

References

Chapter 1

Hawkes K, O'Connell J, Blurton Jones N. Hunter-gatherer studies and human evolution: a very selective review. *Am J Phys Anthropol*. 2018;165:777–800.

Pontzer H, Raichlen DA, Wood BM, Mabulla AZ, Racette SB, Marlowe FW. Hunter-gatherer energetics and human obesity. *PLoS One*. 2012;7, e40503.

Raichlen DA, Pontzer H, Harris JA, et al. Physical activity patterns and biomarkers of cardiovascular disease risk in hunter-gatherers. *Am J Hum Biol*. 2017;29. <https://doi.org/10.1002/ajhb.22919>. Epub 2016 Oct 9.

Eaton SB, Eaton SB. An evolutionary perspective on human physical activity: implications for health. *Comp Biochem Physiol A Mol Integr Physiol*. 2003;136:153–159.

Lee IM, Shiroma EJ, Lobelo F, et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet*. 2012;380:219–229.

Blair SN, Sallis RE, Hutber A, Archer E. Exercise therapy—the public health message. *Scand J Med Sci Sports*. 2012;22:e24–e28.

Chin SH, Kahathuduwa CN, Binks M. Physical activity and obesity: what we know and what we need to know. *Obes Rev*. 2016;17:1226–1244.

Kohl 3rd HW. Physical activity and cardiovascular disease: evidence for a dose response. *Med Sci Sports Exerc*. 2001;33:S472–S483. discussion S493–S494.

Lee IM, Skerrett PJ. Physical activity and all-cause mortality: what is the dose-response relation? *Med Sci Sports Exerc*. 2001;33:S459–S471. discussion S493–S494.

World Health Organization (WHO). Physical Activity, 2019; 2018. <https://www.who.int/news-room/fact-sheets/detail/physical-activity>.

Shrestha N, Kukkonen-Harjula KT, Verbeek JH, Ijaz S, Hermans V, Pedisic Z. Workplace interventions for reducing sitting at work. *Cochrane Database Syst Rev*. 2018;6, CD010912.

Cheatham SW, Stull KR, Fantigrassi M, Motel I. The efficacy of wearable activity tracking technology as part of a weight loss program: a systematic review. *J Sports Med Phys Fitness*. 2018;58:534–548.

Statuta SM, Asif IM, Drezner JA. Relative energy deficiency in sport (RED-S). *Br J Sports Med*. 2017;51:1570–1571.

US Department for Health and Human Services. Physical Activity Guidelines for Americans, 2019; 2018. https://health.gov/paguidelines/second-edition/pdf/Physical_Activity_Guidelines_2nd_edition.pdf.

Centers for Disease Control and Prevention. Physical Activity Guidelines for Americans, 2019; 2019. <https://www.cdc.gov/physicalactivity/downloads/trends-in-the-prevalence-of-physical-activity-508.pdf>.

Statista. Physical Activity—Statistics and Facts, 2019; 2018. <https://www.statista.com/topics/1749/physical-activity/>.

Guthold R, Stevens GA, Riley LM, Bull FC. Worldwide trends in insufficient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys with 1.9 million participants. *Lancet Glob Health*. 2018;6(10):e1077–e1086. [https://doi.org/10.1016/S2214-109X\(18\)30357-7](https://doi.org/10.1016/S2214-109X(18)30357-7).

Guthold R, Stevens GA, Riley LM, Bull FC. Global trends in insufficient physical activity among adolescents: a pooled analysis of 298 population-based surveys with 1.6 million participants. *Lancet Child Adolesc Health*.

2020;4(1):23–35. [https://doi.org/10.1016/S2352-4642\(19\)30323-2](https://doi.org/10.1016/S2352-4642(19)30323-2).

NPR/PBS. New Year's Resolutions, 2019; 2018. http://maristpoll.marist.edu/wp-content/uploads/2018/12/NPR_PBS-NewsHour_Marist-Poll_USA-NOS-and-Tables_New-Years-Resolutions_1812061019-1.pdf#page=3.

Schroeder EC, Welk GJ, Franke WD, Lee DC. Associations of health club membership with physical activity and cardiovascular health. *PLoS One*. 2017;12, e0170471.

Kann L, McManus T, Harris WA, et al. Youth risk behavior surveillance—United States, 2017. *MMWR Surveill Summ*. 2018;67:1–114.

Walston JD. Sarcopenia in older adults. *Curr Opin Rheumatol*. 2012;24:623–627.

Henschel B, Anna M, Gorczyca MS, Chomišek AK. Time Spent Sitting as an independent risk factor for cardiovascular disease. *Am J Lifestyle Med*. 2020;14(2):204–215.

Warren TY, Barry V, Hooker SP, Sui X, Church TS, Blair SN. Sedentary behaviors increase risk of cardiovascular disease mortality in men. *Med Sci Sports Exerc*. 2010;42:879–885.

Agarwal S, Steinmaus C, Harris-Adamson C. Sit-stand workstations and impact on low back discomfort: a systematic review and meta-analysis. *Ergonomics*. 2018;61:538–552.

Shrestha N, Grgic J, Wiesner G, et al. Effectiveness of interventions for reducing non-occupational sedentary behaviour in adults and older adults: a systematic review and meta-analysis. *Br J Sports Med*. 2019;53:1206–1213.

Richardson CR, Newton TL, Abraham JJ, Sen A, Jimbo M, Swartz AM. A meta-analysis of pedometer-based walking interventions and weight loss. *Ann Fam Med*. 2008;6:69–77.

Wycherley TP, Noakes M, Clifton PM, Cleanthous X, Keogh JB, Brinkworth GD. A high-protein diet with resistance exercise training improves weight loss and body composition in overweight and obese patients with type 2 diabetes. *Diabetes Care*. 2010;33:969–976.

Gappmaier E, Lake W, Nelson AG, Fisher AG. Aerobic exercise in water versus walking on land: effects on indices of fat reduction and weight loss of obese women. *J Sports Med Phys Fitness*. 2006;46:564–569.

Kodama S, Saito K, Tanaka S, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA*. 2009;301:2024–2035.

Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation*. 2014;129:S102–S138.

Kwon S, Janz KF, Letuchy EM, Burns TL, Levy SM. Active lifestyle in childhood and adolescence prevents obesity development in young adulthood. *Obesity (Silver Spring)*. 2015;23:2462–2469.

Carlin A, Murphy MH, Gallagher AM. Do interventions to increase walking work? A systematic review of interventions in children and adolescents. *Sports Med*. 2016;46:515–530.

O'Keefe JH, Vogel R, Lavie CJ, Cordain L. Exercise like a hunter-gatherer: a prescription for organic physical fitness. *Prog Cardiovasc Dis*. 2011;53:471–479.

Mesquita PR, Neri SGR, Lima RM, Carpes FP, de David AC. Childhood obesity is associated with altered plantar pressure distribution during running. *Gait Posture*. 2018;62:202–205.

Weston KS, Wisloff U, Coombes JS. High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: a systematic review and meta-analysis. *Br J Sports Med*. 2014;48:1227–1234.

MacInnis MJ, Gibala MJ. Physiological adaptations to interval training and the role of exercise intensity. *J Physiol*. 2017;595:2915–2930.

Karvonen MJ, Kentala E, Mustala O. The effects of training on heart rate; a longitudinal study. *Ann Med Exp Biol Fenn*. 1957;35:307–315.

Ainsworth BE, Haskell WL, Herrmann SD, et al. Compendium of physical activities: a second update of codes and MET values. *Med Sci Sports Exerc*. 2011;43:1575–1581.

Borg G. Borg's Perceived Exertion and Pain Scales. 1st ed. Champaign, IL: Human Kinetics; 1998.

Wasserman K. *Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications*. 5th ed. Philadelphia, Pa.; London: Wolters Kluwer/Lippincott Williams & Wilkins; 2012.

Lansley KE, Dimenna FJ, Bailey SJ, Jones AM. A 'new' method to normalise exercise intensity. *Int J Sports Med*. 2011;32:535–541.

Zaryski C, Smith DJ. Training principles and issues for ultra-endurance athletes. *Curr Sports Med Rep*. 2005;4:165–170.

Hoffman MD, Ong JC, Wang G. Historical analysis of participation in 161 km ultramarathons in North America. *Int J Hist Sport*. 2010;27:1877–1891.

O'Keefe J, Patil H, Lavie C, Magalski A, Vogel R, McCullough P. Potential adverse cardiovascular effects from excessive endurance exercise. *Mayo Clin Proc*. 2012;87:587–595.

George K, Whyte G, Green D, et al. The endurance athletes' heart: acute stress and chronic adaptation. *Br J Sports Med*. 2012;46:29–36.

Wilson M, O'Hanlon R, Prasad S, et al. Diverse patterns of myocardial fibrosis in lifelong, veteran endurance athletes. *J Appl Physiol*. 1985;110(2011):1622–1626.

Tiller NB. Pulmonary and respiratory muscle function in response to marathon and ultra-marathon running: a review. *Sports Med*. 2019;49:1031–1041.

de Oliveira EP, Burini RC. Carbohydrate-dependent, exercise-induced gastrointestinal distress. *Nutrients*. 2014;6:4191–4199.

Jeukendrup AE, Vet-Joop K, Sturk A, et al. Relationship between gastro-intestinal complaints and endotoxaemia, cytokine release and the acute-phase reaction during and after a long-distance triathlon in highly trained men. *Clin Sci (Lond)*. 2000;98:47–55.

Mach N, Fuster-Botella D. Endurance exercise and gut microbiota: a review. *J Sport Health Sci*. 2017;6:179.

Knechtle B, Nikolaidis PT. Physiology and pathophysiology in ultra-marathon running. *Front Physiol*. 2018;9:634.

Tiller NB, Stewart GM, Illidi CR, Levine BD. Exercise is medicine? Cardiorespiratory implications of ultramarathon running. *Curr Sports Med Rep*. 2020;19(8):290–297.

Larsen HB, Sheel AW. The Kenyan runners. *Scand J Med Sci Sports*. 2015;25(Suppl. 4):110–118.

Wilber RL, Pitsiladis YP. Kenyan and Ethiopian distance runners: what makes them so good? *Int J Sports Physiol Perform*. 2012;7:92–102.

Burke LM. Caffeine and sports performance. *Appl Physiol Nutr Metab*. 2008;33:1319–1334.

Yang A, Palmer AA, de Wit H. Genetics of caffeine consumption and responses to caffeine. *Psychopharmacology (Berl)*. 2010;211:245–257.

Huang ZL, Qu WM, Eguchi N, et al. Adenosine A2A, but not A1, receptors mediate the arousal effect of caffeine. *Nat Neurosci*. 2005;8:858–859.

Burke LM, Hawley JA, Jeukendrup A, Morton JP, Stellingwerff T, Maughan RJ. Toward a common understanding of diet-exercise strategies to manipulate fuel availability for training and competition preparation in endurance sport. *Int J Sport Nutr Exerc Metab*. 2018;28:451–463.

Jacobsen N, Melvaer KL, Hensten-Pettersen A. Some properties of salivary amylase: a survey of the literature and some observations. *J Dent Res*. 1972;51:381–388.

Mandel AL, Breslin PA. High endogenous salivary amylase activity is associated with improved glycemic homeostasis following starch ingestion in adults. *J Nutr*. 2012;142:853–858.

Goran MI, Walker R, Allayee H. Genetic-related and carbohydrate-related factors affecting liver fat accumulation. *Curr Opin Clin Nutr Metab Care*. 2012;15:392–396.

Cha S, Kang JH, Lee JH, et al. Impact of genetic variants on the individual potential for body fat loss. *Nutrients*. 2018;10. <https://doi.org/10.3390/nu10030266>.

Puthuchery Z, Skipworth JR, Rawal J, Loosemore M, Van Someren K, Montgomery HE. The ACE gene and

human performance: 12 years on. *Sports Med.* 2011;41:433–448.

Amir O, Amir R, Yamin C, et al. The ACE deletion allele is associated with Israeli elite endurance athletes. *Exp Physiol.* 2007;92(5):881–886.

Kim CH, Cho JY, Jeon JY, et al. ACE DD genotype is unfavorable to Korean short-term muscle power athletes. *Int J Sports Med.* 2010;31(1):65–71.

Riviere G, Lienhard D, Andrieu T, Vieau D, Frey BM, Frey FJ. Epigenetic regulation of somatic angiotensin-converting enzyme by DNA methylation and histone acetylation. *Epigenetics.* 2011;6(4):478–489.

Sharp NC. The human genome and sport, including epigenetics, gene doping, and athletic genomics. *Endocrinol Metab Clin North Am.* 2010;39(1):201–215.

Chapter 2

Hotchkiss RD. The quantitative separation of purines, pyrimidines, and nucleosides by paper chromatography. *J Biol Chem.* 1948;175(1):315–332.

Moore LD, Le T, Fan G. DNA methylation and its basic function. *Neuropsychopharmacology.* 2013;38(1):23–38.

Edwards JR, Yarychivska O, Boulard M, Bestor TH. DNA methylation and DNA methyltransferases.

Epigenetics Chromatin. 2017;10:23–28.

Strachan T, Reid T. *Human Molecular Genetics.* 4th ed. Taylor and Francis Group; 2011.

Tan L, Shi YG. Tet family proteins and 5-hydroxymethylcytosine in development and disease. *Development.* 2012;139(11):1895–1902.

Kroeze LI, van der Reijden B, Jansen JH. 5-hydroxymethylcytosine: an epigenetic mark frequently deregulated in cancer. *Biochim Biophys Acta.* 2015;1855(2):144–154.

Zheng H, Zhou X, Li DK, et al. Genome-wide alteration in DNA hydroxymethylation in the sperm from bisphenol A-exposed men. *PLoS One.* 2017;12(6), e0178535.

Deaton AM, Bird A. CpG islands and the regulation of transcription. *Genes Dev.* 2011;25(10):1010–1022.

Illingworth RS, Bird AP. CpG islands—'a rough guide'. *FEBS Lett.* 2009;583(11):1713–1720.

Field AE, Robertson NA, Wang T, Havas A, Ideker T, Adams PD. DNA methylation clocks in aging: categories, causes, and consequences. *Mol Cell.* 2018;71(6):882–895.

Nile CJ, Read RC, Akil M, Duff GW, Wilson AG. Methylation status of a single CpG site in the IL6 promoter is related to IL6 messenger RNA levels and rheumatoid arthritis. *Arthritis Rheum.* 2008;58(9):2686–2693.

