliano, R.P., Melloni, G.E.M., Park, J.-G., Morrill, V., Blazing, M.A., Ference, B., Stein, E., Stroes, E.S., Braunwald, E., et al. (2022). Association of Apolipoprotein B-containing lipoproteins and risk of myocardial infarction in individuals with and without atherosclerosis: Distinguishing between particle concentration, type, and content. *JAMA Cardiol.* 7(3), 250–256. <http://doi.org/10.1001/jamacardio.2021.5083>.

Martínez-Lapiscina, E.H., Clavero, P., Toledo, E., Estruch, R., Salas-Salvadó, J., Julián, B.S., Sanchez-Tainta, A., Ros, E., Valls-Pedret, C., and Martínez-González, M.Á. (2013). Mediterranean diet improves cognition: The PREDIMED-NAVARRA randomised trial. *J. Neurol. Neurosurg. Psychiatry* 84, 1318–1325. <https://doi.org/10.1136/jnnp-2012-304792>.

Masana, L., Girona, J., Ibarretxe, D., Rodríguez-Calvo, R., Rosales, R., Vallvé, J.-C., Rodríguez-Borjabad, C., Guardiola, M., Rodríguez, M., Guaita-Esteruelas, S., et al. (2018). Clinical and pathophysiological evidence supporting the safety of extremely low LDL levels: The zero-LDL hypothesis. *J. Clin. Lipidol.* 12, 292–299.e3. <https://doi.org/10.1016/j.jacl.2017.12.018>.

Masters, C.L., and Selkoe, D.J. (2012). Biochemistry of amyloid  $\beta$ -protein and amyloid deposits in Alzheimer disease. *Cold Spring Harb. Perspect. Med.* 2, a006262. <https://doi.org/10.1101/cshperspect.a006262>.

Matsuzaki, T., Sasaki, K., Tanizaki, Y., Hata, J., Fujimi, K., Matsui, Y., Sekita, A., Suzuki, S.O., Kanba, S., Kiyohara, Y., et al. (2010). Insulin resistance is associated with the pathology of Alzheimer disease: The Hisayama study. *Neurology* 75, 764–770. <https://doi.org/10.1212/WNL.0b013e3181eee25f>.

Mattison, J.A., Roth, G.S., Beasley, T.M., Tilmont, E.M., Handy, A.H., Herbert, R.L., Longo, D.L., Allison, D.B., Young, J.E., Bryant, M., et al. (2012). Impact of caloric restriction on health and survival in rhesus monkeys: The NIA study. *Nature* 489, <https://doi.org/10.1038/nature11432>.

Maurer, L.F., Schneider, J., Miller, C.B., Espie, C.A., and Kyle, S.D. (2021). The clinical effects of sleep restriction therapy for insomnia: A meta-analysis of randomised controlled trials. *Sleep Med. Rev.* 58, 101493. <https://doi.org/10.1016/j.smr.2021.101493>.

McDonald, R.B., and Ramsey, J.J. (2010). Honoring Clive McCay and 75 years of calorie restriction research. *J. Nutr.* 140, 1205–1210. <https://doi.org/10.3945/jn.110.122804>.

McLaughlin, T., Abbasi, F., Cheal, K., Chu, J., Lamendola, C., and Reaven, G.



(2003). Use of metabolic markers to identify overweight individuals who are insulin resistant. *Ann. Intern. Med.* 139, 802–809. <https://doi.org/10.7326/0003-4819-139-10-200311180-00007>.

McMillin, S.L., Schmidt, D.L., Kahn, B.B., and Witzczak, C.A. (2017). GLUT4 is not necessary for overload-induced glucose uptake or hypertrophic growth in mouse skeletal muscle. *Diabetes* 66, 1491–1500. <https://doi.org/10.2337/db16-1075>.

McNamara, D.J. (2015). The fifty year rehabilitation of the egg. *Nutrients* 7, 8716–8722. <https://doi.org/10.3390/nu7105429>.

Melov, S., Tarnopolsky, M.A., Beckman, K., Felkey, K., and Hubbard, A. (2007). Resistance exercise reverses aging in human skeletal muscle. *PLOS ONE* 2, e465. <https://doi.org/10.1371/journal.pone.0000465>.

Mensah, G. A., Wei, G. S., Sorlie, P. D., Fine, L. J., Rosenberg, Y., Kaufmann, P. G., Mussolino, M. E., Hsu, L. L., Addou, E., Engelgau, M. M., & Gordon, D. (2017). Decline in Cardiovascular Mortality: Possible Causes and Implications. *Circulation research*, 120(2), 366–380. <https://doi.org/10.1161/CIRCRESA-HA.116.309115>.

Mensink, R.P., and Katan, M.B. (1992). Effect of dietary fatty acids on serum lipids and lipoproteins. A meta-analysis of 27 trials. *Arterioscler. Thromb. J. Vasc. Biol.* 12, 911–919. <https://doi.org/10.1161/01.atv.12.8.911>.

Mercken, E.M., Crosby, S.D., Lamming, D.W., JeBailey, L., Krzysik-Walker, S., Villareal, D., Capri, M., Franceschi, C., Zhang, Y., Becker, K., et al. (2013). Calorie restriction in humans inhibits the PI3K/AKT pathway and induces a younger transcription profile. *Aging Cell* 12, 645–651. <https://doi.org/10.1111/accel.12088>.

Michaelson, D.M. (2014). APOE ε4: The most prevalent yet understudied risk factor for Alzheimer's disease. *Alzheimers Dement.* 10, 861–868. <https://doi.org/10.1016/j.jalz.2014.06.015>.

Milewski, M.D., Skaggs, D.L., Bishop, G.A., Pace, J.L., Ibrahim, D.A., Wren,

T.A.L., and Barzdukas, A. (2014). Chronic lack of sleep is associated with increased sports injuries in adolescent athletes. *J. Pediatr. Orthop.* 34, 129–133. <https://doi.org/10.1097/BPO.000000000000151>.

Miller, R.A., Harrison, D.E., Astle, C.M., Baur, J.A., Boyd, A.R., de Cabo, R., Fernandez, E., Flurkey, K., Javors, M.A., Nelson, J.F., et al. (2011). Rapamycin, but not resveratrol or simvastatin, extends life span of genetically heterogeneous mice. *J. Gerontol. Ser. A* 66A, 191–201. <https://doi.org/10.1093/gerona/glq178>.

Mitter, S.S., Oriá, R.B., Kvalsund, M.P., Pamplona, P., Joventino, E.S., Mota, R.M.S., Gonçalves, D.C., Patrick, P.D., Guerrant, R.L., and Lima, A.A.M. (2012). Apolipoprotein E4 influences growth and cognitive responses to micronutrient supplementation in shantytown children from northeast Brazil. *Clinics* 67, 11–18. [https://doi.org/10.6061/clinics/2012\(01\)03](https://doi.org/10.6061/clinics/2012(01)03).

Moco, S., Bino, R.J., Vorst, O., Verhoeven, H.A., de Groot, J., van Beek, T.A., Vervoort, J., and de Vos, C.H.R. (2006). A liquid chromatography-mass spectrometry-based metabolome database for tomato. *Plant Physiol.* 141, 1205–1218. <https://doi.org/10.1104/pp.106.078428>.

Mollenhauer, B., Bibl, M., Trenkwalder, C., Stiens, G., Cepek, L., Steinacker, P., Ciesielczyk, B., Neubert, K., Wiltfang, J., Kretzschmar, H.A., et al. (2005). Follow-up investigations in cerebrospinal fluid of patients with dementia with Lewy bodies and Alzheimer's disease. *J. Neural Transm.* 112, 933–948. <https://doi.org/10.1007/s00702-004-0235-7>.

Montagne, A., Nation, D.A., Sagare, A.P., Barisano, G., Sweeney, M.D., Chakhoyan, A., Pachicano, M., Joe, E., Nelson, A.R., D'Orazio, L.M., et al. (2020). APOE4 leads to blood-brain barrier dysfunction predicting cognitive decline. *Nature* 581, 71–76. <https://doi.org/10.1038/s41586-020-2247-3>.

Moraes, W. dos S., Poyares, D.R., Guilleminault, C., Ramos, L.R., Bertolucci, P.H.F., and Tufik, S. (2006). The effect of donepezil on sleep and REM sleep EEG in patients with Alzheimer disease: A double-blind placebo-controlled study. *Sleep* 29, 199–205. <https://doi.org/10.1093/sleep/29.2.199>.

Mosconi, L., Rahman, A., Diaz, I., Wu, X., Scheyer, O., Hristov, H.W., Val-labhajosula, S., Isaacson, R.S., de Leon, M.J., and Brinton, R.D. (2018). In-creased Alzheimer's risk during the menopause transition: A 3-year longitu-dinal brain imaging study. *PLOS ONE* 13, e0207885. <https://doi.org/10.1371/journal.pone.0207885>.