Rickaby R, El Khoury LY, Samiric T, Raleigh SM. Epigenetic status of the human MMP11 gene promoter is altered in patellar tendinopathy. *J Sports Sci Med.* 2019;18(1):155–159.

Cui H, Cruz-Correa M, Giardiello FM, et al. Loss of IGF2 imprinting: a potential marker of colorectal cancer risk. *Science.* 2003;299(5613):1753–1755.

Sferruzzi-Perri AN. Regulating needs: exploring the role of insulin-like growth factor-2 signalling in maternofetal resource allocation. *Placenta.* 2018;64(Suppl 1):S16–S22.

Do EK, Zucker NL, Huang ZY, et al. Associations between imprinted gene differentially methylated regions, appetitive traits and body mass index in children. *Pediatr Obes.* 2019;14, e12454.

Damaschke NA, Yang B, Bhusari S, et al. Loss of Igf2 gene imprinting in murine prostate promotes widespread neoplastic growth. *Cancer Res.* 2017;77(19):5236–5247.

Bergman D, Halje M, Nordin M, Engstrom W. Insulin-like growth factor 2 in development and disease: a mini-review. *Gerontology.* 2013;59(3):240–249.

Anunziato A. DNA packaging: nucleosomes and chromatin. *Nat Educ.* 2008;1(1):26.

Shahid Z, Simpson B, Singh G. Genetics, histone code. In: *StatPearls.* Treasure Island, FL: StatPearls Publishing LLC; 2019.

Berger SL. Gene activation by histone and factor acetyltransferases. *Curr Opin Cell Biol.* 1999;11(3):336–341.

Saha A, Wittmeyer J, Cairns BR. Chromatin remodelling: the industrial revolution of DNA around histones. *Nat Rev Mol Cell Biol.* 2006;7(6):437–447.

Iwasaki W, Miya Y, Horikoshi N, et al. Contribution of histone N-terminal tails to the structure and stability of nucleosomes. *FEBS Open Bio.* 2013;3:363–369.

Berg JM, Tymoczko JL, Stryer L. *Biochemistry.* 6th ed. New York, NY: W. H. Freeman; 2006.

Rahhal R, Seto E. Emerging roles of histone modifications and HDACs in RNA splicing. *Nucleic Acids Res.* 2019;47(10):4911–4926.

Brown. *Genomes.* 3rd ed. Garland Science; 2006.

Meas R, Mao P. Histone ubiquitylation and its roles in transcription and DNA damage response. *DNA Repair (Amst).* 2015;36:36–42.

Panni S, Prakash A, Bateman A, Orchard S. The yeast noncoding RNA interaction network. *RNA.* 2017;23(10):1479–1492.

Zhang P, Wu W, Chen Q, Chen M. Non-coding RNAs and their integrated networks. *J Integr Bioinform.* 2019. <https://doi.org/10.1515/jib-2019-0027>.

Wei JW, Huang K, Yang C, Kang CS. Non-coding RNAs as regulators in epigenetics (review). *Oncol Rep.* 2017;37(1):3–9.

Lee RC, Feinbaum RL, Ambros V. The *C. elegans* heterochronic gene *lin-4* encodes small RNAs with antisense complementarity to *lin-14*. *Cell.* 1993;75(5):843–854.

Reinhart BJ, Slack FJ, Basson M, et al. The 21-nucleotide *let-7* RNA regulates developmental timing in *Caenorhabditis elegans*. *Nature.* 2000;403(6772):901–906.

Pasquinelli AE, Reinhart BJ, Slack F, et al. Conservation of the sequence and temporal expression of *let-7* heterochronic regulatory RNA. *Nature.* 2000;408(6808):86–89.

Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell.* 2004;116(2):281–297.

O'Brien J, Hayder H, Zayed Y, Peng C. Overview of MicroRNA biogenesis, mechanisms of actions, and circulation. *Front Endocrinol (Lausanne).* 2018;9:402.

Lee Y, Kim M, Han J, et al. MicroRNA genes are transcribed by RNA polymerase II. *EMBO J.* 2004;23(20):4051–4060.

Wahid F, Shehzad A, Khan T, Kim YY. MicroRNAs: synthesis, mechanism, function, and recent clinical trials. *Biochim Biophys Acta.* 2010;1803(11):1231–1243.

Michlewski G, Caceres JF. Post-transcriptional control of miRNA biogenesis. *RNA.* 2019;25(1):1–16.

Rana TM. Illuminating the silence: understanding the structure and function of small RNAs. *Nat Rev Mol Cell Biol.* 2007;8(1):23–36.

Bartel DP. MicroRNAs: target recognition and regulatory functions. *Cell.* 2009;136(2):215–233.

Bink DI, Lozano-Vidal N, Boon RA. Long non-coding RNA in vascular disease and aging. *Noncoding RNA.* 2019;5(1):10.

Ma L, Cao J, Liu L, et al. LncBook: a curated knowledgebase of human long non-coding RNAs. *Nucleic Acids Res.* 2019;47(D1):D128–D134.

Dykes IM, Emanuelli C. Transcriptional and post-transcriptional gene regulation by long non-coding RNA. *Genomics Proteomics Bioinformatics.* 2017;15(3):177–186.

Miao Y, Ajami NE, Huang TS, et al. Enhancer-associated long non-coding RNA LEENE regulates endothelial nitric oxide synthase and endothelial function. *Nat Commun.* 2018;9(1), 292-y.

Romero-Barrios N, Legascue MF, Benhamed M, Ariel F, Crespi M. Splicing regulation by long noncoding RNAs. *Nucleic Acids Res.* 2018;46(5):2169–2184.

Tripathi V, Shen Z, Chakraborty A, et al. Long noncoding RNA MALAT1 controls cell cycle progression by regulating the expression of oncogenic transcription factor B-MYB. *PLoS Genet.* 2013;9(3):1–18.

- Kung JT, Colognori D, Lee JT. Long noncoding RNAs: past, present, and future. *Genetics*. 2013;193(3):651–669.
- Ng K, Pullirsch D, Leeb M, Wutz A. Xist and the order of silencing. *EMBO Rep*. 2007;8(1):34–39.
- Jarroux J, Morillon A, Pinskaya M. History, discovery, and classification of lncRNAs. *Adv Exp Med Biol*. 2017;1008:1–46.
- Borkowetz A. Screening for prostate cancer using prostate-specific antigen (PSA): a commentary on a systematic review and meta-analysis. *Urologe A*. 2019;58(8):925–928.
- Valadi H, Ekström K, Bossios A, Sjöstrand M, Lee JJ, Lotvall JO. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. *Nat Cell Biol*. 2007;9(6):654–659.
- Di Pietro V, Porto E, Ragusa M, et al. Salivary MicroRNAs: diagnostic markers of mild traumatic brain injury in contact-sport. *Front Mol Neurosci*. 2018;11:290.
- Azad NS, El-Khoueiry A, Yin J, et al. Combination epigenetic therapy in metastatic colorectal cancer (mCRC) with subcutaneous 5-azacitidine and entinostat: a phase 2 consortium/stand up 2 cancer study. *Oncotarget*. 2017;8(21):35326–35338.
- Juergens RA, Wrangle J, Vendetti FP, et al. Combination epigenetic therapy has efficacy in patients with refractory advanced non-small cell lung cancer. *Cancer Discov*. 2011;1(7):598–607.
- Caroli A, Cardillo MT, Galea R, Biasucci LM. Potential therapeutic role of microRNAs in ischemic heart disease. *J Cardiol*. 2013;61(5):315–320.
- Lolli A, Sivasubramanian K, Vainieri ML, et al. Hydrogel-based delivery of anti-miR-221 enhances cartilage regeneration by endogenous cells. *J Control Release*. 2019;309:220–230.
- Sun P, Liu DZ, Jickling GC, Sharp FR, Yin KJ. MicroRNA-based therapeutics in central nervous system injuries. *J Cereb Blood Flow Metab*. 2018;38(7):1125–1148.
- van Rooij E, Marshall WS, Olson EN. Toward microRNA-based therapeutics for heart disease: the sense in anti-sense. *Circ Res*. 2008;103(9):919–928.
- Watts AE, Millar NL, Platt J, et al. MicroRNA29a treatment improves early tendon injury. *Mol Ther*. 2017;25(10):2415–2426.
- Meyer KD, Jaffrey SR. The dynamic epitranscriptome: N6-methyladenosine and gene expression control. *Nat Rev Mol Cell Biol*. 2014;15(5):313–326.
- Narayan P, Rottman FM. An in vitro system for accurate methylation of internal adenosine residues in messenger RNA. *Science*. 1988;242(4882):1159–1162.
- Harper JE, Miceli SM, Roberts RJ, Manley JL. Sequence specificity of the human mRNA N6-adenosine methylase in vitro. *Nucleic Acids Res*. 1990;18(19):5735–5741.
- Li J, Yang X, Qi Z, et al. The role of mRNA m(6)A methylation in the nervous system. *Cell Biosci*. 2019;9, 66-y [eCollection 2019].
- Jia G, Fu Y, Zhao X, et al. N6-methyladenosine in nuclear RNA is a major substrate of the obesity-associated FTO. *Nat Chem Biol*. 2011;7(12):885–887.
- Zheng G, Dahl JA, Niu Y, et al. ALKBH5 is a mammalian RNA demethylase that impacts RNA metabolism and mouse fertility. *Mol Cell*. 2013;49(1):18–29.
- Dominissini D, Moshitch-Moshkovitz S, Amariglio N, Rechavi G. Transcriptome-wide mapping of N(6)methyladenosine by m(6)A-seq. *Methods Enzymol*. 2015;560:131–147.
- Heilman KL, Leach RA, Tuck MT. Internal 6-methyladenine residues increase the in vitro translation efficiency of dihydrofolate reductase messenger RNA. *Int J Biochem Cell Biol*. 1996;28(7):823–829.
- Chen T, Hao YJ, Zhang Y, et al. M(6)A RNA methylation is regulated by microRNAs and promotes reprogramming to pluripotency. *Cell Stem Cell*. 2015;16(3):289–301.
- Tavassoly I, Goldfarb J, Iyengar R. Systems biology primer: the basic methods and approaches. *Essays Biochem*. 2018;62(4):487–500.

Assmann TS, Milagro FI, Martinez JA. Crosstalk between microRNAs, the putative target genes and the lncRNA network in metabolic diseases. *Mol Med Rep.* 2019;20(4):3543–3554.

Bianchi M, Renzini A, Adamo S, Moresi V. Coordinated actions of MicroRNAs with other epigenetic factors regulate skeletal muscle development and adaptation. *Int J Mol Sci.* 2017;18(4). <https://doi.org/10.3390/ijms18040840>.

Su Z, Xia J, Zhao Z. Functional complementation between transcriptional methylation regulation and posttranscriptional microRNA regulation in the human genome. *BMC Genomics.* 2011;12(Suppl 5):S15 [Epub 2011 Dec 23].

Chapter 3

Heinemeier KM, Lorentzen MP, Jensen JK, et al. Local trauma in human patellar tendon leads to widespread changes in the tendon gene expression. *J Appl Physiol.* 2016;120:1000–1010. <https://doi.org/10.1152/jappphysiol.00870.2015>.

Sadakierska-Chudy A, Filip M. A comprehensive view of the epigenetic landscape. Part II: histone posttranslational modification, nucleosome level, and chromatin regulation by ncRNAs. *Neurotox Res.* 2015;27:172–197. <https://doi.org/10.1007/s12640-014-9508-6>.

Hull JHK, Ansley P, Ansley L. Human Tissue Act: implications for sports science. *Br J Sports Med.* 2008;42:236–237. <https://doi.org/10.1136/bjism.2007.043307>.

Green ED, Guyer MS. Charting a course for genomic medicine from base pairs to bedside. *Nature.* 2011;470:204–213. <https://doi.org/10.1038/nature09764>.

Williams A, Miah A, Harris R, Montgomery H, Wackerhage H. The BASES expert statement on genetic research and testing in sport and exercise science; 2012. [WWW Document]. URL <http://www.bases.org.uk/write/Images/williams14-15.pdf>.

Vlahovich N, Fricker PA, Brown MA, Hughes D. Ethics of genetic testing and research in sport: a position statement from the Australian Institute of Sport. *Br J Sports Med.* 2017;51:5–11. <https://doi.org/10.1136/bjsports-2016-096661>.

Green RC, Berg JS, Grody WW, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med.* 2013;15:565–574. <https://doi.org/10.1038/gim.2013.73>.

Morgenstern J, Hegele RA, Nisker J. Simple genetics language as source of miscommunication between genetics researchers and potential research participants in informed consent documents. *Public Underst Sci.* 2015;24:751–766. <https://doi.org/10.1177/0963662514528439>.

Joyce NC, Oskarsson B, Jin L-W. Muscle biopsy evaluation in neuromuscular disorders. *Phys Med Rehabil Clin N Am.* 2012;23:609–631. <https://doi.org/10.1016/j.pmr.2012.06.006>.

Greene J, Louis J, Korostynska O, Mason A. State-of-the-art methods for skeletal muscle glycogen analysis in athletes—the need for novel non-invasive techniques. *Biosensors.* 2017;7:11. <https://doi.org/10.3390/bios7010011>.

Jones GC, Corps AN, Pennington CJ, et al. Expression profiling of metalloproteinases and tissue inhibitors of metalloproteinases in normal and degenerate human achilles tendon. *Arthritis Rheum.* 2006;54:832–842. <https://doi.org/10.1002/art.21672>.

Karousou E, Ronga M, Vigetti D, Passi A, Maffulli N. Collagens, proteoglycans, MMP-2, MMP-9 and TIMPs in human achilles tendon rupture RID C-9861-2010. *Clin Orthop Relat Res.* 2008;466:1577–1582. <https://doi.org/10.1007/s11999-008-0255-y>.

Parkinson J, Samiric T, Ilic MZ, Cook J, Feller JA, Handley CJ. Change in proteoglycan metabolism is a characteristic of human patellar tendinopathy. *Arthritis Rheum.* 2010;62:3028–3035.

Antequera F. Structure, function and evolution of CpG island promoters. *Cell Mol Life Sci.* 2003;60:1647–1658. <https://doi.org/10.1007/s00018-003-3088-6>.

Jeziorska DM, Murray RJS, De Gobbi M, et al. DNA methylation of intragenic CpG islands depends on their transcriptional activity during differentiation and disease. *Proc Natl Acad Sci.* 2017;114:E7526–E7535.

<https://doi.org/10.1073/PNAS.1703087114>.

Nagarajan RP, Fouse SD, Bell RJA, Costello JF. Methods for cancer epigenome analysis. *Adv Exp Med Biol*. 2013;754:313–338. https://doi.org/10.1007/978-1-4419-9967-2_15.

Ulahannan N, Grealley JM. Genome-wide assays that identify and quantify modified cytosines in human disease studies. *Epigenetics Chromatin*. 2015;8:5. <https://doi.org/10.1186/1756-8935-8-5>.

Khulan B, Thompson RF, Ye K, et al. Comparative isoschizomer profiling of cytosine methylation: the HELP assay. *Genome Res*. 2006;16:1046–1055. <https://doi.org/10.1101/gr.5273806>.

Oda M, Glass JL, Thompson RF, et al. High-resolution genome-wide cytosine methylation profiling with simultaneous copy number analysis and optimization for limited cell numbers. *Nucleic Acids Res*. 2009;37:3829–3839. <https://doi.org/10.1093/nar/gkp260>.

Kurdyukov S, Bullock M. DNA methylation analysis: choosing the right method. *Biology (Basel)*. 2016;5:3. <https://doi.org/10.3390/biology5010003>.

Yong W-S, Hsu F-M, Chen P-Y. Profiling genome-wide DNA methylation. *Epigenetics Chromatin*. 2016;9:26. <https://doi.org/10.1186/s13072-016-0075-3>.

Teh AL, Pan H, Lin X, et al. Comparison of methyl-capture sequencing vs. Infinium 450K methylation array for methylome analysis in clinical samples. *Epigenetics*. 2016;11:36–48. <https://doi.org/10.1080/15592294.2015.1132136>.

Menyhárt O, Harami-Papp H, Sukumar S, et al. Guidelines for the selection of functional assays to evaluate the hallmarks of cancer. *Biochim Biophys Acta Rev Cancer*. 2016;1866:300–319. <https://doi.org/10.1016/J.BB-CAN.2016.10.002>.

Robinson MD, Stirzaker C, Statham AL, et al. Evaluation of affinity-based genome-wide DNA methylation data: effects of CpG density, amplification bias, and copy number variation. *Genome Res*. 2010;20:1719–1729. <https://doi.org/10.1101/gr.110601.110>.

Pelizzola M, Koga Y, Urban AE, et al. MEDME: an experimental and analytical methodology for the estimation of DNA methylation levels based on microarray derived MeDIP-enrichment. *Genome Res*. 2008;18:1652–1659. <https://doi.org/10.1101/gr.080721.108>.

Wilson GA, Beck S. Computational analysis and integration of MeDIP-Seq methylome data. In: Kulski, ed. *Next Generation Sequencing: Advances, Applications and Challenges*. InTech; 2016.

Down TA, Rakyan VK, Turner DJ, et al. A Bayesian deconvolution strategy for immunoprecipitation-based DNA methylome analysis. *Nat Biotechnol*. 2008;26:779–785. <https://doi.org/10.1038/nbt1414>.

Chavez L, Jozefczuk J, Grimm C, et al. Computational analysis of genome-wide DNA methylation during the differentiation of human embryonic stem cells along the endodermal lineage. *Genome Res*. 2010;20:1441–1450. <https://doi.org/10.1101/gr.110114.110>.

Rauch T, Li H, Wu X, Pfeifer GP. MIRA-assisted microarray analysis, a new technology for the determination of DNA methylation patterns, identifies frequent methylation of homeodomain-containing genes in lung cancer cells. *Cancer Res*. 2006;66:7939–7947. <https://doi.org/10.1158/0008-5472.CAN-06-1888>.

Olkhov-Mitsel E, Bapat B. Strategies for discovery and validation of methylated and hydroxymethylated DNA biomarkers. *Cancer Med*. 2012;1:237–260. <https://doi.org/10.1002/cam4.22>.

Harris RA, Wang T, Coarfa C, et al. Comparison of sequencing-based methods to profile DNA methylation and identification of monoallelic epigenetic modifications. *Nat Biotechnol*. 2010;28:1097–1105. <https://doi.org/10.1038/nbt.1682>.

Bock C, Tomazou EM, Brinkman AB, et al. Quantitative comparison of genome-wide DNA methylation mapping technologies. *Nat Biotechnol*. 2010;28:1106–1114. <https://doi.org/10.1038/nbt.1681>.

Beikircher G, Pulverer W, Hofner M, Noehammer C, Weinhaeusel A. Multiplexed and Sensitive DNA Methylation Testing Using Methylation-Sensitive Restriction Enzymes “MSRE-qPCR”. New York, NY: Humana Press; 2018:407–424. https://doi.org/10.1007/978-1-4939-7481-8_21.

Lizardi PM, Yan Q, Wajapeyee N. DNA bisulfite sequencing for single-nucleotide-resolution DNA methylation detection. *Cold Spring Harb Protoc.* 2017;2017. <https://doi.org/10.1101/pdb.prot094839>. *pdb. prot094839*.

Raine A, Liljedahl U, Nordlund J. Data quality of whole genome bisulfite sequencing on Illumina platforms. *PLoS One.* 2018;13. <https://doi.org/10.1371/journal.pone.0195972>, e0195972.

Lövkvißt C, Dodd IB, Sneppen K, Haerter JO. DNA methylation in human epigenomes depends on local topology of CpG sites. *Nucleic Acids Res.* 2016;44:5123–5132. <https://doi.org/10.1093/nar/gkw124>.

Lišter R, O'Malley RC, Tonti-Filippini J, et al. Highly integrated single-base resolution maps of the epigenome in *Arabidopsis*. *Cell.* 2008;133:523–536. <https://doi.org/10.1016/J.CELL.2008.03.029>.

Lišter R, Pelizzola M, Downen RH, et al. Human DNA methylomes at base resolution show widespread epigenomic differences. *Nature.* 2009;462:315–322. <https://doi.org/10.1038/nature08514>.

Grehl C, Kuhlmann M, Becker C, Glaser B, Grosse I. How to design a whole-genome bisulfite sequencing experiment. *Epigenomes.* 2018;2(4):21. <https://doi.org/10.3390/epigenomes2040021>.

Miura F, Enomoto Y, Dairiki R, Ito T. Amplification-free whole-genome bisulfite sequencing by post-bisulfite adaptor tagging. *Nucleic Acids Res.* 2012;40:e136. <https://doi.org/10.1093/nar/gks454>.

Chervova O, Conde L, Guerra-Assunção JA, et al. The Personal Genome Project-UK, an open access resource of human multi-omics data. *Sci Data.* 2019;6:257. <https://doi.org/10.1038/s41597-019-0205-4>.

Consortium P-U. Personal Genome Project UK (PGP-UK): a research and citizen science hybrid project in support of personalized medicine. *BMC Med Genomics.* 2018;11:108. <https://doi.org/10.1186/s12920-018-0423-1>.

Volkov P, Bacos K, Ofori JK, et al. Whole-genome bisulfite sequencing of human pancreatic islets reveals novel differentially methylated regions in type 2 diabetes pathogenesis. *Diabetes.* 2017;66:1074–1085. <https://doi.org/10.2337/db16-0996>.

Meissner A, Gnirke A, Bell G, Ramsahoye B, Lander E, Jaenisch R. Reduced representation bisulfite sequencing for comparative high-resolution DNA methylation analysis. *Nucleic Acids Res.* 2005;33(18):5868–5877. <https://doi.org/10.1093/nar/gki901>.

Krueger F, Andrews SR. Bismark: a flexible aligner and methylation caller for Bisulfite-Seq applications. *Bioinformatics.* 2011;27:1571–1572. <https://doi.org/10.1093/bioinformatics/btr167>.

Xi Y, Bock C, Müller F, Sun D, Meissner A, Li W. RRBSMAP: a fast, accurate and user-friendly alignment tool for reduced representation bisulfite sequencing. *Bioinformatics.* 2012;28:430–432. <https://doi.org/10.1093/bioinformatics/btr668>.

Ziller MJ, Müller F, Liao J, et al. Genomic distribution and inter-sample variation of non-CpG methylation across human cell types. *PLoS Genet.* 2011;7. <https://doi.org/10.1371/journal.pgen.1002389>, e1002389.

Gel B, Serra E. karyoplote R: an R/Bioconductor package to plot customizable genomes displaying arbitrary data. *Bioinformatics.* 2017;33:3088–3090. <https://doi.org/10.1093/bioinformatics/btx346>.

Sandoval J, Heyn H, Moran S, et al. Validation of a DNA methylation microarray for 450,000 CpG sites in the human genome. *Epigenetics.* 2011;6:692–702. <https://doi.org/10.4161/epi.6.6.16196>.

Moran S, Arribas C, Esteller M. Validation of a DNA methylation microarray for 850,000 CpG sites of the human genome enriched in enhancer sequences. *Epigenomics.* 2016;8:389–399. <https://doi.org/10.2217/epi.15.114>.

Pidsley R, Wong CCY, Volta M, Lunnon K, Mill J, Schalkwyk LC. A data-driven approach to preprocessing Illumina 450K methylation array data. *BMC Genomics.* 2013;14:293. <https://doi.org/10.1186/1471-2164-14-293>.

Maksimovic J, Gordon L, Oshlack A. SWAN: subset-quantile within array normalization for Illumina Infinium HumanMethylation450 BeadChips. *Genome Biol.* 2012;13:R44. <https://doi.org/10.1186/gb-2012-13-6-r44>.

Suchiman HED, Sliker RC, Kremer D, Slagboom PE, Heijmans BT, Tobi EW. Design, measurement and processing of region-specific DNA methylation assays: the mass spectrometry-based method EpiTYPER. *Front Genet.* 2015;6:287. <https://doi.org/10.3389/fgene.2015.00287>.

Ambardar S, Gupta R, Trakroo D, Lal R, Vakhlu J. High throughput sequencing: an overview of sequencing chem-

istry. *Indian J Microbiol.* 2016;56:394–404. <https://doi.org/10.1007/s12088-016-0606-4>.

Busato F, Dejeux E, El Abdalaoui H, Gut IG, Tošć J. *Quantitative DNA Methylation Analysis at SingleNucleotide Resolution by Pyrosequencing®*. New York, NY: Humana Press; 2018:427–445. https://doi.org/10.1007/978-1-4939-7481-8_22.

Poulin M, Zhou JY, Yan L, Shioda T. *Pyrosequencing Methylation Analysis*. New York, NY: Humana Press; 2018:283–296. https://doi.org/10.1007/978-1-4939-8751-1_17.

Alnaes G, Ronneberg J, Kristensen V, Tošć J. Heterogeneous DNA methylation patterns in the GSTP1 promoter lead to discordant results between assay technologies and impede its implementation as epigenetic biomarkers in breast cancer. *Genes (Basel)*. 2015;6:878–900. <https://doi.org/10.3390/genes6030878>.

Lehmann U. Quantitative validation and quality control of Pyrosequencing® assays. *Methods Mol Biol.* 2015;39–46. https://doi.org/10.1007/978-1-4939-2715-9_4.

Quillien V, Lavenu A, Ducray F, et al. Validation of the high-performance of pyrosequencing for clinical MGMT testing on a cohort of glioblastoma patients from a prospective dedicated multicentric trial. *Oncotarget.* 2016;7:61916–61929. <https://doi.org/10.18632/oncotarget.11322>.

Moison C, Assemat F, Daunay A, Arimondo PB, Tošć J. DNA methylation analysis of ChIP products at single nucleotide resolution by Pyrosequencing®. *Methods Mol Biol.* 2015;315–333. https://doi.org/10.1007/978-1-4939-2715-9_22.

Kreutz M, Schock G, Kaiser J, Hochstein N, Peišt R. *PyroMark® Instruments, Chemistry, and Software for Pyrosequencing® Analysis*. New York, NY: Humana Press; 2015:17–27. https://doi.org/10.1007/978-1-4939-2715-9_2.

Park PJ. ChIP-seq: advantages and challenges of a maturing technology. *Nat Rev Genet.* 2009;10:669–680. <https://doi.org/10.1038/nrg2641>.

Pellegrini M, Ferrari R. *Epigenetic Analysis: ChIP-chip and ChIP-seq*. Humana Press; 2012:377–387. https://doi.org/10.1007/978-1-61779-400-1_25.

Pott S, Lieb JD. What are super-enhancers? *Nat Genet.* 2015;47:8–12. <https://doi.org/10.1038/ng.3167>.

Marinov GK. A decade of ChIP-seq. *Brief Funct Genomics.* 2018;17:77–79. <https://doi.org/10.1093/bfpg/ely012>.

Dahl JA, Gilfillan GD. How low can you go? Pushing the limits of low-input ChIP-seq. *Brief Funct Genomics.* 2018;17:89–95. <https://doi.org/10.1093/bfpg/elx037>.

Langmead B, Salzberg SL. Fast gapped-read alignment with Bowtie 2. *Nat Methods.* 2012;9:357–359. <https://doi.org/10.1038/nmeth.1923>.

Zheng Y, Liu L, Shukla GC. A comprehensive review of web-based non-coding RNA resources for cancer research. *Cancer Lett.* 2017;407:1–8. <https://doi.org/10.1016/J.CANLET.2017.08.015>.

Zhao S, Fung-Leung W-P, Bittner A, Ngo K, Liu X. Comparison of RNA-Seq and microarray in transcriptome profiling of activated T cells. *PLoS One.* 2014;9. <https://doi.org/10.1371/journal.pone.0078644>, e78644.

Ma F, Fuqua BK, Hasin Y, et al. A comparison between whole transcript and 3' RNA sequencing methods using Kapa and Lexogen library preparation methods. *BMC Genomics.* 2019;20:9. <https://doi.org/10.1186/s12864-018-5393-3>.

Mantione KJ, Kream RM, Kuzelova H, et al. Comparing bioinformatic gene expression profiling methods: microarray and RNA-Seq. *Med Sci Monit Basic Res.* 2014;20:138–142. <https://doi.org/10.12659/MSMBR.892101>.

Byron SA, Van Keuren-Jensen KR, Engelthaler DM, Carpten JD, Craig DW. Translating RNA sequencing into clinical diagnostics: opportunities and challenges. *Nat Rev Genet.* 2016;17:257–271. <https://doi.org/10.1038/nrg.2016.10>.

Chapter 4

Kanherkar RR, Bhatia-dey N, Csoka AB. Epigenetics across the human lifespan. *Front Cell Dev Biol.* 2014;2:1–19. <https://doi.org/10.3389/fcell.2014.00049>.

Kucharski R, Maleszka J, Foret S, Maleszka R. Nutritional control of reproductive status in honeybees via DNA methylation. *Science.* 2008;319(5871):1827–1830. <https://doi.org/10.1126/science.1153069>.