Motomura, Y., Kitamura, S., Oba, K., Terasawa, Y., Enomoto, M., Katayose, Y., Hida, A., Moriguchi, Y., Higuchi, S., and Mishima, K. (2013). Sleep debt elicits negative emotional reaction through diminished amygdala-anterior cingulate functional connectivity. *PLOS ONE* 8, e56578. <https://doi.org/10.1371/journal.pone.0056578>.

Mukherjee, S. (2011). *The emperor of all maladies: A biography of cancer*. New York: Scribner.

Mullane, K., and Williams, M. (2020). Alzheimer's disease beyond amy-loid: Can the repetitive failures of amyloid-targeted therapeutics inform future approaches to dementia drug discovery? *Biochem. Pharmacol.* 177, 113945. <https://doi.org/10.1016/j.bcp.2020.113945>.

Müller, U., Winter, P., and Graeber, M.B. (2013). A presenilin 1 mutation in the first case of Alzheimer's disease. *Lancet Neurol.* 12, 129–130. [https://doi.org/10.1016/S1474-4422\(12\)70307-1](https://doi.org/10.1016/S1474-4422(12)70307-1).

Naci, H., and Ioannidis, J.P.A. (2015). Comparative effectiveness of exercise and drug interventions on mortality outcomes: Metaepidemiological study. *Br. J. Sports Med.* 49, 1414–1422. <https://doi.org/10.1136/bjsports-2015-f5577rep>.

Naghshi, S., Sadeghian, M., Nasiri, M., Mobarak, S., Asadi, M., and Sade-ghi, O. (2020). Association of total nut, tree nut, peanut, and peanut butter consumption with cancer incidence and mortality: A comprehensive system-atic review and dose-response meta-analysis of observational studies. *Adv. Nutr.* 12, 793–808. <https://doi.org/10.1093/advances/nmaa152>.

Naimi, T.S., Stockwell, T., Zhao, J., Xuan, Z., Dangardt, F., Saitz, R., Liang, W.,

and Chikritzhs, T. (2017). Selection biases in observational studies affect associations between “moderate” alcohol consumption and mortality. *Addiction* 112, 207–214. <https://doi.org/10.1111/add.13451>.

Nakamura, T., Shoji, M., Harigaya, Y., Watanabe, M., Hosoda, K., Cheung, T.T., Shaffer, L.M., Golde, T.E., Younkin, L.H., and Younkin, S.G. (1994). Amyloid beta protein levels in cerebrospinal fluid are elevated in early-onset Alzheimer’s disease. *Ann. Neurol.* 36, 903–911. <https://doi.org/10.1002/ana.410360616>.

Nasir, K., Cainzos-Achirica, M., Valero-Elizondo, J., Ali, S.S., Havistin, R., Lakshman, S., Blaha, M.J., Blankstein, R., Shapiro, M.D., Arias, L., et al. (2022). Coronary atherosclerosis in an asymptomatic U.S. population. *JACC Cardiovasc. Imaging* 15(9), 1619–1621. <https://doi.org/10.1016/j.jcmg.2022.03.010>.

NCI (National Cancer Institute). (2015). Risk factors: Age. <https://www.cancer.gov/about-cancer/causes-prevention/risk/age>.

———. (2021). Risk factors: Age. <https://www.cancer.gov/about-cancer/causes-prevention/risk/age>.

———. (2022a). Obesity and cancer. Fact sheet, April 5. <https://www.cancer.gov/about-cancer/causes-prevention/risk/obesity/obesity-fact-sheet>.

———. (2022b). SEER survival statistics—SEER Cancer Query Systems. <https://seer.cancer.gov/canques/survival.html>.

Nedeltcheva, A.V., Kessler, L., Imperial, J., and Penev, P.D. (2009). Exposure to recurrent sleep restriction in the setting of high caloric intake and physical inactivity results in increased insulin resistance and reduced glucose tolerance. *J. Clin. Endocrinol. Metab.* 94, 3242–3250. <https://doi.org/10.1210/jc.2009-0483>.

Neth, B.J., and Craft, S. (2017). Insulin resistance and Alzheimer’s disease: Bioenergetic linkages. *Front. Aging Neurosci.* 9, 345. <https://doi.org/10.3389/fnagi.2017.00345>.

Neu, S.C., Pa, J., Kukull, W., Beekly, D., Kuzma, A., Gangadharan, P., Wang, L.-S., Romero, K., Arneric, S.P., Redolfi, A., et al. (2017). Apolipoprotein E genotype and sex risk factors for Alzheimer disease: A meta-analysis. *JAMA Neurol.* 74, 1178–1189. <https://doi.org/10.1001/jamaneurol.2017.2188>.

Newman, A.B., Kupelian, V., Visser, M., Simonsick, E.M., Goodpaster, B.H., Kritchevsky, S.B., Tylavsky, F.A., Rubin, S.M., and Harris, T.B. (2006). Strength, but not muscle mass, is associated with mortality in the Health, Aging and Body Composition Study cohort. *J. Gerontol. Ser. A* 61, 72–77. <https://doi.org/10.1093/gerona/61.1.72>.

Newman, C.B., Preiss, D., Tobert, J.A., Jacobson, T.A., Page, R.L., Goldstein, L.B., Chin, C., Tannock, L.R., Miller, M., Raghuv eer, G., et al. (2019). Statin safety and associated adverse events: A scientific statement from the American Heart Association. *Arterioscler. Thromb. Vasc. Biol.* 39, e38–e81. <https://doi.org/10.1161/ATV.0000000000000073>.

New York Times. (1985). New evidence, old debate. September 12. <https://www.nytimes.com/1985/09/12/us/new-evidence-old-debate.html>.

Ngandu, T., Lehtisalo, J., Solomon, A., Levälähti, E., Ahtiluoto, S., Antikainen, R., Bäckman, L., Hänninen, T., Jula, A., Laatikainen, T., et al. (2015). A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): A randomised controlled trial. *Lancet* 385, 2255–2263. [https://doi.org/10.1016/S0140-6736\(15\)60461-5](https://doi.org/10.1016/S0140-6736(15)60461-5).

NHTSA (National Highway Traffic Safety Administration). (2022a). Early estimates of motor vehicle traffic fatalities and fatality rate by sub-categories in 2021. *Traffic Safety Facts*, May. <https://crashstats.nhtsa.dot.gov/Api/Public/ViewPublication/813298>.

———. (2022b). *Fatality and Injury Reporting System Tool (FIRST)*. <https://cdan.dot.gov/query>.

Nicklas, B.J., Chmelo, E., Delbono, O., Carr, J.J., Lyles, M.F., and Marsh, A.P.

(2015). Effects of resistance training with and without caloric restriction on physical function and mobility in overweight and obese older adults: A randomized controlled trial. *Am. J. Clin. Nutr.* 101, 991–999. <https://doi.org/10.3945/ajcn.114.105270>.

NIDDK (National Institute of Diabetes and Digestive and Kidney Diseases). (2018). *Diabetes in America*. 3rd ed. Bethesda, MD: NIDDK.

Ninonuevo, M.R., Park, Y., Yin, H., Zhang, J., Ward, R.E., Clowers, B.H., German, J.B., Freeman, S.L., Killeen, K., Grimm, R., et al. (2006). A strategy for annotating the human milk glycome. *J. Agric. Food Chem.* 54, 7471–7480. <https://doi.org/10.1021/jf0615810>.

Nuttall, F.Q., and Gannon, M.C. (2006). The metabolic response to a high-protein, low-carbohydrate diet in men with type 2 diabetes mellitus. *Metabolism* 55, 243–251. <https://doi.org/10.1016/j.metabol.2005.08.027>.

Nymo, S., Coutinho, S.R., Jørgensen, J., Rehfeld, J.F., Truby, H., Kulseng, B., and Martins, C. (2017). Timeline of changes in appetite during weight loss with a ketogenic diet. *Int. J. Obes.* 41, 1224–1231. <https://doi.org/10.1038/ijo.2017.96>.

O'Donoghue, M.L., Fazio, S., Giugliano, R.P., et al. (2019). Lipoprotein(a), PCSK9 inhibition, and cardiovascular risk. *Circulation*, 139(12):1483-1492. doi:10.1161/ CIRCULATIONAHA.118.037184.

Ogden, C.L., Fryar, C.D., Carroll, M.D., and Flegal, K.M. (2004). Mean body weight, height, and body mass index, United States 1960–2002. *Adv. Data* 1–17.

Ohayon, M.M., Carskadon, M.A., Guilleminault, C., and Vitiello, M.V. (2004). Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: Developing normative sleep values across the human lifespan. *Sleep* 27, 1255–1273. <https://doi.org/10.1093/sleep/27.7.1255>.

O'Keefe, J.H., Cordain, L., Harris, W.H., Moe, R.M., and Vogel, R. (2004). Optimal low-density lipoprotein is 50 to 70 mg/dl: Lower is better and physio-

logically normal. *J. Am. Coll. Cardiol.* 43, 2142–2146. <https://doi.org/10.1016/j.jacc.2004.03.046>.

Oliveira, C., Cotrim, H., and Arrese, M. (2019). Nonalcoholic fatty liver disease risk factors in Latin American populations: Current scenario and perspectives. *Clin. Liver Dis.* 13, 39–42. <https://doi.org/10.1002/cld.759>.

Oriá, R.B., Patrick, P.D., Blackman, J.A., Lima, A.A.M., and Guerrant, R.L. (2007). Role of apolipoprotein E4 in protecting children against early childhood diarrhea outcomes and implications for later development. *Med. Hypotheses* 68, 1099–1107. <https://doi.org/10.1016/j.mehy.2006.09.036>.

Orphanet (2022). Orphanet: 3 hydroxyisobutyric aciduria. [https://www.orpha.net/consor/cgi-bin/OC\\_Exp.php?Lng=EN&Expert=939](https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=939).

Osorio, R.S., Pirraglia, E., Agüera-Ortiz, L.F., During, E.H., Sacks, H., Ayappa, I., Walsleben, J., Mooney, A., Hussain, A., Glodzik, L., et al. (2011). Greater risk of Alzheimer's disease in older adults with insomnia. *J. Am. Geriatr. Soc.* 59, 559–562. <https://doi.org/10.1111/j.1532-5415.2010.03288.x>.

Oulhaj, A., Jerneén, F., Refsum, H., Smith, A.D., and de Jager, C.A. (2016). Omega-3 fatty acid status enhances the prevention of cognitive decline by B vitamins in mild cognitive impairment. *J. Alzheimers Dis.* 50, 547–557. <https://doi.org/10.3233/JAD-150777>.

Oyetaquin-White, P., Suggs, A., Koo, B., Matsui, M.S., Yarosh, D., Cooper, K.D., and Baron, E.D. (2015). Does poor sleep quality affect skin ageing? *Clin. Exp. Dermatol.* 40, 17–22. <https://doi.org/10.1111/ced.12455>.

Patel, A.K., Reddy, V., and Araujo, J.F. (2022). *Physiology, sleep stages*. Treasure Island, FL: StatPearls.

Patel, D., Steinberg, J., and Patel, P. (2018). Insomnia in the elderly: A review. *J. Clin. Sleep Med.* 14, 1017–1024. <https://doi.org/10.5664/jcsm.7172>.

Peng, B., Yang, Q., B Joshi, R., Liu, Y., Akbar, M., Song, B.-J., Zhou, S., and Wang, X. (2020). Role of alcohol drinking in Alzheimer's disease, Parkinson's

disease, and amyotrophic lateral sclerosis. *Int. J. Mol. Sci.* 21, 2316. <https://doi.org/10.3390/ijms21072316>.

Perls, T.T. (2017). Male centenarians: How and why are they different from their female counterparts? *J. Am. Geriatr. Soc.* 65, 1904–1906. <https://doi.org/10.1111/jgs.14978>.

Pesch, B., Kendzia, B., Gustavsson, P., Jöckel, K.-H., Johnen, G., Pohlabein, H., Olsson, A., Ahrens, W., Gross, I.M., Brüske, I., et al. (2012). Cigarette smoking and lung cancer—relative risk estimates for the major histological types from a pooled analysis of case-control studies. *Int. J. Cancer* 131, 1210–1219. <https://doi.org/10.1002/ijc.27339>.

Petersen, K.F., Dufour, S., Savage, D.B., Bilz, S., Solomon, G., Yonemitsu, S., Cline, G.W., Befroy, D., Zeman, L., Kahn, B.B., et al. (2007). The role of skeletal muscle insulin resistance in the pathogenesis of the metabolic syndrome. *Proc. Natl. Acad. Sci.* 104, 12587–12594. <https://doi.org/10.1073/pnas.0705408104>.

Petersen, M.C., and Shulman, G.I. (2018). Mechanisms of insulin action and insulin resistance. *Physiol. Rev.* 98, 2133–2223. <https://doi.org/10.1152/physrev.00063.2017>.

Pfister, R., Sharp, S.J., Luben, R., Khaw, K.-T., and Wareham, N.J. (2011). No evidence of an increased mortality risk associated with low levels of glycated haemoglobin in a non-diabetic UK population. *Diabetologia* 54, 2025–2032. <https://doi.org/10.1007/s00125-011-2162-0>.

Phinney, S., and Volek, J. (2018). The science of nutritional ketosis and appetite. *Virta* (blog), July 25. <https://www.virtahealth.com/blog/ketosis-appetite-hunger>.

Picard, C. (2018). The secrets to living to 100 (according to people who've done it). *Good Housekeeping*.

Picton, J.D., Marino, A.B., and Nealy, K.L. (2018). Benzodiazepine use and cognitive decline in the elderly. *Am. J. Health. Syst. Pharm.* 75, e6–e12. <https://doi.org/10.1093/ajhp/75.10.e6>.



[doi.org/10.2146/ajhp160381](https://doi.org/10.2146/ajhp160381).

Pollack, A. (2005). Huge genome project is proposed to fight cancer. *New York Times*, March 28. <https://www.nytimes.com/2005/03/28/health/huge-genome-project-is-proposed-to-fight-cancer.html>.

Pontzer, H., Wood, B.M., and Raichlen, D.A. (2018). Hunter-gatherers as models in public health. *Obes. Rev.* 19, 24–35. <https://doi.org/10.1111/obr.12785>.

Potvin, O., Lorrain, D., Forget, H., Dubé, M., Grenier, S., Prévaille, M., and Hudon, C. (2012). Sleep quality and 1-year incident cognitive impairment in community-dwelling older adults. *Sleep* 35, 491–499. <https://doi.org/10.5665/sleep.1732>.

Powell-Wiley, T.M., Poirier, P., Burke, L.E., Després, J.-P., Gordon-Larsen, P., Lavie, C.J., Lear, S.A., Ndumele, C.E., Neeland, I.J., Sanders, P., et al. (2021). Obesity and cardiovascular disease: A scientific statement from the American Heart Association. *Circulation* 143, e984–e1010. <https://doi.org/10.1161/CIR.0000000000000973>.

Prather, A.A., Bogdan, R., and Hariri, A.R. (2013). Impact of sleep quality on amygdala reactivity, negative affect, and perceived stress. *Psychosom. Med.* 75, 350–358. <https://doi.org/10.1097/PSY.0b013e31828ef15b>.

Prati, D., Taioli, E., Zanella, A., del a Torre, E., Butelli, S., Del Vecchio, E., Vianello, L., Zanuso, F., Mozzi, F., Milani, S., et al. (2002). Updated definitions of healthy ranges for serum alanine aminotransferase levels. *Ann. Intern. Med.* 137, 1–10. <https://doi.org/10.7326/0003-4819-137-1-200207020-00006>.

Proctor, R.N. (1995). *Cancer wars: How politics shapes what we know and don't know about cancer*. New York: Basic Books.

———. (2001). Tobacco and the global lung cancer epidemic. *Nat. Rev. Cancer* 1, 82–86. <https://doi.org/10.1038/35094091>.

Rabinovici, G.D., Gatsonis, C., Apgar, C., Chaudhary, K., Gareen, I., Hanna,

L., Hendrix, J., Hillner, B.E., Olson, C., Lesman-Segev, O.H., et al. (2019). Association of amyloid positron emission tomography with subsequent change in clinical management among medicare beneficiaries with mild cognitive impairment or dementia. *JAMA* 321, 1286–1294. <https://doi.org/10.1001/jama.2019.2000>.

Rahman, A., Schelbaum, E., Hoffman, K., Diaz, I., Hristov, H., Andrews, R., Jett, S., Jackson, H., Lee, A., Sarva, H., et al. (2020). Sex-driven modifiers of Alzheimer risk: A multimodality brain imaging study. *Neurology* 95, e166–e178. <https://doi.org/10.1212/WNL.0000000000009781>.

Raichle, M.E., and Gusnard, D.A. (2002). Appraising the brain's energy budget. *Proc. Natl. Acad. Sci.* 99, 10237–10239. <https://doi.org/10.1073/pnas.172399499>.

Rajpathak, S.N., Liu, Y., Ben-David, O., Reddy, S., Atzmon, G., Crandall, J., and Barzilai, N. (2011). Lifestyle factors of people with exceptional longevity. *J. Am. Geriatr. Soc.* 59, 1509–1512. <https://doi.org/10.1111/j.1532-5415.2011.03498.x>.

Rao, M.N., Neylan, T.C., Grunfeld, C., Mulligan, K., Schambelan, M., and Schwarz, J.-M. (2015). Subchronic sleep restriction causes tissue-specific insulin resistance. *J. Clin. Endocrinol. Metab.* 100, 1664–1671. <https://doi.org/10.1210/jc.2014-3911>.

Raskind, M.A., Peskind, E.R., Hoff, D.J., Hart, K.L., Holmes, H.A., Warren, D., Shofer, J., O'Connell, J., Taylor, F., Gross, C., et al. (2007). A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. *Biol. Psychiatry* 61, 928–934. <https://doi.org/10.1016/j.biopsych.2006.06.032>.