Waterland RA, Jirtle RL. Transposable elements: targets for early nutritional effects on epigenetic gene regulation. *Mol Cell Biol.* 2003;23(15):5293–5300. <https://doi.org/10.1128/MCB.23.15.5293-5300.2003>.

Mandy M, Nyirenda M, Nyirenda M. Developmental origins of health and disease: the relevance to developing nations. *Int Health.* 2018;10:66–70. <https://doi.org/10.1093/inthealth/ihy006>.

Gluckman PD, Hanson MA. Developmental origins of disease paradigm: a mechanistic and evolutionary perspective. *Pediatr Res.* 2004;56(3):311–317. <https://doi.org/10.1203/01.PDR.0000135998.08025.FB>.

Lee H-S, Barraza-Villarreal A, Hernandez-Vargas H, et al. Modulation of DNA methylation states and infant immune system by dietary supplementation with ω -3 PUFA during pregnancy in an intervention study. *Am J Clin Nutr.* 2013;98(2):480–487. <https://doi.org/10.3945/ajcn.112.052241>. United States.

Benayoun BA, Pollina EA, Brunet A. Epigenetic regulation of ageing: linking environmental inputs to genomic stability. *Nat Rev Mol Cell Biol.* 2015;16(10):593–610. <https://doi.org/10.1038/nrm4048>. Nature Publishing Group.

Brunet A, Berger SL. Epigenetics of aging and aging-related disease. *J Gerontol A Biol Sci Med Sci.* 2014;69(Suppl 1):S17–S20. <https://doi.org/10.1093/gerona/glu042>.

Park LK, Friso S, Choi S-W. Nutritional influences on epigenetics and age-related disease. *Proc Nutr Soc.* 2012;71(1):75–83. <https://doi.org/10.1017/S0029665111003302>.

Portela A, Esteller M. Epigenetic modifications and human disease. *Nat Biotechnol.* 2010;28(10):1057–1068. <https://doi.org/10.1038/nbt.1685>. Nature Publishing Group.

Smith TW, Orleans CT, Jenkins CD. Prevention and health promotion: decades of progress, new emerging challenges and an emerging agenda. *Health Psychol.* 2004;23(2):126–131. <https://doi.org/10.1037/0278-6133.23.2.126>.

Vogelberg FR, Isaacson Barash C, Pursel M. Personalized medicine: part 1: evolution and development into therapeutics. *P T.* 2010;35(10):560–576.

NIH. What is Genomic Medicine? National Human Genome Research Institute; 2018. Available at: <https://www.genome.gov/27552451/what-is-genomic-medicine/>. Accessed 23 September 2018.

The Academy of Medical Sciences. Stratified, Personalised or P4 Medicine: A New Direction for Placing the Patient at the Centre of Healthcare and Health Education; 2015.

Campión J, Milagro FI, Goyenechea E, Martínez JA. TNF- α promoter methylation as a predictive biomarker for weight-loss response. *Obesity.* 2009;17(6):1293–1297. <https://doi.org/10.1038/oby.2008.679>. Nature Publishing Group.

Altucci L, Rots MG. Epigenetic drugs : from chemistry via biology to medicine and back. *Clin Epigenetics.* 2016;5–7. <https://doi.org/10.1186/s13148-016-0222-5>.

Clarke TC, Black LI, Stussman BJ, Barnes PM, Nahin RL. Trends in the use of complementary health approaches among adults: United States, 2002–2012; 2015. National health statistics reports.

Hussey B, Lindley MR, Maštana SS. Omega 3 fatty acids, inflammation and DNA methylation: an overview. *Clin Lipidol.* 2017;12:1.

Jones PA, Takai D. The role of DNA methylation in mammalian epigenetics. *Science (New York, NY).* 2001;293(5532):1068–1070. <https://doi.org/10.1126/science.1063852>.

Bird A. DNA methylation patterns and epigenetic memory. *Genes Dev.* 2002;16(1):6–21. <https://doi.org/10.1101/gad.947102>.

Breiling A, Lyko F. Epigenetic regulatory functions of DNA modifications: 5-methylcytosine and beyond. *Epi-*

genetics Chromatin. 2015;8(1):24. <https://doi.org/10.1186/s13072-015-0016-6>. BioMed central.

Lam LL, Emberly E, Fraser HB, et al. Factors underlying variable DNA methylation in a human community cohort. *Proc Natl Acad Sci*. 2012;109(Suppl_2):17253–17260. <https://doi.org/10.1073/pnas.1121249109>.

Bacalini MG, Friso S, Olivieri F, et al. Present and future of anti-ageing epigenetic diets. *Mech Ageing Dev*. 2014;136–137:101–115. <https://doi.org/10.1016/j.mad.2013.12.006>. Elsevier Ireland Ltd.

Choi S-W, Friso S. Epigenetics: a new bridge between nutrition and health. *Adv Nutr*. 2010;1(1):8–16. <https://doi.org/10.3945/an.110.1004>.

Gomes MVM, Toffoli LV, Arruda DW, et al. Age-related changes in the global DNA methylation profile of leukocytes are linked to nutrition but are not associated with the MTHFR C677T genotype or to functional capacities. *PLoS One*. 2012;7(12):e52570. <https://doi.org/10.1371/journal.pone.0052570>. Edited by H. Suzuki.

Joyce BT, Gao T, Liu L, et al. Longitudinal study of DNA methylation of inflammatory genes and cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2015. <https://doi.org/10.1158/1055-9965.EPI-15-0198>.

Prokhortchouk E, Defossez PA. The cell biology of DNA methylation in mammals. *Biochim Biophys Acta*. 2008;1783(11):2167–2173. <https://doi.org/10.1016/j.bbamcr.2008.07.015>.

Goll MG, Kirpekar F, Maggert KA, et al. Methylation of tRNAAsp by the DNA methyltransferase homolog Dnmt2. *Science (New York, NY)*. 2006;311(5759):395–398. <https://doi.org/10.1126/science.1120976>.

Gros C, Fahy J, Halby L, et al. DNA methylation inhibitors in cancer: recent and future approaches. *Biochimie*. 2012;94(11):2280–2296. <https://doi.org/10.1016/j.biochi.2012.07.025>. Elsevier Masson SAS.

Moore LD, Le T, Fan G. DNA methylation and its basic function. *Neuropsychopharmacology*. 2013;38(1):23–38. <https://doi.org/10.1038/npp.2012.112>. Nature Publishing Group.

Gilbert SF. Ageing and cancer as diseases of epigenesis. *J Biosci*. 2009;34(4):601–604. <https://doi.org/10.1007/s12038-009-0077-4>.

Jones MJ, Goodman SJ, Kobor MS. DNA methylation and healthy human aging. *Aging Cell*. 2015;14(6):924–932. <https://doi.org/10.1111/accel.12349>.

Wilson VL, Smith RA, Ma S, Cutler RG. Genomic 5-methyldeoxycytidine decreases with age. *J Biol Chem*. 1987;262(21):9948–9951.

Ehrlich M. DNA methylation in cancer: too much, but also too little. *Oncogene*. 2002;21(35):5400–5413. <https://doi.org/10.1038/sj.onc.1205651>.

Jones PA, Baylin SB. The epigenomics of cancer. *Cell*. 2007;128(4):683–692. <https://doi.org/10.1016/j.cell.2007.01.029>.

Muka T, Koromani F, Portilla E, et al. The role of epigenetic modifications in cardiovascular disease: a systematic review. *Int J Cardiol*. 2016;212:174–183. <https://doi.org/10.1016/j.ijcard.2016.03.062>. The Authors.

Amarasekera M, Noakes P, Strickland D, Saffery R, Martino DJ, Prescott SL. Epigenome-wide analysis of neonatal CD4 + T-cell DNA methylation sites potentially affected by maternal fish oil supplementation. *Epigenetics*. 2014;9(12):1570–1576. <https://doi.org/10.4161/15592294.2014.983366>. United States.

Arpón A, Milagro F, Razquin C, et al. Impact of consuming extra-virgin olive oil or nuts within a Mediterranean diet on DNA methylation in peripheral white blood cells within the PREDIMED-Navarra randomized controlled trial: a role for dietary lipids. *Nutrients*. 2017;10(1):15. <https://doi.org/10.3390/nu10010015>.

Aslibekyan S, Wiener HW, Havel PJ, et al. DNA methylation patterns are associated with n-3 fatty acid intake in Yup'ik people. *J Nutr*. 2014;144(4):425–430. <https://doi.org/10.3945/jn.113.187203>. United States.

Cui T, Hester AG, Seeds MC, et al. Impact of genetic and epigenetic variations within the FADS cluster on the composition and metabolism of polyunsaturated fatty acids in prostate cancer. *Prostate*. 2016;76(13):1182–1191. <https://doi.org/10.1002/pros.23205>. United States.

do Amaral CL, Milagro FI, Curi R, Martínez JA. DNA methylation pattern in overweight women under an energy-restricted diet supplemented with fish oil. *Biomed Res Int*. 2014;2014:1–10. <https://doi.org/10.1155/2014/675021>.

Hermisdorff HH, Mansego ML, Campión J, Milagro FI, Zulet MA, Martínez JA. TNF-alpha promoter methylation in peripheral white blood cells: relationship with circulating TNF α , truncal fat and n-6 PUFA intake in young women. *Cytokine*. 2013;64(1):265–271. <https://doi.org/10.1016/j.cyto.2013.05.028>. Elsevier Ltd.

Hoile SP, Clarke-Harris R, Huang R-C, et al. Supplementation with N-3 long-chain polyunsaturated fatty acids or olive oil in men and women with renal disease induces differential changes in the DNA methylation of FADS2 and ELOVL5 in peripheral blood mononuclear cells. *PLoS One*. 2014;9(10):e109896. <https://doi.org/10.1371/journal.pone.0109896>. Edited by W.-H. Schunck. United States.

Karimi M, Vedi I, Levi YF, et al. DHA-rich n-3 fatty acid supplementation decreases DNA methylation in blood leukocytes: the OmegAD study. *Am J Clin Nutr*. 2017;106(4):1157–1165.

Lee H, Barraza-Villarreal A, Biessy C, et al. Dietary supplementation with polyunsaturated fatty acid during pregnancy modulates DNA methylation at IGF2/H19 imprinted genes and growth of infants. *Physiol Genomics*. 2014;46:851–857.

Lind MV, Martino D, Harsløf LBS, Kyjovska ZO, Kristensen M, Lauritzen L. Genome-wide identification of mononuclear cell DNA methylation sites potentially affected by fish oil supplementation in young infants: a pilot study. *Prostaglandins Leukot Essent Fatty Acids*. 2015;101:1–7. <https://doi.org/10.1016/j.plefa.2015.07.003>.

Ma Y, Smith CE, Lai C-Q, et al. The effects of omega-3 polyunsaturated fatty acids and genetic variants on methylation levels of the interleukin-6 gene promoter. *Mol Nutr Food Res*. 2016;60(2):410–419. <https://doi.org/10.1002/mnfr.201500436>. Germany.

McMorrow AM, Connaughton RM, Magalhães TR, et al. Personalized cardio-metabolic responses to an anti-inflammatory nutrition intervention in obese adolescents: a randomized controlled crossover trial. *Mol Nutr Food Res*. 2018;e1701008. <https://doi.org/10.1002/mnfr.201701008>.

Milagro FI, Gómez-Abellán P, Campión J, Martínez JA, Ordovás JM, Garaulet M. CLOCK, PER2 and BMAL1 DNA methylation: association with obesity and metabolic syndrome characteristics and monounsaturated fat intake. *Chronobiol Int*. 2012;29(9):1180–1194.

Perfilyev A, Dahlman I, Gillberg L, et al. Impact of polyunsaturated and saturated fat overfeeding on the DNA-methylation pattern in human adipose tissue: a randomized controlled trial. *Am J Clin Nutr*. 2017;105(4):991–1000. <https://doi.org/10.3945/ajcn.116.143164>. United States.

Rahbar E, Waits CMK, Kirby EH, et al. Allele-specific methylation in the FADS genomic region in DNA from human saliva, CD4+ cells, and total leukocytes. *Clin Epigenetics*. 2018;10(1):46. <https://doi.org/10.1186/s13148-018-0480-5>.

Tremblay BL, Guénard F, Rudkowska I, Lemieux S, Couture P, Vohl M-C. Epigenetic changes in blood leukocytes following an omega-3 fatty acid supplementation. *Clin Epigenetics*. 2017;9(1):43. <https://doi.org/10.1186/s13148-017-0345-3>.

van Dijk SJ, Zhou J, Peters TJ, et al. Effect of prenatal DHA supplementation on the infant epigenome: results from a randomized controlled trial. *Clin Epigenetics*. 2016;8(1):114. <https://doi.org/10.1186/s13148016-0281-7>. Germany: Clinical Epigenetics.

Voisin S, Almén MS, Moschonis G, et al. Dietary fat quality impacts genome-wide DNA methylation patterns in a cross-sectional study of Greek preadolescents. *Eur J Hum Genet*. 2015;23(5):654–662. <https://doi.org/10.1038/ejhg.2014.139>. England.

Bersamin A, Luick BR, King IB, Stern JS, Zidenberg-Cherr S. Westernizing diets influence fat intake, red blood cell fatty acid composition, and health in remote Alaskan native communities in the Center for Alaska Native Health Study. *J Am Diet Assoc*. 2008;108(2):266–273. <https://doi.org/10.1016/j.jada.2007.10.046>.

Chen RZ, Pettersson U, Beard C, Jackson-Grusby L, Jaenisch R. DNA hypomethylation leads to elevated mutation rates. *Nature*. 1998;395(6697):89–93. <https://doi.org/10.1038/25779>.

Das UN. Beneficial effect(s) of n-3 fatty acids in cardiovascular diseases: but, why and how? *Prostaglandins Leu-*

ket Essent Fatty Acids. 2000;63(6):351–362. <https://doi.org/10.1054/plef.2000.0226>.

Harris WS. N-3 fatty acids and serum lipoproteins: human studies. *Am J Clin Nutr.* 1997;65(5 Suppl):1645S–1654S.

Raatz SK, Johnson LK, Rosenberger TA, Picklo MJ. Twice weekly intake of farmed Atlantic salmon (*Salmo salar*) positively influences lipoprotein concentration and particle size in overweight men and women. *Nutr Res.* 2016;36(9):899–906. <https://doi.org/10.1016/j.nutres.2016.06.011>. Elsevier B.V.

Dekkers KF, van Iterson M, Slieker RC, et al. Blood lipids influence DNA methylation in circulating cells. *Genome Biol.* 2016;17(1):138. <https://doi.org/10.1186/s13059-016-1000-6>.

Burdge GC, Jones AE, Wootton SA. Eicosapentaenoic and docosapentaenoic acids are the principal products of α -linolenic acid metabolism in young men. *Br J Nutr.* 2002;88(4):355–363. <https://doi.org/10.1079/BJN2002662>.

Burdge GC, Wootton SA. Conversion of α -linolenic acid to eicosapentaenoic, docosapentaenoic and docosahexaenoic acids in young women. *Br J Nutr.* 2002;88(4):411–420. <https://doi.org/10.1079/BJN2002689>.

Lohner S, Fekete K, Marosvölgyi T, Decsi T. Gender differences in the long-chain polyunsaturated fatty acid status: systematic review of 51 publications. *Ann Nutr Metab.* 2013;62(2):98–112. <https://doi.org/10.1159/000345599>.

Zhang FF, Cardarelli R, Carroll J, et al. Significant differences in global genomic DNA methylation by gender and race/ethnicity in peripheral blood. *Epigenetics.* 2011;6(5):623–629. <https://doi.org/10.4161/epi.6.5.15335>.

Dedeurwaerder S, Defrance M, Bizet M, Calonne E, Bontempi G, Fuks F. A comprehensive overview of Infinium HumanMethylation450 data processing. *Brief Bioinform.* 2014;15(6):929–941. <https://doi.org/10.1093/bib/bbt054>.

Lander ES, Linton LM, Birren B, et al. Initial sequencing and analysis of the human genome. *Nature.* 2001;409(6822):860–921. <https://doi.org/10.1038/35057062>.

Kochanek S, Renz D, Doerfler W. DNA methylation in the Alu sequences of diploid and haploid primary human cells. *EMBO J.* 1993;12(3):1141–1151.

Schmid CW. Does SINE evolution preclude Alu function? *Nucleic Acids Res.* 1998;26(20):4541–4550. <https://doi.org/10.1093/nar/26.20.4541>.

Zhu Z-Z, Hou L, Bollati V, et al. Predictors of global methylation levels in blood DNA of healthy subjects: a combined analysis. *Int J Epidemiol.* 2012;41(1):126–139. <https://doi.org/10.1093/ije/dyq154>.

Agodi A, Barchitta M, Quattrocchi A, et al. Low fruit consumption and folate deficiency are associated with LINE-1 hypomethylation in women of a cancer-free population. *Genes Nutr.* 2015;10(5):30. <https://doi.org/10.1007/s12263-015-0480-4>. Springer Berlin Heidelberg.

Garcia-Lacarte M, Milagro FI, Zulet MA, Martinez JA, Mansego ML. LINE-1 methylation levels, a biomarker of weight loss in obese subjects, are influenced by dietary antioxidant capacity. *Redox Rep.* 2016;21(2):67–74. <https://doi.org/10.1179/1351000215Y.0000000029>.

Marques-Rocha JL, Milagro FI, Mansego ML, Mourão DM, Martínez JA, Bressan J. LINE-1 methylation is positively associated with healthier lifestyle but inversely related to body fat mass in healthy young individuals. *Epigenetics.* 2016;11(1):49–60. <https://doi.org/10.1080/15592294.2015.1135286>.

Zhang FF, Morabia A, Carroll J, et al. Dietary patterns are associated with levels of global genomic DNA methylation in a cancer-free population. *J Nutr.* 2011;141(6):1165–1171. <https://doi.org/10.3945/jn.110.134536>.

Baccarelli A, Wright R, Bollati V, et al. Ischemic heart disease and stroke in relation to blood DNA methylation. *Epidemiology.* 2010;21(6):819–828. <https://doi.org/10.1097/EDE.0b013e3181f20457>.

Joyce BT, Gao T, Zheng Y, et al. Prospective changes in global DNA methylation and cancer incidence and mortality. *Br J Cancer.* 2016;115(4):465–472. <https://doi.org/10.1038/bjc.2016.205>.

Schulz WA, Steinhoff C, Florl AR. Methylation of endogenous human retroelements in health and disease. In: Doerfler W, Böhm P, eds. *DNA Methylation: Development, Genetic Disease and Cancer*. Berlin, Heidelberg: Springer; 2006:211–250. https://doi.org/10.1007/3-540-31181-5_11.

Bollati V, Schwartz J, Wright R, et al. Decline in genomic DNA methylation through aging in a cohort of elderly

subjects. *Mech Ageing Dev.* 2009;130(4):234–239. <https://doi.org/10.1016/j.mad.2008.12.003>.

Jintaridith P, Mutirangura A. Distinctive patterns of age-dependent hypomethylation in interspersed repetitive sequences. *Physiol Genomics.* 2010;41(2):194–200. <https://doi.org/10.1152/physiolgenomics.00146.2009>.

Gorjão R, Azevedo-Martins AK, Rodrigues HG, et al. Comparative effects of DHA and EPA on cell function. *Pharmacol Ther.* 2009;122(1):56–64. <https://doi.org/10.1016/j.pharmthera.2009.01.004>. Elsevier Inc.

Mickleborough TD, Tecklenburg SL, Montgomery GS, Lindley MR. Eicosapentaenoic acid is more effective than docosahexaenoic acid in inhibiting proinflammatory mediator production and transcription from LPS-induced human asthmatic alveolar macrophage cells. *Clin Nutr.* 2009;28(1):71–77. <https://doi.org/10.1016/j.clnu.2008.10.012>. Elsevier Ltd and European Society for Clinical Nutrition and Metabolism.

Turk HF, Chapkin RS. Membrane lipid raft organization is uniquely modified by n-3 polyunsaturated fatty acids. *Prostaglandins Leukot Essent Fatty Acids.* 2013;88(1):43–47. <https://doi.org/10.1016/j.plefa.2012.03.008>. Elsevier.

Kim W, Fan Y-Y, Barhoumi R, Smith R, McMurray DN, Chapkin RS. N-3 polyunsaturated fatty acids suppress the localization and activation of signaling proteins at the immunological synapse in murine CD4+

T cells by affecting lipid raft formation. *J Immunol.* 2008;181(9):6236–6243. <https://doi.org/10.4049/jimmunol.181.9.6236>.

Chapkin RS, Wang N, Fan Y-Y, Lupton JR, Prior IA. Docosahexaenoic acid alters the size and distribution of cell surface microdomains. *Biochim Biophys Acta Biomembr.* 2008;1778(2):466–471. <https://doi.org/10.1016/j.bbmem.2007.11.003>.

Klok MD, Jakobsdottir S, Drent ML. The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. *Obes Rev.* 2007;8(1):21–34. <https://doi.org/10.1111/j.1467-789X.2006.00270.x>.

Reseland JE, Haugen F, Hollung K, et al. Reduction of leptin gene expression by dietary polyunsaturated fatty acids. *J Lipid Res.* 2001;42(5):743–750.

Shen W, Wang C, Xia L, et al. Epigenetic modification of the leptin promoter in diet-induced obese mice and the effects of N-3 polyunsaturated fatty acids. *Sci Rep.* 2014;4:5282. <https://doi.org/10.1038/srep05282>.

Fan C, Liu X, Shen W, Deckelbaum RJ, Qi K. The regulation of leptin, leptin receptor and pro-opiomelanocortin expression by N-3 PUFAs in diet-induced obese mice is not related to the methylation of their promoters. *Nutr Metab.* 2011;8(1):31. <https://doi.org/10.1186/1743-7075-8-31>. England: BioMed Central Ltd.

Alexander Aguilera A, Hernández Díaz G, Lara Barcelata M, Angulo Guerrero O, Oliart Ros RM. Induction of Cd36 expression elicited by fish oil PUFA in spontaneously hypertensive rats. *J Nutr Biochem.* 2006;17(11):760–765. <https://doi.org/10.1016/j.jnutbio.2005.12.007>.

Vallvé J-C, Uliaque K, Girona J, et al. Unsaturated fatty acids and their oxidation products stimulate CD36 gene expression in human macrophages. *Atherosclerosis.* 2002;164(1):45–56.

Silverstein RL, Febbraio M. CD36, a scavenger receptor involved in immunity, metabolism, angiogenesis, and behavior. *Sci Signal.* 2009;2(72):re3-re3. <https://doi.org/10.1126/scisignal.272re3>.

Bouwens M, van de Rest O, Dellschaft N, et al. Fish-oil supplementation induces antiinflammatory gene expression profiles in human blood mononuclear cells. *Am J Clin Nutr.* 2009;90(2):415–424. <https://doi.org/10.3945/ajcn.2009.27680>.

Benatti P, Peluso G, Nicolai R, Calvani M. Polyunsaturated fatty acids: biochemical, nutritional and epigenetic properties. *J Am Coll Nutr.* 2004;23(4):281–302. <https://doi.org/10.1080/07315724.2004.10719371>. Routledge.

Marquardt A, Stöhr H, White K, Weber BHF. cDNA cloning, genomic structure, and chromosomal localization of three members of the human fatty acid desaturase family. *Genomics.* 2000;66(2):175–183. <https://doi.org/10.1006/geno.2000.6196>.

Nakamura MT, Nara TY. Structure, function, and dietary regulation of $\Delta 6$, $\Delta 5$, and $\Delta 9$ desaturases. *Annu Rev Nutr.* 2004;24(1):345–376. <https://doi.org/10.1146/annurev.nutr.24.121803.063211>.

Glaser C, Heinrich J, Koletzko B. Role of FADS1 and FADS2 polymorphisms in polyunsaturated fatty acid metab-

olism. *Metabolism*. 2010;59(7):993–999. <https://doi.org/10.1016/j.metabol.2009.10.022>.

Calder PC. Marine omega-3 fatty acids and inflammatory processes: effects, mechanisms and clinical relevance. *Biochim Biophys Acta*. 2015;1851(4):469–484. <https://doi.org/10.1016/j.bbali.2014.08.010>. Elsevier B.V.

Caughey GE, Mantzioris E, Gibson RA, Cleland LG, James MJ. The effect on human tumor necrosis factor alpha and interleukin 1 beta production of diets enriched in n-3 fatty acids from vegetable oil or fish oil. *Am J Clin Nutr*. 1996;63(1):116–122.

Chapter 5

Swinburn BA, Sacks G, Hall KD, Finegood DT, Moodie ML, Gortmaker SL. The global obesity pandemic: shaped by global drivers and local environments. *Lancet*. 2011;378(9793):804–814.

Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2014;384(9945):766–781.

NCD Risk Factor Collaboration. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pool analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. *Lancet*. 2017;390(10113):2627–2642.

World Health Organization. Obesity and Overweight Fact Sheet; 2020. <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>; Accessed 8 July 2020.

GBD 2015 Obesity Collaborators, Afshin A, Forouzanfar MH, et al. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med*. 2017;377(1):13–27.

Bhaskaran K, Dos-Santos-Silva I, Leon DA, Douglas IJ, Smeeth L. Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3.6 million adults in the UK. *Lancet Diabetes Endocrinol*. 2018;6(12):922–953.

Sung H, Siegel R, Torre LA, et al. Global patterns in excess body weight and the associated cancer burden. *CA Cancer J Clin*. 2019;69(2):88–112.

Roberto CA, Swinburn B, Hawkes C, et al. Patchy progress on obesity prevention: emerging examples, entrenched barriers, and new thinking. *Lancet*. 2015;385(9985):2400–2409.

Romieu I, Dossus L, Barquera S, et al. Willett WC; IARC working group on energy balance and obesity. Energy balance and obesity: what are the main drivers? *Cancer Causes Control*. 2017;28(3):247–258.

McAllister EJ, Dhurandhar NV, Keith SW, et al. Ten putative contributors to the obesity epidemic. *Crit Rev Food Sci Nutr*. 2009;49(10):868–913.

Hruby A, Hu FB. The epidemiology of obesity: a big picture. *Pharmacoeconomics*. 2015;33(7):673–689.

van Dijk SJ, Tellam RL, Morrison JL, Muhlhauser BS, Molloy PL. Recent developments on the role of epigenetics in obesity and metabolic disease. *Clin Epigenetics*. 2015;7:66.

Lopomo A, Burgio E, Migliore L. Epigenetics of obesity. *Prog Mol Biol Transl Sci*. 2016;140:151–184.

Dhasarathy A, Roemmich JN, Claycombe KJ. Influence of maternal obesity, diet and exercise on epigenetic regulation of adipocytes. *Mol Aspects Med*. 2017;54:37–49.

Lee HS. Impact of maternal diet on the epigenome during in utero life and the developmental programming of diseases in childhood and adulthood. *Nutrients*. 2015;7(11):9492–9507.

Huvenne H, Dubern B, Clément K, Poitou C. Rare genetic forms of obesity: clinical approach and current treatments in 2016. *Obes Facts*. 2016;9(3):158–173.

Thaker VV. Genetic and epigenetic causes of obesity. *Adolesc Med State Art Rev*. 2017;28(2):379–405.

Albuquerque D, Stice E, Rodríguez-López R, Manco L, Nóbrega C. Current review of genetics of human obesity: from molecular mechanisms to an evolutionary perspective. *Mol Genet Genomics*. 2015;290(4):1191–1221.

Rankinen T, Zuberi A, Chagnon YC, et al. The human obesity gene map: the 2005 update. *Obesity (Silver Spring)*.

2006;14(4):529–644.

Messerschmidt DM, Knowles BB, Solter D. DNA methylation dynamics during epigenetic reprogramming in the germline and preimplantation embryos. *Genes Dev.* 2014;28(8):812–828.

Okano M, Bell DW, Haber DA, Li E. DNA methyltransferases Dnmt3a and Dnmt3b are essential for de novo methylation and mammalian development. *Cell.* 1999;99(3):247–257.

Reik W. Stability and flexibility of epigenetic gene regulation in mammalian development. *Nature.* 2007;447:425–432.

Elena G, Bruna C, Benedetta M, Stefania DC, Giuseppe C. Prader-Willi syndrome: clinical aspects. *J Obes.* 2012;2012:473941.

Iughetti L, Bosio L, Corrias A, et al. Pituitary height and neuroradiological alterations in patients with Prader-Labhart-Willi syndrome. *Eur J Pediatr.* 2008;167(6):701–702.

McAllister CJ, Whittington JE, Holland AJ. Development of the eating behaviour in Prader-Willi syndrome: advances in our understanding. *Int J Obes (Lond).* 2011;35(2):188–197.