Raskind, M.A., Peskind, E.R., Kanter, E.D., Petrie, E.C., Radant, A., Thompson, C.E., Dobie, D.J., Hoff, D., Rein, R.J., Straits-Tröster, K., et al. (2003). Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: A placebo-controlled study. *Am. J. Psychiatry* 160, 371–373. <https://doi.org/10.1176/appi.ajp.160.2.371>.

Ratnakumar, A., Zimmerman, S.E., Jordan, B.A., and Mar, J.C. (2019). Estrogen activates Alzheimer's disease genes. *Alzheimers Dement.* 5, 906–917. <https://doi.org/10.1016/j.trci.2019.09.004>.

Real, T. (1998). *I don't want to talk about it: Overcoming the secret legacy of male depression.* New York: Scribner.

Reddy, O.C., and van der Werf, Y.D. (2020). The sleeping brain: Harnessing the power of the glymphatic system through lifestyle choices. *Brain Sci.* 10, 868. <https://doi.org/10.3390/brainsci10110868>.

Reiman, E.M., Arboleda-Velasquez, J.F., Quiroz, Y.T., Huentelman, M.J., Beach, T.G., Caselli, R.J., Chen, Y., Su, Y., Myers, A.J., Hardy, J., et al. (2020). Exceptionally low likelihood of Alzheimer's dementia in APOE2 homozygotes from a 5,000-person neuropathological study. *Nat. Commun.* 11, 667. <https://doi.org/10.1038/s41467-019-14279-8>.

Reiman, E.M., Caselli, R.J., Yun, L.S., Chen, K., Bandy, D., Minoshima, S., Thibodeau, S.N., and Osborne, D. (1996). Preclinical evidence of Alzheimer's disease in persons homozygous for the epsilon 4 allele for apolipoprotein E. *N. Engl. J. Med.* 334, 752–758. <https://doi.org/10.1056/NEJM199603213341202>.

Reimers, C.D., Knapp, G., and Reimers, A.K. (2012). Does physical activity increase life expectancy? A review of the literature. *J. Aging Res.* 2012, 243958. <https://doi.org/10.1155/2012/243958>.

Repantis, D., Wermuth, K., Tsamitros, N., Danker-Hopfe, H., Bublitz, J.C., Kühn, S., and Dresler, M. (2020). REM sleep in acutely traumatized individuals and interventions for the secondary prevention of post-traumatic stress disorder. *Eur. J. Psychotraumatology* 11, 1740492. <https://doi.org/10.1080/20008198.2020.1740492>.

Reutrakul, S., and Van Cauter, E. (2018). Sleep influences on obesity, insulin resistance, and risk of type 2 diabetes. *Metabolism* 84, 56–66. <https://doi.org/10.1016/j.metabol.2018.02.010>.

Revelas, M., Thalamuthu, A., Oldmeadow, C., Evans, T.-J., Armstrong, N.J.,

Kwok, J.B., Brodaty, H., Schofield, P.R., Scott, R.J., Sachdev, P.S., et al. (2018). Review and meta-analysis of genetic polymorphisms associated with exceptional human longevity. *Mech. Ageing Dev.* 175, 24–34. <https://doi.org/10.1016/j.mad.2018.06.002>.

Richter, E.A. (2021). Is GLUT4 translocation the answer to exercise-stimulated muscle glucose uptake? *Am. J. Physiol.-Endocrinol. Metab.* 320, E240–E243. <https://doi.org/10.1152/ajpendo.00503.2020>.

Riis, J.A. (1901). *The making of an American*. United States: Aegypan.

Ritchie, H., and Roser, M. (2018). Causes of death. *Our World in Data*. <https://ourworldindata.org/causes-of-death>.

Rosenberg, A., Mangialasche, F., Ngandu, T., Solomon, A., Kivipelto, M. (2020). Multidomain interventions to prevent cognitive impairment, Alzheimer’s disease, and dementia: From FINGER to world-wide FINGERS. *J. Prev. Alzheimers Dis.* 7(1): 29–36. <https://doi.org/10.14283/jpad.2019.41>.

Rosenberg, S.A., and Barr, J.M. (1992). *The transformed cell*. New York: Putnam.

Roy, J., and Forest, G. (2018). Greater circadian disadvantage during evening games for the National Basketball Association (NBA), National Hockey League (NHL) and National Football League (NFL) teams travelling westward. *J. Sleep Res.* 27, 86–89. <https://doi.org/10.1111/jsr.12565>.

Rozenytr, P., von Haehling, S., Lainscak, M., Nowak, J.U., Kalantar-Zadeh, K., Polonski, L., and Anker, S.D. (2010). The effects of a high-caloric protein-rich oral nutritional supplement in patients with chronic heart failure and cachexia on quality of life, body composition, and inflammation markers: A randomized, double-blind pilot study. *J. Cachexia Sarcopenia Muscle* 1, 35–42. <https://doi.org/10.1007/s13539-010-0008-0>.

Rupp, T.L., Wesensten, N.J., and Balkin, T.J. (2012). Trait-like vulnerability to total and partial sleep loss. *Sleep* 35, 1163–1172. <https://doi.org/10.5665/sleep.2010>.

Sabatini, D.M., Erdjument-Bromage, H., Lui, M., Tempst, P., and Snyder, S.H. (1994). RAFT1: A mammalian protein that binds to FKBP12 in a rapamycin-dependent fashion and is homologous to yeast TORs. *Cell* 78, 35–43. [https://doi.org/10.1016/0092-8674\(94\)90570-3](https://doi.org/10.1016/0092-8674(94)90570-3).

Samra, R.A. (2010). Fats and satiety. In *Fat detection: Taste, texture, and post ingestive effects*, ed. J.-P. Montmayeur and J. le Coutre. Boca Raton, FL: CRC Press/Taylor and Francis.

San-Millán, I., and Brooks, G.A. (2018). Assessment of metabolic flexibility by means of measuring blood lactate, fat, and carbohydrate oxidation responses to exercise in professional endurance athletes and less-fit individuals. *Sports Med. Auckl. NZ* 48, 467–479. <https://doi.org/10.1007/s40279-017-0751-x>.

Sasco, A.J., Secretan, M.B., and Straif, K. (2004). Tobacco smoking and cancer: A brief review of recent epidemiological evidence. *Lung Cancer Amst. Neth.* 45, Suppl 2, S3–9. <https://doi.org/10.1016/j.lungcan.2004.07.998>.

Saul, S. (2006). Record sales of sleeping pills are causing worries. *New York Times*, February 7. <https://www.nytimes.com/2006/02/07/business/record-sales-of-sleeping-pills-are-causing-worries.html>.

Sawka, M.N., Gonzalez, R.R., and Pandolf, K.B. (1984). Effects of sleep deprivation on thermoregulation during exercise. *Am. J. Physiol.* 246, R72–77. <https://doi.org/10.1152/ajpregu.1984.246.1.R72>.

Schoenfeld, B.J., and Aragon, A.A. (2018). How much protein can the body use in a single meal for muscle-building? Implications for daily protein distribution. *J. Int. Soc. Sports Nutr.* 15, 10. <https://doi.org/10.1186/s12970-018-0215-1>.

Schwingshackl, L., Schwedhelm, C., Hoffmann, G., Knüppel, S., Laure Preterre, A., Iqbal, K., Bechthold, A., De Henauw, S., Michels, N., Devleeschauwer, B., et al. (2018). Food groups and risk of colorectal cancer. *Int. J. Cancer* 142, 1748–1758. <https://doi.org/10.1002/ijc.31198>.

Schwingshackl, L., Zähringer, J., Beyerbach, J., Werner, S., Hesecker, H., Kozletzko, B., and Meerpoh, J. Total dietary fat intake, fat quality, and health outcomes: A scoping review of systematic reviews of prospective studies. *Ann. Nutr. Metab.* 77(1), 4–15. <https://doi.org/10.1159/000515058>.

Sebastiani, P., Gurinovich, A., Nygaard, M., Sasaki, T., Sweigart, B., Bae, H., Andersen, S.L., Villa, F., Atzmon, G., Christensen, K., et al. (2019). APOE alleles and extreme human longevity. *J. Gerontol. Ser. A* 74, 44–51. <https://doi.org/10.1093/gerona/gly174>.

Sebastiani, P., Nussbaum, L., Andersen, S.L., Black, M.J., and Perls, T.T. (2016). Increasing sibling relative risk of survival to older and older ages and the importance of precise definitions of “aging,” “life span,” and “longevity.” *J. Gerontol. A. Biol. Sci. Med. Sci.* 71, 340–346. <https://doi.org/10.1093/gerona/glv020>.

Seidelin, K.N. (1995). Fatty acid composition of adipose tissue in humans: Implications for the dietary fat-serum cholesterol-CHD issue. *Prog. Lipid Res.* 34, 199–217. [https://doi.org/10.1016/0163-7827\(95\)00004-J](https://doi.org/10.1016/0163-7827(95)00004-J).

Seifert, T., Brassard, P., Wissenberg, M., Rasmussen, P., Nordby, P., Stallknecht, B., Adser, H., Jakobsen, A.H., Pilegaard, H., Nielsen, H.B., et al. (2010). Endurance training enhances BDNF release from the human brain. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 298, R372–377. <https://doi.org/10.1152/ajpregu.00525.2009>.

Selvarani, R., Mohammed, S., and Richardson, A. (2021). Effect of rapamycin on aging and age-related diseases—past and future. *GeroScience* 43, 1135–1158. <https://doi.org/10.1007/s11357-020-00274-1>.

Serna, E., Gambini, J., Borrás, C., Abdelaziz, K.M., Mohammed, K., Belenguier, A., Sanchis, P., Avellana, J.A., Rodríguez-Mañás, L., and Viña, J. (2012). Centenarians, but not octogenarians, up-regulate the expression of microRNAs. *Sci. Rep.* 2, 961. <https://doi.org/10.1038/srep00961>.

Shahid, A., Wilkinson, K., Marcu, S., and Shapiro, C.M. (2011). Insomnia

Severity Index (ISI). In *STOP, THAT and one hundred other sleep scales*, ed. A. Shahid, K. Wilkinson, S. Marcu, and C.M. Shapiro, 191–193. New York: Springer New York.

Shan, Z., Ma, H., Xie, M., Yan, P., Guo, Y., Bao, W., Rong, Y., Jackson, C.L., Hu, F.B., and Liu, L. (2015). Sleep duration and risk of type 2 diabetes: A meta-analysis of prospective studies. *Diabetes Care* 38, 529–537. <https://doi.org/10.2337/dc14-2073>.

Shephard, R.J. (2009). Maximal oxygen intake and independence in old age. *Br.J.Sports Med.* 43, 342–346. <https://doi.org/10.1136/bjism.2007.044800>.

Shmagel, A., Ngo, L., Ensrud, K., and Foley, R. (2018). Prescription medication use among community-based US adults with chronic low back pain: A cross-sectional population based study. *J. Pain* 19, 1104–1112. <https://doi.org/10.1016/j.jpain.2018.04.004>.

Siegel, R.L., Miller, K.D., Fuchs, H.E., and Jemal, A. (2021). Cancer statistics, 2021. *CA. Cancer J. Clin.* 71, 7–33. <https://doi.org/10.3322/caac.21654>.

Slayday, R.E., Gustavson, D.E., Elman, J.A., Beck, A., McEvoy, L.K., Tu, X.M., Fang, B., Hauger, R.L., Lyons, M.J., McKenzie, R.E., et al. (2021). Interaction between alcohol consumption and apolipoprotein E (ApoE) genotype with cognition in middle-aged men. *J. Int. Neuropsychol. Soc.* 27, 56–68. <https://doi.org/10.1017/S1355617720000570>.

Sleeman, J., and Steeg, P.S. (2010). Cancer metastasis as a therapeutic target. *Eur.J. Cancer* 46, 1177–1180. <https://doi.org/10.1016/j.ejca.2010.02.039>.

Small, G.W., Ercoli, L.M., Silverman, D.H.S., Huang, S.-C., Komo, S., Bookheimer, S.Y., Lavretsky, H., Miller, K., Siddarth, P., Rasgon, N.L., et al. (2000). Cerebral metabolic and cognitive decline in persons at genetic risk for Alzheimer's disease. *Proc. Natl. Acad. Sci.* 97, 6037–6042.

Smith, A.D., Smith, S.M., de Jager, C.A., Whitbread, P., Johnston, C., Agacinski, G., Oulhaj, A., Bradley, K.M., Jacoby, R., and Refsum, H. (2010). Homocysteine-lowering by B Vitamins slows the rate of accelerated brain atro-

phy in mild cognitive impairment: A randomized controlled trial. *PLOS ONE* 5, e12244. <https://doi.org/10.1371/journal.pone.0012244>.

Smith, C., and Lapp, L. (1991). Increases in number of REMS and REM density in humans following an intensive learning period. *Sleep* 14, 325–330. <https://doi.org/10.1093/sleep/14.4.325>.

Smith, C., and Smith, D. (2003). Ingestion of ethanol just prior to sleep onset impairs memory for procedural but not declarative tasks. *Sleep* 26, 185–191.

Sniderman, A.D., Bhopal, R., Prabhakaran, D., Sarrafzadegan, N., and Tchernof, A. (2007). Why might South Asians be so susceptible to central obesity and its atherogenic consequences? The adipose tissue overflow hypothesis. *Int. J. Epidemiol.* 36, 220–225. <https://doi.org/10.1093/ije/dyl245>.

Sniderman, A.D., Thanassoulis, G., Williams, K., and Pencina, M. (2016). Risk of premature cardiovascular disease vs the number of premature cardiovascular events. *JAMA Cardiol.* 1, 492–494. <https://doi.org/10.1001/jamacardio.2016.0991>.

Sokol, D.K. (2013). “First do no harm” revisited. *BMJ* 347, f6426. <https://doi.org/10.1136/bmj.f6426>.

Soran, H., Ho, J.H., and Durrington, P.N. (2018). Acquired low cholesterol: Diagnosis and relevance to safety of low LDL therapeutic targets. *Curr. Opin. Lipidol.* 29, 318–326. <https://doi.org/10.1097/MOL.0000000000000526>.

Spaeth, A.M., Dinges, D.F., and Goel, N. (2015). Resting metabolic rate varies by race and by sleep duration. *Obesity* 23, 2349–2356. <https://doi.org/10.1002/oby.21198>.

Spencer, C. (2005). *Genes, aging and immortality*. Upper Saddle River, NJ: Pearson.

Sperling, R.A., Aisen, P.S., Beckett, L.A., Bennett, D.A., Craft, S., Fagan, A.M., Iwatsubo, T., Jack, C.R., Kaye, J., Montine, T.J., et al. (2011). Toward defin-



ing the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 7, 280–292. <https://doi.org/10.1016/j.jalz.2011.03.003>.

Spiegel, K., Leproult, R., L'hermite-Balériaux, M., Copinschi, G., Penev, P.D., and Van Cauter, E. (2004b). Leptin levels are dependent on sleep duration: Relationships with sympathovagal balance, carbohydrate regulation, cortisol, and thyrotropin. *J. Clin. Endocrinol. Metab.* 89, 5762–5771. <https://doi.org/10.1210/jc.2004-1003>.

Spiegel, K., Leproult, R., and Van Cauter, E. (1999). Impact of sleep debt on metabolic and endocrine function. *Lancet* 354, 1435–1439. [https://doi.org/10.1016/S0140-6736\(99\)01376-8](https://doi.org/10.1016/S0140-6736(99)01376-8).

Spiegel, K., Tasali, E., Penev, P., and Cauter, E.V. (2004a). Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann. Intern. Med.* 141, 846–850. <https://doi.org/10.7326/0003-4819-141-11-200412070-00008>.

Spillane, S., Shiels, M.S., Best, A.F., Haozous, E.A., Withrow, D.R., Chen, Y., Berrington de González, A., and Freedman, N.D. (2020). Trends in alcohol-induced deaths in the United States, 2000–2016. *JAMA Netw. Open* 3, e1921451. <https://doi.org/10.1001/jamanetworkopen.2019.21451>.

Spira, A.P., Gamaldo, A.A., An, Y., Wu, M.N., Simonsick, E.M., Bilgel, M., Zhou, Y., Wong, D.F., Ferrucci, L., and Resnick, S.M. (2013). Self-reported sleep and  $\beta$ -amyloid deposition in community-dwelling older adults. *JAMA Neurol.* 70, 1537–1543. <https://doi.org/10.1001/jamaneurol.2013.4258>.

Sprecher, K.E., Bendlin, B.B., Racine, A.M., Okonkwo, O.C., Christian, B.T., Kosciak, R.L., Sager, M.A., Asthana, S., Johnson, S.C., and Benca, R.M. (2015). Amyloid burden is associated with self-reported sleep in non-demented late middle-aged adults. *Neurobiol. Aging* 36, 2568–2576. <https://doi.org/10.1016/j.neurobiolaging.2015.05.004>.

Stamatakis, K.A., and Punjabi, N.M. (2010). Effects of sleep fragmentation on glucose metabolism in normal subjects. *Chest* 137, 95–101. <https://doi.org/10.1378/chest.09-0791>.

Standl, E., Schnell, O., and Ceriello, A. (2011). Postprandial hyperglycemia and glycemic variability: Should we care? *Diabetes Care* 34, Suppl 2, S120–127. <https://doi.org/10.2337/dc11-s206>.

Stary, H.C. (2003). *Atlas of atherosclerosis progression and regression*. Boca Raton, FL: CRC Press.

Stefan, N., Schick, F., and Häring, H.-U. (2017). Causes, characteristics, and consequences of metabolically unhealthy normal weight in humans. *Cell Metab.* 26, 292–300. <https://doi.org/10.1016/j.cmet.2017.07.008>.