Ohta T, Gray TA, Rogan PK, et al. Imprinting-mutation mechanisms in Prader-Willi syndrome. *Am J Hum Genet.* 1999;64(2):397–413.

Buiting K, Saitoh S, Gross S, et al. Inherited microdeletions in the Angelman and Prader-Willi syndromes define an imprinting centre on human chromosome 15. *Nat Genet.* 1995;9:395–400.

Burnett LC, LeDuc CA, Sulsona CR, et al. Deficiency in prohormone convertase PC1 impairs prohormone processing in Prader-Willi syndrome. *J Clin Invest.* 2017;127(1):293–305.

Stijnen P, Ramos-Molina B, O’Rahilly S, Creemers JW. PCSK1 mutations and human endocrinopathies: from obesity to gastrointestinal disorders. *Endocr Rev.* 2016;37(4):347–371.

Williams C, Driscoll D, Dagli A. Clinical and genetic aspects of Angelman syndrome. *Genet Med.* 2010;12:385–395.

Knoll JH, Nicholls RD, Magenis RE, Graham Jr JM, Lalande M, Latt SA. Angelman and Prader-Willi syndromes share a common chromosome 15 deletion but differ in parental origin of the deletion. *Am J Med Genet.* 1989;32(2):285–290.

Clayton-Smith J. Clinical research on Angelman syndrome in the United Kingdom: observations on 82 affected individuals. *Am J Med Genet.* 1993;46(1):12–15.

Barry RJ, Leitner RP, Clarke AR, Einfeld SL. Behavioral aspects of Angelman syndrome: a case control study. *Am J Med Genet A.* 2005;132A(1):8–12.

Matsuura T, Sutcliffe JS, Fang P, et al. De novo truncating mutations in E6-AP ubiquitin-protein ligase gene (UBE3A) in Angelman syndrome. *Nat Genet.* 1997;15:74–77.

Kishino T, Lalande M, Wagstaff J. UBE3A/E6-AP mutations cause Angelman syndrome. *Nat Genet.* 1997;15(1):70–73 [published correction appears in *Nat Genet.* 1997;15(4):411].

Kim J, Lee B, Kim DH, et al. UBE3A suppresses overnutrition-induced expression of the steatosis target genes of MLL4 by degrading MLL4. *Hepatology.* 2019;69(3):1122–1134.

Heintzman ND, Stuart RK, Hon G, et al. Distinct and predictive chromatin signatures of transcriptional promoters and enhancers in the human genome. *Nat Genet.* 2007;39(3):311–318.

van Dijk S, Molloy P, Varinli H, Morrison JL, Muhlhausler BS. Members of EpiSCOPE. Epigenetics and human obesity. *Int J Obes (Lond).* 2015;39:85–97.

Huang RC, Galati JC, Burrows S, et al. DNA methylation of the IGF2/H19 imprinting control region and adiposity distribution in young adults. *Clin Epigenetics.* 2012;4(1):21.

Perkins E, Murphy SK, Murtha AP, et al. Insulin-like growth factor 2/H19 methylation at birth and risk of overweight and obesity in children. *J Pediatr.* 2012;161(1):31–39.

Bergman D, Halje M, Nordin M, Engström W. Insulin-like growth factor 2 in development and disease: a mini-re-

view. *Gerontology*. 2013;59(3):240–249.

Sandhu MJS, Gibson JM, Heald AH, Dunger DB, Wareham NJ. Low circulating IGF-II concentrations predict weight gain and obesity in humans. *Diabetes*. 2003;52:1403–1408.

Nordin M, Bergman D, Halje M, Engström W, Ward A. Epigenetic regulation of the *Igf2/H19* gene cluster. *Cell Prolif*. 2014;47:189–199.

Monnier P, Martinet C, Pontis J, Stancheva I, Ait-Si-Ali S, Dandolo L. H19 lncRNA controls gene expression of the imprinted gene network by recruiting MBD1. *Proc Natl Acad Sci U S A*. 2013;110(51):20693–20698.

Clark AJ. 60 YEARS OF POMC: the proopiomelanocortin gene: discovery, deletion and disease. *J Mol Endocrinol*. 2016;56(4):T27–T37.

Kuehnen P, Mischke M, Wiegand S, et al. An Alu element-associated hypermethylation variant of the POMC gene is associated with childhood obesity. *PLoS Genet*. 2012;8(3), e1002543.

Dick KJ, Nelson CP, Tsaprouni L, et al. DNA methylation and body-mass index: a genome-wide analysis. *Lancet*. 2014;383(9933):1990–1998.

Su S, Zhu H, Xu X, et al. DNA methylation of the *LY86* gene is associated with obesity, insulin resistance, and inflammation. *Twin Res Hum Genet*. 2014;17(3):183–191.

Clarke-Harris R, Wilkin TJ, Hosking J, et al. *PGC1 α* promoter methylation in blood at 5-7 years predicts adiposity from 9 to 14 years (*EarlyBird 50*). *Diabetes*. 2014;63(7):2528–2537.

Jufvas A, Sjödin S, Lundqvist K, Amin R, Vener AV, Strålfors P. Global differences in specific histone H3 methylation are associated with overweight and type 2 diabetes. *Clin Epigenetics*. 2013;5(1):15.

Iacomino G, Siani A. Role of microRNAs in obesity and obesity-related diseases. *Genes Nutr*. 2017;12:23.

Heneghan HM, Miller N, McAnena OJ, O'Brien T, Kerin MJ. Differential miRNA expression in omental adipose tissue and in the circulation of obese patients identifies novel metabolic biomarkers. *J Clin Endocrinol Metab*. 2011;96(5):E846–E850.

Ortega FJ, Moreno-Navarrete JM, Pardo G, et al. MiRNA expression profile of human subcutaneous adipose and during adipocyte differentiation. *PLoS One*. 2010;5(2), e9022.

Feinberg AP, Irizarry RA, Fradin D, et al. Personalized epigenomic signatures that are stable over time and covary with body mass index. *Sci Transl Med*. 2010;2(49):49ra67 [Erratum in: *Sci Transl Med*. 2011;3(65):65er1].

Gertz J, Varley KE, Reddy TE, et al. Analysis of DNA methylation in a three-generation family reveals widespread genetic influence on epigenetic regulation. *PLoS Genet*. 2011;7(8), e1002228.

Lienert F, Wirbelauer C, Som I, Dean A, Mohn F, Schübeler D. Identification of genetic elements that autonomously determine DNA methylation states. *Nat Genet*. 2011;43(11):1091–1097.

Tobi EW, Slagboom PE, van Dongen J, et al. Prenatal famine and genetic variation are independently and additively associated with DNA methylation at regulatory loci within *IGF2/H19*. *PLoS One*. 2012;7(5), e37933.

Barker DJ. The fetal and infant origins of adult disease. *BMJ*. 1990;301(6761):1111.

Lucas A. Programming by early nutrition in man. *Ciba Found Symp*. 1991;156:38–50 [discussion 50–55].

Heijmans BT, Tobi EW, Stein AD, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proc Natl Acad Sci U S A*. 2008;105(44):17046–17049.

Waterland RA, Kellermayer R, Laritsky E, et al. Season of conception in rural gambia affects DNA methylation at putative human metastable epialleles. *PLoS Genet*. 2010;6(12), e1001252.

Dominguez-Salas P, Moore SE, Baker MS, et al. Maternal nutrition at conception modulates DNA methylation of human metastable epialleles. *Nat Commun*. 2014;5:3746.

Stein AD, Kahn HS, Rundle A, Zybert PA, van der Pal-de Bruin K, Lumey LH. Anthropometric measures in middle age after exposure to famine during gestation: evidence from the Dutch famine. *Am J Clin Nutr*. 2007;85:869–876.

Lumey LH, Stein AD, Kahn HS, Romijn JA. Lipid profiles in middle-aged men and women after famine exposure during gestation: the Dutch hunger winter families study. *Am J Clin Nutr*. 2009;89:1737–1743.

Ravelli AC, van der Meulen JH, Michels RP, et al. Glucose tolerance in adults after prenatal exposure to famine. *Lancet*. 1998;351:173–177.

Parlee SD, MacDougald OA. Maternal nutrition and risk of obesity in offspring: the Trojan horse of developmental plasticity. *Biochim Biophys Acta*. 2014;1842(3):495–506.

Hales CN, Barker DJ. The thrifty phenotype hypothesis. *Br Med Bull*. 2001;60:5–20.

Gluckman PD, Hanson MA. Developmental origins of disease paradigm: a mechanistic and evolutionary perspective. *Pediatr Res*. 2004;56(3):311–317.

Fraser A, Tilling K, Macdonald-Wallis C, et al. Association of maternal weight gain in pregnancy with offspring obesity and metabolic and vascular traits in childhood. *Circulation*. 2010;121(23):2557–2564.

Lawlor DA, Relton C, Sattar N, Nelson SM. Maternal adiposity—a determinant of perinatal and offspring outcomes? *Nat Rev Endocrinol*. 2012;8(11):679–688.

Gaillard R, Steegers EA, Duijts L, et al. Childhood cardiometabolic outcomes of maternal obesity during pregnancy: the generation R study. *Hypertension*. 2014;63(4):683–691.

Sharp GC, Lawlor DA, Richmond RC, et al. Maternal pre-pregnancy BMI and gestational weight gain, offspring DNA methylation and later offspring adiposity: findings from the Avon longitudinal study of parents and children. *Int J Epidemiol*. 2015;44(4):1288–1304.

Liu X, Chen Q, Tsai HJ, et al. Maternal preconception body mass index and offspring cord blood DNA methylation: exploration of early life origins of disease. *Environ Mol Mutagen*. 2014;55(3):223–230.

Morales E, Groom A, Lawlor DA, Relton CL. DNA methylation signatures in cord blood associated with maternal gestational weight gain: results from the ALSPAC cohort. *BMC Res Notes*. 2014;7:278.

Joubert BR, den Dekker HT, Felix JF, et al. Maternal plasma folate impacts differential DNA methylation in an epigenome-wide meta-analysis of newborns. *Nat Commun*. 2016;7:10577.

Cooper WN, Khulan B, Owens S, et al. DNA methylation profiling at imprinted loci after periconceptional micronutrient supplementation in humans: results of a pilot randomized controlled trial. *FASEB J*. 2012;26(5):1782–1790.

Richmond RC, Sharp GC, Herbert G, et al. The long-term impact of folic acid in pregnancy on offspring DNA methylation: follow-up of the Aberdeen folic acid supplementation trial (AFAST). *Int J Epidemiol*. 2018;47(3):928–937.

Wang G, Hu FB, Mištry KB, et al. Association between maternal prepregnancy body mass index and plasma folate concentrations with child metabolic health. *JAMA Pediatr*. 2016;170(8), e160845.

Steegers-Theunissen RP, Obermann-Borst SA, Kremer D, et al. Periconceptional maternal folic acid use of 400 microg per day is related to increased methylation of the IGF2 gene in the very young child. *PLoS One*. 2009;4(11), e7845.

Daniel M, Tollefsbol TO. Epigenetic linkage of aging, cancer and nutrition. *J Exp Biol*. 2015;218(Pt 1):59–70.

Fernandes GFS, Silva GDB, Pavan AR, Chiba DE, Chin CM, Dos Santos JL. Epigenetic regulatory mechanisms induced by resveratrol. *Nutrients*. 2017;9(11):1201.

Franzago M, Fraticelli F, Stuppia L, Vitacolonna E. Nutrigenetics, epigenetics and gestational diabetes: consequences in mother and child. *Epigenetics*. 2019;14(3):215–235.

Reichetzeder C, Dwi Putra SE, Pfab T, et al. Increased global placental DNA methylation levels are associated with gestational diabetes. *Clin Epigenetics*. 2016;8:82.

Lowe Jr WL, Scholtens DM, Lowe LP, et al. HAPO follow-up study cooperative research group. Association of gestational diabetes with maternal disorders of glucose metabolism and childhood adiposity. *JAMA*. 2018;320(10):1005–1016.

Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. *Nature*. 1998;395(6704):763–770.

Montague CT, Farooqi IS, Whitehead JP, et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature*. 1997;387(6636):903–908.

Melzner I, Scott V, Dorsch K, et al. Leptin gene expression in human preadipocytes is switched on by maturation-induced demethylation of distinct CpGs in its proximal promoter. *J Biol Chem*. 2002;277(47):45420–45427.

Lesseur C, Armstrong DA, Paquette AG, Li Z, Padbury JF, Marsit CJ. Maternal obesity and gestational diabetes are associated with placental leptin DNA methylation. *Am J Obstet Gynecol*. 2014;211(6):654 [e1-9].

Nogues P, Dos Santos E, Jammes H, et al. Maternal obesity influences expression and DNA methylation of the adiponectin and leptin systems in human third-trimester placenta. *Clin Epigenetics*. 2019;11(1):20.

Liu Y, Murphy SK, Murtha AP, et al. Depression in pregnancy, infant birth weight and DNA methylation of imprint regulatory elements. *Epigenetics*. 2012;7(7):735–746.

Chamorro-García R, Blumberg B. Transgenerational effects of obesogens and the obesity epidemic. *Curr Opin Pharmacol*. 2014;19:153–158.

Baillie-Hamilton PF. Chemical toxins: a hypothesis to explain the global obesity epidemic. *J Altern Complement Med*. 2002;8(2):185–192.

Axson JE, Libonati JR. Impact of parental exercise on epigenetic modifications inherited by offspring: a systematic review. *Physiol Rep*. 2019;7(22), e14287.

McCullough LE, Mendez MA, Miller EE, Murtha AP, Murphy SK, Hoyo C. Associations between prenatal physical activity, birth weight, and DNA methylation at genomically imprinted domains in a multiethnic newborn cohort. *Epigenetics*. 2015;10(7):597–606.

Schou Andersen C, Juhl M, Gamborg M, Sørensen TI, Nohr EA. Maternal recreational exercise during pregnancy in relation to children's BMI at 7 years of age. *Int J Pediatr*. 2012;2012:920583.

Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, et al. Endocrine-disrupting chemicals: an endocrine society scientific statement. *Endocr Rev*. 2009;30(4):293–342.

Halldorsson TI, Rytter D, Haug LS, et al. Prenatal exposure to perfluorooctanoate and risk of overweight at 20 years of age: a prospective cohort study. *Environ Health Perspect*. 2012;120(5):668–673.

Vaiserman A. Early-life exposure to endocrine disrupting chemicals and later-life health outcomes: an epigenetic bridge? *Aging Dis*. 2014;5(6):419–429.