Stickgold, R., Whidbee, D., Schirmer, B., Patel, V., and Hobson, J.A. (2000). Visual discrimination task improvement: A multi-step process occurring during sleep. *J. Cogn. Neurosci.* 12, 246–254. <https://doi.org/10.1162/089892900562075>.

Stomrud, E., Hansson, O., Zetterberg, H., Blennow, K., Minthon, L., and Londos, E. (2010). Correlation of longitudinal cerebrospinal fluid biomarkers with cognitive decline in healthy older adults. *Arch. Neurol.* 67, 217–223. <https://doi.org/10.1001/archneurol.2009.316>.

Strobe, M. (2021). U.S. overdose deaths topped 100,000 in one year, officials say. *AP News*, November 17. <https://apnews.com/article/overdose-deaths-fentanyl-health-f34b022d75a1eb9776e27903ab40670f>.

Stroes, E.S., Thompson, P.D., Corsini, A., Vladutiu, G.D., Raal, F.J., Ray, K.K., Roden, M., Stein, E., Tokgözoğlu, L., Nordestgaard, B.G., et al. (2015). Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. *Eur. Heart J.* 36, 1012–1022. <https://doi.org/10.1093/eurheartj/ehv043>.

Strong, R., Miller, R.A., Astle, C.M., Baur, J.A., de Cabo, R., Fernandez, E.,

Guo, W., Javors, M., Kirkland, J.L., Nelson, J.F., et al. (2013). Evaluation of resveratrol, green tea extract, curcumin, oxaloacetic acid, and medium-chain triglyceride oil on life span of genetically heterogeneous mice. *J. Gerontol. Ser. A* 68, 6–16. <https://doi.org/10.1093/gerona/gls070>.

Strozyk, D., Blennow, K., White, L.R., and Launer, L.J. (2003). CSF Abeta 42 levels correlate with amyloid-neuropathology in a population-based autopsy study. *Neurology* 60, 652–656. <https://doi.org/10.1212/01.wnl.0000046581.81650.d0>.

Sudimac, S., Sale, V., and Kühn, S. (2022). How nature nurtures: Amygdala activity decreases as the result of a one-hour walk in nature. *Mol Psychiatry*. <https://doi.org/10.1038/s41380-022-01720-6>.

Sumithran, P., Prendergast, L.A., Delbridge, E., Purcell, K., Shulkes, A., Kriketos, A., and Proietto, J. (2013). Ketosis and appetite-mediating nutrients and hormones after weight loss. *Eur. J. Clin. Nutr.* 67, 759–764. <https://doi.org/10.1038/ejcn.2013.90>.

Suzuki, K., Elkind, M.S., Boden-Albala, B., Jin, Z., Berry, G., Di Tullio, M.R., Sacco, R.L., and Homma, S. (2009). Moderate alcohol consumption is associated with better endothelial function: A cross sectional study. *BMC Cardiovasc. Disord.* 9, 8. <https://doi.org/10.1186/1471-2261-9-8>.

Tabata, I., Nishimura, K., Kouzaki, M., Hirai, Y., Ogita, F., Miyachi, M., and Yamamoto, K. (1996). Effects of moderate-intensity endurance and high-intensity intermittent training on anaerobic capacity and VO<sub>2</sub>max. *Med. Sci. Sports Exerc.* 28, 1327–1330. <https://doi.org/10.1097/00005768-199610000-00018>.

Taieb, J., Gallois, C. (2020). Adjuvant chemotherapy for stage III colon cancer. *Cancers*, 12(9), 2679. <https://doi.org/10.3390/cancers12092679>.

Tang, C., Liu, C., Fang, P., Xiang, Y., and Min, R. (2019). Work-related accumulated fatigue among doctors in tertiary hospitals: A cross-sectional survey in six provinces of China. *Int. J. Environ. Res. Public Health* 16, E3049. <https://doi.org/10.3390/ijerph16173049>.

Tanweer, S.A.W. (2021). How smart phones effects health. *Tech neck:*

Causes and preventions. *Pak. J. Phys. Ther.* 02–02. <https://sites2.uol.edu.pk/journals/PJPT/article/view/1135>.

Tapiola, T., Pirttilä, T., Mikkonen, M., Mehta, P.D., Alafuzoff, I., Koivisto, K., and Soininen, H. (2000). Three-year follow-up of cerebrospinal fluid tau, beta-amyloid 42 and 40 concentrations in Alzheimer's disease. *Neurosci. Lett.* 280, 119–122. [https://doi.org/10.1016/s0304-3940\(00\)00767-9](https://doi.org/10.1016/s0304-3940(00)00767-9).

Tapiola, T., Alafuzoff, I., Herukka, S.-K., Parkkinen, L., Hartikainen, P., Soininen, H., and Pirttilä, T. (2009). Cerebrospinal fluid  $\beta$ -amyloid 42 and tau proteins as biomarkers of Alzheimer-type pathologic changes in the brain. *Arch. Neurol.* 66, 382–389. <https://doi.org/10.1001/archneurol.2008.596>.

Tasali, E., Leproult, R., Ehrmann, D.A., and Van Cauter, E. (2008). Slow-wave sleep and the risk of type 2 diabetes in humans. *Proc. Natl. Acad. Sci.* 105, 1044–1049. <https://doi.org/10.1073/pnas.0706446105>.

Tatebe, H., and Shiozaki, K. (2017). Evolutionary conservation of the components in the TOR signaling pathways. *Biomolecules* 7, 77. <https://doi.org/10.3390/biom7040077>.

Taylor, J. (2009). "Cigarettes, whisky, and wild, wild women." *Independent*, June 20. <https://www.independent.co.uk/life-style/health-and-families/health-news/cigarettes-whisky-and-wild-wild-women-1710744.html>.

Tchernof, A., and Després, J.-P. (2013). Pathophysiology of human visceral obesity: An update. *Physiol. Rev.* 93, 359–404. <https://doi.org/10.1152/physrev.00033.2011>.

Templeman, I., Smith, H.A., Chowdhury, E., Chen, Y.-C., Carroll, H., Johnson-Bonson, D., Hengist, A., Smith, R., Creighton, J., Clayton, D., et al. (2021). A randomized controlled trial to isolate the effects of fasting and energy restriction on weight loss and metabolic health in lean adults. *Sci. Transl. Med.* 13, eabd8034. <https://doi.org/10.1126/scitranslmed.abd8034>.

Thanassoulis, G., Sniderman, A.D., and Pencina, M.J. (2018). A long-term benefit approach vs standard risk-based approaches for statin eligibility in

primary prevention. *JAMA Cardiol.* 3, 1090–1095. <https://doi.org/10.1001/jamacardio.2018.3476>.

Tieland, M., Dirks, M.L., van der Zwaluw, N., Verdijk, L.B., van de Rest, O., de Groot, L.C.P.G.M., and van Loon, L.J.C. (2012a). Protein supplementation increases muscle mass gain during prolonged resistance-type exercise training in frail elderly people: A randomized, double-blind, placebo-controlled trial. *J. Am. Med. Dir. Assoc.* 13, 713–719. <https://doi.org/10.1016/j.jamda.2012.05.020>.

Tieland, M., van de Rest, O., Dirks, M.L., van der Zwaluw, N., Mensink, M., van Loon, L.J.C., and de Groot, L.C.P.G.M. (2012b). Protein supplementation improves physical performance in frail elderly people: A randomized, double-blind, placebo-controlled trial. *J. Am. Med. Dir. Assoc.* 13, 720–726. <https://doi.org/10.1016/j.jamda.2012.07.005>.

Tolboom, N., van der Flier, W.M., Yaqub, M., Boellaard, R., Verwey, N.A., Blankenstein, M.A., Windhorst, A.D., Scheltens, P., Lammertsma, A.A., and van Berckel, B.N.M. (2009). Relationship of cerebrospinal fluid markers to 11C-PIB and 18F-FDDNP binding. *J. Nucl. Med.* 50, 1464–1470. <https://doi.org/10.2967/jnumed.109.064360>.

Trappe, S., Hayes, E., Galpin, A., Kaminsky, L., Jemiolo, B., Fink, W., Trappe, T., Jansson, A., Gustafsson, T., and Tesch, P. (2013). New records in aerobic power among octogenarian lifelong endurance athletes. *J. Appl. Physiol.* 114, 3–10. <https://doi.org/10.1152/jappphysiol.01107.2012>.

Trumble, B.C., and Finch, C.E. (2019). The exposome in human evolution: From dust to diesel. *Q. Rev. Biol.* 94, 333–394. <https://doi.org/10.1086/706768>.

Tsimikas, S., Fazio, S., Ferdinand, K.C., Ginsberg, H.N., Koschinsky, M.L., Santica, M., Moriarity, P.M., Rader, D.J., Remaley, A.T., Reyes-Soffer, G., et al. (2018). NHLBI Working Group recommendations to reduce lipoprotein(a)-mediated risk of cardiovascular disease and aortic stenosis. *J. Am. Coll. Cardiol.* 71(2), 177–192.