Kippler M, Engström K, Mlakar SJ, et al. Sex-specific effects of early life cadmium exposure on DNA methylation and implications for birth weight. *Epigenetics*. 2013;8(5):494–503.

Järup L, Akesson A. Current status of cadmium as an environmental health problem. *Toxicol Appl Pharmacol*. 2009;238(3):201–208.

Lee CC, Shih YC, Kang ML, et al. Naa10p inhibits beige adipocyte-mediated thermogenesis through N-acetylation of Pgc1 α . *Mol Cell*. 2019;76(3):500–515.

Hackett JA, Sengupta R, Zyllicz JJ, et al. Germline DNA demethylation dynamics and imprint erasure through 5-hydroxymethylcytosine. *Science*. 2013;339(6118):448–452.

Soubry A, Schildkraut JM, Murtha A, et al. Paternal obesity is associated with IGF2 hypomethylation in newborns: results from a newborn epigenetics study (NEST) cohort. *BMC Med*. 2013;11:29.

Soubry A, Murphy SK, Wang F, et al. Newborns of obese parents have altered DNA methylation patterns at imprinted genes. *Int J Obes (Lond)*. 2015;39(4):650–657.

Wikenius E, Moe V, Smith L, Heiervang ER, Berglund A. DNA methylation changes in infants between 6 and 52 weeks. *Sci Rep*. 2019;9(1):17587.

Demerath EW, Guan W, Grove ML, et al. Epigenome-wide association study (EWAS) of BMI, BMI change and waist circumference in African American adults identifies multiple replicated loci. *Hum Mol Genet*. 2015;24(15):4464–4479.

Indrio F, Martini S, Francavilla R, et al. Epigenetic matters: the link between early nutrition, microbiome, and long-term health development. *Front Pediatr*. 2017;5:178.

Gao X, Salomon C, Freeman DJ. Extracellular vesicles from adipose tissue—a potential role in obesity and type 2

diabetes? *Front Endocrinol (Lausanne)*. 2017;8:202.

Jiménez-Chillarón JC, Díaz R, Martínez D, et al. The role of nutrition on epigenetic modifications and their implications on health. *Biochimie*. 2012;94(11):2242–2263.

Ferrante SC, Nadler EP, Pillai DK, et al. Adipocyte-derived exosomal miRNAs: a novel mechanism for obesity-related disease. *Pediatr Res*. 2015;77(3):447–454.

Pardo F, Villalobos-Labra R, Sobrevia B, Toledo F, Sobrevia L. Extracellular vesicles in obesity and diabetes mellitus. *Mol Aspects Med*. 2018;60:81–91.

Ziller MJ, Gu H, Müller F, et al. Charting a dynamic DNA methylation landscape of the human genome. *Nature*. 2013;500(7463):477–481.

Huang S, Litt M, Blakey CA. *Epigenetic Gene Expression and Regulation*. Elsevier Inc; 2015.

Gibney ER, Nolan CM. *Epigenetics and gene expression*. *Heredity (Edinb)*. 2010;105(1):4–13.

Teschendorff AE, West J, Beck S. Age-associated epigenetic drift: implications, and a case of epigenetic thrift? *Hum Mol Genet*. 2013;22(R1):R7–R15.

Wilson VL, Smith RA, Ma S, Cutler RG. Genomic 5-methyldeoxycytidine decreases with age. *J Biol Chem*. 1987;262(21):9948–9951.

Gopalan S, Carja O, Fagny M, et al. Trends in DNA methylation with age replicate across diverse human populations. *Genetics*. 2017;206(3):1659–1674.

Heyn H, Li N, Ferreira HJ, et al. Distinct DNA methylomes of newborns and centenarians. *Proc Natl Acad Sci U S A*. 2012;109(26):10522–10527.

McClay JL, Aberg KA, Clark SL, et al. A methylome-wide study of aging using massively parallel sequencing of the methyl-CpG-enriched genomic fraction from blood in over 700 subjects. *Hum Mol Genet*. 2014;23(5):1175–1185.

Moskalev A, Vaiserman AM. *Epigenetics of aging and longevity*. In: *Translational Epigenetics*. vol. 4. Elsevier Inc; 2018.

Maleszewska M, Mawer JSP, Tessarz P. Histone modifications in ageing and lifespan regulation. *Curr Mol Bio Rep*. 2016;2:26–35.

Garagnani P, Bacalini MG, Pirazzini C, et al. Methylation of ELOVL2 gene as a new epigenetic marker of age. *Aging Cell*. 2012;11(6):1132–1134.

Pauter AM, Olsson P, Asadi A, et al. Elov12 ablation demonstrates that systemic DHA is endogenously produced and is essential for lipid homeostasis in mice. *J Lipid Res*. 2014;55(4):718–728.

Fraga MF, Ballestar E, Paz MF, et al. Epigenetic differences arise during the lifetime of monozygotic twins. *Proc Natl Acad Sci U S A*. 2005;102(30):10604–10609 [Version 2].

Kanherkar RR, Bhatia-Dey N, Csoka AB. *Epigenetics across the human lifespan*. *Front Cell Dev Biol*. 2014;2:49.

Wahl S, Drong A, Lehne B, et al. Epigenome-wide association study of body mass index, and the adverse outcomes of adiposity. *Nature*. 2017;541(7635):81–86.

Ideraabdullah FY, Zeisel SH. Dietary modulation of the epigenome. *Physiol Rev*. 2018;98(2):667–695.

Ye J. Improving insulin sensitivity with HDAC inhibitor. *Diabetes*. 2013;62(3):685–687.

Ntanasis-Stathopoulos J, Tzanninis JG, Philippou A, Koutsilieris M. Epigenetic regulation on gene expression induced by physical exercise. *J Musculoskelet Neuronal Interact*. 2013;13(2):133–146.

Barrès R, Yan J, Egan B, et al. Acute exercise remodels promoter methylation in human skeletal muscle. *Cell Metab*. 2012;15(3):405–411.

Summermatter S, Handschin C. PGC-1 α and exercise in the control of body weight. *Int J Obes (Lond)*. 2012;36(11):1428–1435.

Nitert MD, Dayeh T, Volkov P, et al. Impact of an exercise intervention on DNA methylation in skeletal muscle from first-degree relatives of patients with type 2 diabetes. *Diabetes*. 2012;61(12):3322–3332.

Rönn T, Volkov P, Davegårdh C, et al. A six months exercise intervention influences the genome-wide DNA meth-

ylation pattern in human adipose tissue. *PLoS Genet.* 2013;9(6), e1003572.

Xu T, Liu Q, Yao J, Dai Y, Wang H, Xiao J. Circulating microRNAs in response to exercise. *Scand J Med Sci Sports.* 2015;25(2):e149–e154.

Improta Caria AC, Nonaka CKV, Pereira CS, Soares MBP, Macambira SG, Souza BSF. Exercise training-induced changes in MicroRNAs: beneficial regulatory effects in hypertension, type 2 diabetes, and obesity. *Int J Mol Sci.* 2018;19(11):3608.

Nielsen S, Åkerström T, Rinnov A, et al. The miRNA plasma signature in response to acute aerobic exercise and endurance training. *PLoS One.* 2014;9(2), e87308.

Yu Y, Du H, Wei S, et al. Adipocyte-derived exosomal MiR-27a induces insulin resistance in skeletal muscle through repression of PPAR γ . *Theranostics.* 2018;8(8):2171–2188.

Barres R, Kirchner H, Rasmussen M, et al. Weight loss after gastric bypass surgery in human obesity remodels promoter methylation. *Cell Rep.* 2013;3(4):1020–1027.

Sanchis-Gomar F, Garcia-Gimenez JL, Perez-Quilis C, Gomez-Cabrera MC, Pallardo FV, Lippi G. Physical exercise as an epigenetic modulator: eustress, the “positive stress” as an effector of gene expression. *J Strength Cond Res.* 2012;26(12):3469–3472.

Chapter 6

Lee I-M, Shiroma EJ, Lobelo F, et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet.* 2012;380:219–229. [https://doi.org/10.1016/S0140-6736\(12\)61031-9](https://doi.org/10.1016/S0140-6736(12)61031-9).

Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep.* 1985;100:126–131. <http://www.ncbi.nlm.nih.gov/pubmed/3920711>.

Pedersen BK, Saltin B. Exercise as medicine—evidence for prescribing exercise as therapy in 26 different chronic diseases. *Scand J Med Sci Sports.* 2015;25:1–72. <https://doi.org/10.1111/sms.12581>.

Moxley E, Habtzi D. A systematic review comparing dose response of exercise on cardiovascular and all-cause mortality. *Home Health Care Manage Pract.* 2019;31:263–273. <https://doi.org/10.1177/1084822319831929>.

Lear SA, Hu W, Rangarajan S, et al. The effect of physical activity on mortality and cardiovascular disease in 130000 people from 17 high-income, middle-income, and low-income countries: the PURE study. *Lancet.* 2017;390:2643–2654. [https://doi.org/10.1016/S0140-6736\(17\)31634-3](https://doi.org/10.1016/S0140-6736(17)31634-3).

Lamonte MJ, Blair SN, Church TS. Physical activity and diabetes prevention. *J Appl Physiol.* 2005;99:1205–1213. <https://doi.org/10.1152/jappphysiol.00193.2005>.

Friedenreich CM. Physical activity and breast cancer: review of the epidemiologic evidence and biologic mechanisms. *Recent Results Cancer Res.* 2011;188:125–139. https://doi.org/10.1007/978-3-642-10858-7_11.

Harriss DJ, Atkinson G, Batterham A, et al. Lifestyle factors and colorectal cancer risk (2): a systematic review and meta-analysis of associations with leisure-time physical activity. *Color Dis.* 2009;11:689–701. <https://doi.org/10.1111/j.1463-1318.2009.01767.x>.

Olsen CM, Bain CJ, Jordan SJ, et al. Recreational physical activity and epithelial ovarian cancer: a case-control study, systematic review, and meta-analysis. *Cancer Epidemiol Biomark Prev.* 2007;16:2321–2330. <https://doi.org/10.1158/1055-9965.EPI-07-0566>.

O’Rorke MA, Cantwell MM, Cardwell CR, Mulholland HG, Murray LJ. Can physical activity modulate pancreatic cancer risk? A systematic review and meta-analysis. *Int J Cancer.* 2010;126:2957–2968. <https://doi.org/10.1002/ijc.24997>.

Reimers CD, Knapp G, Reimers AK. Does physical activity increase life expectancy? A review of the literature. *J Aging Res.* 2012;2012:1–9. <https://doi.org/10.1155/2012/243958>.

Hallal PC, Andersen LB, Bull FC, et al. Global physical activity levels: surveillance progress, pitfalls, and prospects. *Lancet*. 2012;380:247–257. [https://doi.org/10.1016/S0140-6736\(12\)60646-1](https://doi.org/10.1016/S0140-6736(12)60646-1).

Centers for Disease Control and Prevention. Adult participation in aerobic and muscle-strengthening physical activities—United States. *Morb Mortal Wkly Rep*. 2011;62(2013):326–330.

World Health Organisation. *Global Recommendations on Physical Activity for Health*. World Health Organisation; 2010.

Piercy KL, Troiano RP, Ballard RM, et al. The physical activity guidelines for Americans. *J Am Med Assoc*. 2018;320:2020–2028. <https://doi.org/10.1001/jama.2018.14854>.

Jetté M, Sidney K, Blümchen G. Metabolic equivalents (METs) in exercise testing, exercise prescription, and evaluation of functional capacity. *Clin Cardiol*. 1990;13:555–565. <https://doi.org/10.1002/clc.4960130809>.

Haskell WL, Lee I-M, Pate RR, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation*. 2007;116:1081–1093. <https://doi.org/10.1161/CIRCULATION.107.185649>.

Eklblom B, Åstrand PO, Saltin B, Stenberg J, Wallström B. Effect of training on circulatory response to exercise. *J Appl Physiol*. 1968;24:518–528. <https://doi.org/10.1152/jappl.1968.24.4.518>.

Saltin B, Blomqvist G, Mitchell JH, Johnson RL, Wildenthal K, Chapman CB. Response to exercise after bed rest and after training. *Circulation*. 1968;38:VII1–78. <http://www.ncbi.nlm.nih.gov/pubmed/5696236>.

Klausen K, Andersen LB, Pelle I. Adaptive changes in work capacity, skeletal muscle capillarization and enzyme levels during training and detraining. *Acta Physiol Scand*. 1981;113:9–16. <https://doi.org/10.1111/j.1748-1716.1981.tb06854.x>.

Holloszy JO. Biochemical adaptations in muscle. Effects of exercise on mitochondrial oxygen uptake and respiratory enzyme activity in skeletal muscle. *J Biol Chem*. 1967;242:2278–2282. <http://www.ncbi.nlm.nih.gov/pubmed/4290225>.

Gollnick PD, King DW. Effect of exercise and training on mitochondria of rat skeletal muscle. *Am J Phys*. 1969;216:1502–1509. www.physiology.org/journal/ajplegacy.

Clausen JSR, Marott JL, Holtermann A, Gyntelberg F, Jensen MT. Midlife cardiorespiratory fitness and the long-term risk of mortality: 46 years of follow-up. *J Am Coll Cardiol*. 2018;72:987–995. <https://doi.org/10.1016/j.jacc.2018.06.045>.

Laukkanen JA, Zaccardi F, Khan H, Kurl S, Jae SY, Rauramaa R. Long-term change in cardiorespiratory fitness and all-cause mortality: a population-based follow-up study. *Mayo Clin Proc*. 2016;91:1183–1188. <https://doi.org/10.1016/j.mayocp.2016.05.014>.

Gupta S, Rohatgi A, Ayers CR, et al. Cardiorespiratory fitness and classification of risk of cardiovascular disease mortality. *Circulation*. 2011;123:1377–1383. <https://doi.org/10.1161/CIRCULATIONAHA.110.003236>.

Kodama S, Saito K, Tanaka S, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *J Am Med Assoc*. 2009;301:2024–2035. <https://doi.org/10.1001/jama.2009.681>.

Zaccardi F, O'Donovan G, Webb DR, et al. Cardiorespiratory fitness and risk of type 2 diabetes mellitus: a 23-year cohort study and a meta-analysis of prospective studies. *Atherosclerosis*. 2015;243:131–137. <https://doi.org/10.1016/j.atherosclerosis.2015.09.016>.

Kraemer WJ, Ratamess NA. Fundamentals of resistance training: progression and exercise prescription. *Med Sci Sports Exerc*. 2004;36:674–688. <https://doi.org/10.1249/01.mss.0000121945.36635.61>.