Tuchman, A. (2009). Diabetes and the public's health. *Lancet* 374, 1140–1141. [https://doi.org/10.1016/S0140-6736\(09\)61730-X](https://doi.org/10.1016/S0140-6736(09)61730-X).

United States Census Bureau. (2022). National population by characteristics: 2020–2021 tables>median age and age by sex>annual estimates of the resident population by single year of age and Sex for the United States: April 1, 2020 to July 1, 2021 (NC-EST2021-SYASEX).

Uretsky, S., Rozanski, A., Singh, P., Supariwala, A., Atluri, P., Bangalore, S., Pappas, T.W., Fisher, E.A., and Peters, M.R. (2011). The presence, characterization and prognosis of coronary plaques among patients with zero coronary calcium scores. *Int. J. Cardiovasc. Imaging* 27, 805–812. <https://doi.org/10.1007/s10554-010-9730-0>.

Urfer, S.R., Kaeberlein, T.L., Mailheau, S., Bergman, P.J., Creevy, K.E., Promislow, D.E.L., and Kaeberlein, M. (2017). A randomized controlled trial to establish effects of short-term rapamycin treatment in 24 middle-aged companion dogs. *GeroScience* 39, 117–127. <https://doi.org/10.1007/s11357-017-9972-z>.

Urry, E., and Landolt, H.-P. (2015). Adenosine, caffeine, and performance: From cognitive neuroscience of sleep to sleep pharmacogenetics. In *Sleep, neuronal plasticity and brain function*, ed. P. Meerlo, R.M. Benca, and T. Abel, 331–366. Berlin: Springer.

Van Ancum, J.M., Pijnappels, M., Jonkman, N.H., Scheerman, K., Verlaan, S., Meskers, C.G.M., and Maier, A.B. (2018). Muscle mass and muscle strength are associated with pre- and post-hospitalization falls in older male inpatients: A longitudinal cohort study. *BMC Geriatr.* 18, 116. <https://doi.org/10.1186/s12877-018-0812-5>.

Van Cauter, E., Caufriez, A., Kerkhofs, M., Van Onderbergen, A., Thorner, M.O., and Copinschi, G. (1992). Sleep, awakenings, and insulin-like growth factor-I modulate the growth hormone (GH) secretory response to GH-releasing hormone. *J. Clin. Endocrinol. Metab.* 74, 1451–1459. <https://doi.org/10.1210/jcem.74.6.1592893>.

van Charante, E., Richard, E., Eurelings, L.S., van Dalen, J-W., Ligthart, S.A., van Bussel, E.F., Hoevenaar-Blom, M.P., Vermeulen, M., van Gool, W. A. (2016). Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): A cluster-randomised controlled trial. *Lancet* 388, 797–805. [https://doi.org/ 10.1016/ S0140-6736\(16\)30950-3](https://doi.org/10.1016/S0140-6736(16)30950-3).

Vander Heiden, M.G., Cantley, L.C., and Thompson, C.B. (2009). Understanding the Warburg effect: The metabolic requirements of cell proliferation. *Science* 324, 1029–1033. <https://doi.org/10.1126/science.1160809>.

van der Helm, E., and Walker, M.P. (2009). Overnight therapy? The role of sleep in emotional brain processing. *Psychol. Bull.* 135, 731–748. <https://doi.org/10.1037/a0016570>.

Van Dongen, H.P.A., Baynard, M.D., Maislin, G., and Dinges, D.F. (2004). Systematic interindividual differences in neurobehavioral impairment from sleep loss: Evidence of trait-like differential vulnerability. *Sleep* 27, 423–433.

Van Dongen, H.P.A., Maislin, G., Mullington, J.M., and Dinges, D.F. (2003). The cumulative cost of additional wakefulness: Dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep* 26, 117–126. <https://doi.org/10.1093/sleep/26.2.117>.

Varady, K.A., and Gabel, K. (2019). Safety and efficacy of alternate day fasting. *Nat. Rev. Endocrinol.* 15, 686–687. <https://doi.org/10.1038/s41574-019-0270-y>.

Vendelbo, M.H., Møller, A.B., Christensen, B., Nellemann, B., Clasen, B.F.F., Nair, K.S., Jørgensen, J.O.L., Jessen, N., and Møller, N. (2014). Fasting increases human skeletal muscle net phenylalanine release and this is associated with decreased mTOR signaling. *PLOS ONE* 9, e102031. <https://doi.org/10.1371/journal.pone.0102031>.

Veronese, N., Koyanagi, A., Cereda, E., Maggi, S., Barbagallo, M., Dominguez, L.J., and Smith, L. (2022). Sarcopenia reduces quality of life in the long-

term: Longitudinal analyses from the English longitudinal study of ageing. *Eur. Geriatr. Med.* 13, 633–639. <https://doi.org/10.1007/s41999-022-00627-3>.

Voight, B.F., Peloso, G.M., Orho-Melander, M., Frikke-Schmidt, R., Barbalic, M., Jensen, M.K., Hindy, G., Hólm, H., Ding, E.L., Johnson, T., et al. (2012). Plasma HDL cholesterol and risk of myocardial infarction: A Mendelian randomisation study. *Lancet* 380, 572–580. [https://doi.org/10.1016/S0140-6736\(12\)60312-2](https://doi.org/10.1016/S0140-6736(12)60312-2).

Voulgari, C., Tentolouris, N., Dilaveris, P., Tousoulis, D., Katsilambros, N., and Stefanadis, C. (2011). Increased heart failure risk in normal-weight people with metabolic syndrome compared with metabolically healthy obese individuals. *J. Am. Coll. Cardiol.* 58, 1343–1350. <https://doi.org/10.1016/j.jacc.2011.04.047>.

Wade, N. (2009). Dieting monkeys offer hope for living longer. *New York Times*, July 9. <https://www.nytimes.com/2009/07/10/science/10aging.html>.

Wahlund, L.-O., and Blennow, K. (2003). Cerebrospinal fluid biomarkers for disease stage and intensity in cognitively impaired patients. *Neurosci. Lett.* 339, 99–102. [https://doi.org/10.1016/s0304-3940\(02\)01483-0](https://doi.org/10.1016/s0304-3940(02)01483-0).

Waks, A.G., and Winer, E.P. (2019). Breast cancer treatment: A review. *JAMA*, 321(3), 288–300. <https://doi.org/10.1001/jama.2018.19323>.

Walker, M.P. (2009). The role of slow wave sleep in memory processing. *J. Clin. Sleep Med.* 5, S20–S26.

———. (2017). *Why we sleep: Unlocking the power of sleep and dreams*. New York: Scribner.

Wallace, D.F. (2009). *This is water: Some thoughts, delivered on a significant occasion, about living a compassionate life*. New York: Little, Brown.

Wang, C., and Holtzman, D.M. (2020). Bidirectional relationship between sleep and Alzheimer’s disease: Role of amyloid, tau, and other factors. *Neuropsychopharmacology* 45, 104–120. <https://doi.org/10.1038/s41386-019-0478-5>.



Wang, N., Fulcher, J., Abeysuriya, N., Park, L., Kumar, S., Di Tanna, G.L., Wilcox, I., Keech, A., Rodgers, A., and Lal, S. (2020). Intensive LDL cholesterol-lowering treatment beyond current recommendations for the prevention of major vascular events: A systematic review and meta-analysis of randomised trials including 327037 participants. *Lancet Diabetes Endocrinol.* 8, 36–49. [https://doi.org/10.1016/S2213-8587\(19\)30388-2](https://doi.org/10.1016/S2213-8587(19)30388-2).

Wang, Y., and Brinton, R.D. (2016). Triad of risk for late onset Alzheimer's: Mitochondrial haplotype, APOE genotype and chromosomal sex. *Front. Aging Neurosci.* 8, 232. <https://doi.org/10.3389/fnagi.2016.00232>.

Wang, Y., Jones, B.F., and Wang, D. (2019). Early-career setback and future career impact. *Nat. Commun.* 10, 4331. <https://doi.org/10.1038/s41467-019-12189-3>.

Warburg, O. (1924). Warburg: The metabolism of cancer cells. Google Scholar.

———. (1956). On the origin of cancer cells. *Science* 123, 309–314. <https://doi.org/10.1126/science.123.3191.309>.

Watanabe, K., Oba, K., Suzuki, T., Ouchi, M., Suzuki, K., Futami-Suda, S., Sekimizu, K., Yamamoto, N., and Nakano, H. (2011). Oral glucose loading attenuates endothelial function in normal individual. *Eur. J. Clin. Invest.* 41, 465–473. <https://doi.org/10.1111/j.1365-2362.2010.02424.x>.

Watson, A.M. (2017). Sleep and athletic performance. *Curr. Sports Med. Rep.* 16, 413–418. <https://doi.org/10.1249/JSR.0000000000000418>.

Watson, J.D. (2009). Opinion | To fight cancer, know the enemy. *New York Times*, August 5. <https://www.nytimes.com/2009/08/06/opinion/06watson.html>.

Wen, C.P., Wai, J.P.M., Tsai, M.K., Yang, Y.C., Cheng, T.Y.D., Lee, M.-C., Chan, H.T., Tsao, C.K., Tsai, S.P., and Wu, X. (2011). Minimum amount of physical activity for reduced mortality and extended life expectancy: A prospective cohort study. *Lancet* 378, 1244–1253. <https://doi.org/10.1016/S0140->

6736(11)60749-6.

Westerterp, K.R., Yamada, Y., Sagayama, H., Ainslie, P.N., Andersen, L.F., Anderson, L.J., Arab, L., Baddou, I., Bedu-Addo, K., Blaak, E.E., et al. (2021). Physical activity and fat-free mass during growth and in later life. *Am. J. Clin. Nutr.* 114, 1583–1589. <https://doi.org/10.1093/ajcn/nqab260>.

WHI (Women's Health Initiative). n.d. About WHI—Dietary Modification Trial. Accessed September 28, 2022. <https://sp.whi.org/about/SitePages/Dietary%20Trial.aspx>.

WHO (World Health Organization). (2019). Global health estimates: Leading causes of death. <https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-leading-causes-of-death>.

Willcox, B.J., Donlon, T.A., He, Q., Chen, R., Grove, J.S., Yano, K., Masaki, K.H., Willcox, D.C., Rodriguez, B., and Curb, J.D. (2008). FOXO3A genotype is strongly associated with human longevity. *Proc. Natl. Acad. Sci.* 105, 13987–13992. <https://doi.org/10.1073/pnas.0801030105>.

Wilson, M.A., and McNaughton, B.L. (1994). Reactivation of hippocampal ensemble memories during sleep. *Science* 265, 676–679. <https://doi.org/10.1126/science.8036517>.

Winer, J.R., Mander, B.A., Helfrich, R.F., Maass, A., Harrison, T.M., Baker, S.L., Knight, R.T., Jagust, W.J., and Walker, M.P. (2019). Sleep as a potential biomarker of tau and  $\beta$ -amyloid burden in the human brain. *J. Neurosci.* 39, 6315–6324. <https://doi.org/10.1523/JNEUROSCI.0503-19.2019>.

Wishart, D.S., Tzur, D., Knox, C., Eisner, R., Guo, A.C., Young, N., Cheng, D., Jewell, K., Arndt, D., Sawhney, S., et al. (2007). HMDB: The Human Metabolome Database. *Nucleic Acids Res.* 35, D521–526. <https://doi.org/10.1093/nar/gkl923>.

Wolters, F.J., and Ikram, M.A. (2019). Epidemiology of vascular dementia. *Arterioscler. Thromb. Vasc. Biol.* 39, 1542–1549. <https://doi.org/10.1161/ATVBAHA.119.311908>.

Wu, G. (2016). Dietary protein intake and human health. *Food Funct.* 7, 1251–1265. <https://doi.org/10.1039/c5fo01530h>.

Xu, J. (2016). Mortality among centenarians in the United States, 2000–2014. *NCHS Data Brief* 233. <https://www.cdc.gov/nchs/products/databriefs.htm>.

Xue, Q.-L. (2011). The frailty syndrome: Definition and natural history. *Clin. Geriatr. Med.* 27, 1–15. <https://doi.org/10.1016/j.cger.2010.08.009>.

Yamamoto, T., Yagi, S., Kinoshita, H., Sakamoto, Y., Okada, K., Uryuhara, K., Morimoto, T., Kaihara, S., and Hosotani, R. (2015). Long-term survival after resection of pancreatic cancer: A single-center retrospective analysis. *World J. Gastroenterol.* 21, 262–268. <https://doi.org/10.3748/wjg.v21.i1.262>.

Yamazaki, R., Toda, H., Libourel, P.-A., Hayashi, Y., Vogt, K.E., and Sakurai, T. (2020). Evolutionary origin of distinct NREM and REM sleep. *Front. Psychol.* 11, 567618. <https://doi.org/10.3389/fpsyg.2020.567618>.

Yan, Y., Wang, X., Chaput, D., Shin, M.K., Koh, Y., Gan, L., Pieper, A.A., Woo, J.A.A., Kang, D.E. (2022). X-linked ubiquitin-specific peptidase 11 increases tauopathy vulnerability in women. *Cell*, 185: 21, 3913-3930.e19. <https://doi.org/10.1016/j.cell.2022.09.002>.

Yassine, H.N., Braskie, M.N., Mack, W.J., Castor, K.J., Fonteh, A.N., Schneider, L.S., Harrington, M.G., and Chui, H.C. (2017). Association of docosahexaenoic acid supplementation with Alzheimer disease stage in apolipoprotein E ε4 carriers. *JAMA Neurol.* 74, 339–347. <https://doi.org/10.1001/jamaneurol.2016.4899>.

Yasuno, F., Minami, H., Hattori, H., and Alzheimer's Disease Neuroimaging Initiative (2020). Interaction effect of Alzheimer's disease pathology and education, occupation, and socioeconomic status as a proxy for cognitive reserve on cognitive performance: In vivo positron emission tomography study. *Psychogeriatr.* 20, 585–593. <https://doi.org/10.1111/psyg.12552>.

Yin, J., Jin, X., Shan, Z., Li, S., Huang, H., Li, P., Peng, X., Peng, Z., Yu, K., Bao,

W., Yang, W., Chen, X., Liu, L. (2017). Relationship of sleep duration with all-cause mortality and cardiovascular events. *JAHA* 117. <https://www.ahajournals.org/doi/full/10.1161/JAHA.117.005947>.

Yoo, S.-S., Gujar, N., Hu, P., Jolesz, F.A., and Walker, M.P. (2007). The human emotional brain without sleep: A prefrontal amygdala disconnect. *Curr. Biol.* 17, R877–878. <https://doi.org/10.1016/j.cub.2007.08.007>.

Youlden, D.R., Cramb, S.M., and Baade, P.D. (2008). The international epidemiology of lung cancer: Geographical distribution and secular trends. *J. Thorac. Oncol.* 3, 819–831. <https://doi.org/10.1097/JTO.0b013e31818020eb>.

Youngstedt, S.D., O'Connor, P.J., Crabbe, J.B., and Dishman, R.K. (2000). The influence of acute exercise on sleep following high caffeine intake. *Physiol. Behav.* 68, 563–570. [https://doi.org/10.1016/S0031-9384\(99\)00213-9](https://doi.org/10.1016/S0031-9384(99)00213-9).

Zelman, S. (1952). The liver in obesity. *Arch. Intern. Med.* 90, 141–156. <https://doi.org/10.1001/archinte.1952.00240080007002>.

Zethelius, B., and Cederholm, J. (2015). Comparison between indexes of insulin resistance for risk prediction of cardiovascular diseases or development of diabetes. *Diabetes Res. Clin. Pract.* 110, 183–192. <https://doi.org/10.1016/j.diabres.2015.09.003>.

Zhang, Y., Zhang, Y., Du, S., Wang, Q., Xia, H., and Sun, R. (2020). Exercise interventions for improving physical function, daily living activities and quality of life in community-dwelling frail older adults: A systematic review and meta-analysis of randomized controlled trials. *Geriatr. Nur.* 41, 261–273. <https://doi.org/10.1016/j.gerinurse.2019.10.006>.

Zheng, Y., Fan, S., Liao, W., Fang, W., Xiao, S., and Liu, J. (2017). Hearing impairment and risk of Alzheimer's disease: A meta-analysis of prospective cohort studies. *Neurol. Sci.* 38, 233–239. <https://doi.org/10.1007/s10072-016-2779-3>.

Zheng, Y., Lv, T., Wu, J., and Lyu, Y. (2022). Trazodone changed the polysomnographic sleep architecture in insomnia disorder: A systematic review and meta-analysis. *Scientific reports*, 12(1), 14453. <https://doi.org/10.1038/>

s41598-022-18776-7.

Zhou, C., Wu, Q., Wang, Z., Wang, Q., Liang, Y., and Liu, S. (2020). The effect of hormone replacement therapy on cognitive function in female patients with Alzheimer's disease: A meta-analysis. *Am. J. Alzheimers Dis. Other Demen.* 35, 1533317520938585. <https://doi.org/10.1177/1533317520938585>.

Ziemichód, W., Grabowska, K., Kurowska, A., and Biała, G. (2022). A comprehensive review of daridorexant, a dual-orexin receptor antagonist as new approach for the treatment of insomnia. *Molecules* 27(18), 6041. <https://doi.org/10.3390/molecules27186041>.

Zuccarelli, L., Galasso, L., Turner, R., Coffey, E.J.B., Bessone, L., and Strapazon, G. (2019). Human physiology during exposure to the cave environment: A systematic review with implications for aerospace medicine. *Front. Physiol.* 10.