Timpa S, Petersson IF, Zhou C, Englund M. Muscle strength in adolescent men and risk of cardiovascular disease events and mortality in middle age: a prospective cohort study. *BMC Med*. 2014;12:62. <https://doi.org/10.1186/1741-7015-12-62>.

Celis-Morales CA, Welsh P, Lyall DM, et al. Associations of grip strength with cardiovascular, respiratory, and

cancer outcomes and all cause mortality: prospective cohort study of half a million UK Biobank participants. *BMJ*. 2018;361. <https://doi.org/10.1136/bmj.k1651>.

Ruiz JR, Sui X, Lobelo F, et al. Muscular strength and adiposity as predictors of adulthood cancer mortality in men. *Cancer Epidemiol Biomark Prev*. 2009;18:1468–1476. <https://doi.org/10.1158/1055-9965.EPI-08-1075>.

Newman AB, Kupelian V, Visser M, et al. Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. *J Gerontol A Biol Sci Med Sci*. 2006;61:72–77. <https://doi.org/10.1093/gerona/61.1.72>.

Li R, Xia J, Zhang XI, et al. Associations of muscle mass and strength with all-cause mortality among US older adults. *Med Sci Sports Exerc*. 2018;50:458–467. <https://doi.org/10.1249/MSS.0000000000001448>.

García-Hermoso A, Cavero-Redondo I, Ramírez-Vélez R, et al. Muscular strength as a predictor of all-cause mortality in an apparently healthy population: a systematic review and meta-analysis of data from approximately 2 million men and women. *Arch Phys Med Rehabil*. 2018;99:2100–2113. e5 <https://doi.org/10.1016/j.apmr.2018.01.008>.

Heymtsfield SB, Thomas DM, Bosy-Westphal A, Müller MJ. The anatomy of resting energy expenditure: body composition mechanisms. *Eur J Clin Nutr*. 2019;73:166–171. <https://doi.org/10.1038/s41430-018-0319-3>.

Eves ND, Plotnikoff RC. Resistance training and type 2 diabetes: considerations for implementation at the population level. *Diabetes Care*. 2006;29:1933–1941. <https://doi.org/10.2337/dc05-1981>.

Srikanthan P, Karlamangla AS. Relative muscle mass is inversely associated with insulin resistance and prediabetes. Findings from the third National Health and Nutrition Examination Survey. *J Clin Endocrinol Metab*. 2011;96:2898–2903. <https://doi.org/10.1210/jc.2011-0435>.

Després JP, Bouchard C, Savard R, Tremblay A, Marcotte M, Thériault G. The effect of a 20-week endurance training program on adipose-tissue morphology and lipolysis in men and women. *Metabolism*. 1984;33:235–239. [https://doi.org/10.1016/0026-0495\(84\)90043-X](https://doi.org/10.1016/0026-0495(84)90043-X).

Bouchard C, Rankinen T. Individual differences in response to regular physical activity. *Med Sci Sports Exerc*. 2001;33:S446–S451. discussion S452–S453 <https://doi.org/10.1097/00005768-200106001-00013>.

Lortie G, Simoneau JA, Hamel P, Boulay MR, Landry F, Bouchard C. Responses of maximal aerobic power and capacity to aerobic training. *Int J Sports Med*. 1984;5:232–236. <https://doi.org/10.1055/s-2008-1025911>.

Hubal MJ, Gordish-Dressman H, Thompson PD, et al. Variability in muscle size and strength gain after unilateral resistance training. *Med Sci Sports Exerc*. 2005;37:964–972. <http://www.acsm-msse.org>.

Erskine RM, Stewart C. Inter-individual variability in the adaptation of human muscle specific tension to progressive resistance training. *Eur J Appl Physiol*. 2010;110:1117–1125. EVACS-Shaking hands with science View project Human muscle; growth and development View project <https://doi.org/10.1007/s00421-010-1601-9>.

Ahtiainen JP, Walker S, Peltonen H, et al. Heterogeneity in resistance training-induced muscle strength and mass responses in men and women of different ages. *Age (Dordr)*. 2016;38:10. <https://doi.org/10.1007/s11357-015-9870-1>.

Bouchard C, Blair SN, Church TS, et al. Adverse metabolic response to regular exercise: is it a rare or common occurrence? *PLoS One*. 2012;7:e37887. <https://doi.org/10.1371/journal.pone.0037887>.

Hautala AJ, Kiviniemi AM, Makikallio TH. Individual differences in the responses to endurance and resistance training. *Eur J Appl Physiol*. 2006;96:535–542. <https://doi.org/10.1007/s00421-005-0116-2>. Sudden Cardiac Death and ECG View project FinnValve View project.

Karavirta L, Häkkinen K, Kauhanen A, et al. Individual responses to combined endurance and strength training in older adults. *Med Sci Sports Exerc*. 2011;43:484–490. <https://doi.org/10.1249/MSS.0b013e3181f1bf0d>.

Montero D, Lundby C. Refuting the myth of non-response to exercise training: ‘non-responders’ do respond to higher dose of training. *J Physiol*. 2017;595:3377–3387. <https://doi.org/10.1113/JP273480>.

Eynon N, Ruiz JR, Oliveira J, Duarte JA, Birk R, Lucia A. Genes and elite athletes: a roadmap for future research. *J Physiol*. 2011;589:3063–3070. <https://doi.org/10.1113/jphysiol.2011.207035>.

Bouchard C. Genomic predictors of trainability. *Exp Physiol*. 2012;97:347–352. <https://doi.org/10.1113/expphysi->

ol.2011.058735. Blackwell Publishing Ltd.

Bouchard C, An P, Rice T, et al. Familial aggregation of VO₂(max) response to exercise training: results from the HERITAGE Family Study. *J Appl Physiol*. 1999;87(3):1003–1008. <https://doi.org/10.1152/jappl.1999.87.3.1003>.

Zempo H, Miyamoto-Mikami E, Kikuchi N, Fuku N, Miyachi M, Murakami H. Heritability estimates of muscle strength-related phenotypes: a systematic review and meta-analysis. *Scand J Med Sci Sports*. 2017;27:1537–1546. <https://doi.org/10.1111/sms.12804>.

Bray MS, Hagberg JM, Pérusse L, et al. The human gene map for performance and health-related fitness phenotypes: the 2006–2007 update. *Med Sci Sports Exerc*. 2009;41:35–73. <https://doi.org/10.1249/mss.0b013e3181844179>.

Ahmetov II, Egorova ES, Gabdrakhmanova LJ, Fedotovskaya ON. Genes and athletic performance: an update. *Med Sport Sci*. 2016;61:41–54. <https://doi.org/10.1159/000445240>.

Gjeveštađ GO, Holven KB, Ulven SM. Effects of exercise on gene expression of inflammatory markers in human peripheral blood cells: a systematic review. *Curr Cardiovasc Risk Rep*. 2015;9:34. <https://doi.org/10.1007/s12170-015-0463-4>.

Coffey VG, Hawley JA. The molecular basis of training adaptation. *Sports Med*. 2007;37:737–763. <https://doi.org/10.2165/00007256-200737090-00001>.

Egan B, Zierath JR. Exercise metabolism and the molecular regulation of skeletal muscle adaptation. *Cell Metab*. 2013;17:162–184. <https://doi.org/10.1016/j.cmet.2012.12.012>.

Waddington CH. The epigenotype. *Int J Epidemiol*. 1942;41(2012):10–13. <https://doi.org/10.1093/ije/dyr184>.

Kanherkar RR, Bhatia-Dey N, Csoka AB. Epigenetics across the human lifespan. *Front Cell Dev Biol*. 2014;2:1–19. <https://doi.org/10.3389/fcell.2014.00049>.

Rivera CM, Ren B. Mapping human epigenomes. *Cell*. 2013;155:39–55. <https://doi.org/10.1016/j.cell.2013.09.011>.

Grazioli E, Dimauro I, Mercatelli N, et al. Physical activity in the prevention of human diseases: role of epigenetic modifications. *BMC Genomics*. 2017;18:802. <https://doi.org/10.1186/s12864-017-4193-5>.

Martin EM, Fry RC. Environmental influences on the epigenome: exposure-associated DNA methylation in human populations. *Annu Rev Public Health*. 2018;39:309–333. <https://doi.org/10.1146/annurev-publhealth-040617-014629>.

Egger G, Liang G, Aparicio A, Jones PA. Epigenetics in human disease and prospects for epigenetic therapy. *Nature*. 2004;429:457–463. <https://doi.org/10.1038/nature02625>.

Baylin SB, Jones PA. Epigenetic determinants of cancer. *Cold Spring Harb Perspect Biol*. 2016;8:a019505. <https://doi.org/10.1101/cshperspect.a019505>.

Moore LD, Le T, Fan G. DNA methylation and its basic function. *Neuropsychopharmacology*. 2013;38:23–38. <https://doi.org/10.1038/npp.2012.112>.

Comper SJ, Palmiter RD. DNA methylation controls the inducibility of the mouse metallothionein-I gene in lymphoid cells. *Cell*. 1981;25:233–240. <http://www.ncbi.nlm.nih.gov/pubmed/6168387>.

Brenet F, Moh M, Funk P, et al. DNA methylation of the first exon is tightly linked to transcriptional silencing. *PLoS One*. 2011;6. <https://doi.org/10.1371/journal.pone.0014524>.

Jones PA. Functions of DNA methylation: Islands, start sites, gene bodies and beyond. *Nat Rev Genet*. 2012;13:484–492. <https://doi.org/10.1038/nrg3230>.

Bird AP, Wolffe AP. Methylation-induced repression—belts, braces, and chromatin. *Cell*. 1999;99:451–454. [https://doi.org/10.1016/S0092-8674\(00\)81532-9](https://doi.org/10.1016/S0092-8674(00)81532-9).

Bogdanović O, Veenstra GJC. DNA methylation and methyl-CpG binding proteins: developmental requirements and function. *Chromosoma*. 2009;118:549–565. <https://doi.org/10.1007/s00412-009-0221-9>.

Aran D, Toperoff G, Rosenberg M, Hellman A. Replication timing-related and gene body-specific methylation of active human genes. *Hum Mol Genet*. 2011;20:670–680. <https://doi.org/10.1093/hmg/ddq513>.

Chodavarapu RK, Feng S, Bernatavichute YV, et al. Relationship between nucleosome positioning and DNA methylation. *Nature*. 2010;466:388–392. <https://doi.org/10.1038/nature09147>.

Shukla S, Kavak E, Gregory M, et al. CTCF-promoted RNA polymerase II pausing links DNA methylation to splicing. *Nature*. 2011;479:74–79. <https://doi.org/10.1038/nature10442>.

Pradhan S, Bacolla A, Wells RD, Roberts RJ. Recombinant human DNA (cytosine-5) methyltransferase. *J Biol Chem*. 1999;274:33002–33010. <https://doi.org/10.1074/jbc.274.46.33002>.

Okano M, Bell DW, Haber DA, Li E. DNA methyltransferases Dnmt3a and Dnmt3b are essential for de novo methylation and mammalian development. *Cell*. 1999;99:247–257. [https://doi.org/10.1016/S0092-8674\(00\)81656-6](https://doi.org/10.1016/S0092-8674(00)81656-6).

Chen T, Ueda Y, Dodge JE, Wang Z, Li E. Establishment and maintenance of genomic methylation patterns in mouse embryonic stem cells by Dnmt3a and Dnmt3b. *Mol Cell Biol*. 2003;23:5594–5605. <https://doi.org/10.1128/MCB.23.16.5594>.

Kareta MS, Botello ZM, Ennis JJ, Chou C, Chédin F. Reconstitution and mechanism of the stimulation of de novo methylation by human DNMT3L. *J Biol Chem*. 2006;281:25893–25902. <https://doi.org/10.1074/jbc.M603140200>.

McGhee JD, Felsenfeld G. Nucleosome structure. *Annu Rev Biochem*. 1980;49:1115–1156. <https://doi.org/10.1146/annurev.bi.49.070180.005343>.

Dong X, Weng Z. The correlation between histone modifications and gene expression. *Epigenomics*. 2013;5:113–116. <https://doi.org/10.2217/epi.13.13>.

Alaskhar Alhamwe B, Khalaila R, Wolf J, et al. Histone modifications and their role in epigenetics of atopy and allergic diseases. *Allergy Asthma Clin Immunol*. 2018;14:39. <https://doi.org/10.1186/s13223-018-0259-4>.

Allfrey VG, Faulkner R, Mirsky AE. Acetylation and methylation of histones and their possible role in the regulation of RNA synthesis. *Proc Natl Acad Sci U S A*. 1964;51:786–794. <https://doi.org/10.1073/pnas.51.5.786>.

Clancey S, Brown W. Translation: DNA to mRNA to protein. *Nat Educ*. 2008;1:101. <https://www.nature.com/scitable/topicpage/translation-dna-to-mrna-to-protein-393>.

Ohno S. So much “junk” DNA in our genome. *Brookhaven Symp Biol*. 1972;23:366–370. <http://www.ncbi.nlm.nih.gov/pubmed/5065367>.

Encode Consortium. An integrated encyclopedia of DNA elements in the human genome. *Nature*. 2012;489:57–74. <https://doi.org/10.1038/nature11247>.

Peschansky VJ, Wahlestedt C. Non-coding RNAs as direct and indirect modulators of epigenetic regulation. *Epigenetics*. 2014;9:3–12. <https://doi.org/10.4161/epi.27473>.

Choudhuri S. Small noncoding RNAs: biogenesis, function, and emerging significance in toxicology. *J Biochem Mol Toxicol*. 2010;24:195–216. <https://doi.org/10.1002/jbt.20325>.

Lee RC, Feinbaum RL, Ambros V. The *C. elegans* heterochronic gene *lin-4* encodes small RNAs with antisense complementarity to *lin-14*. *Cell*. 1993;75:843–854. <http://www.ncbi.nlm.nih.gov/pubmed/8252621>.

Hammond SM. An overview of microRNAs. *Adv Drug Deliv Rev*. 2015;87:3–14. <https://doi.org/10.1016/j.addr.2015.05.001>.

Zhang F, Wang D. The pattern of microRNA binding site distribution. *Genes (Basel)*. 2017;8. <https://doi.org/10.3390/genes8110296>.

Duursma AM, Kedde M, Schrier M, le Sage C, Agami R. miR-148 targets human DNMT3b protein coding region. *RNA*. 2008;14:872–877. <https://doi.org/10.1261/rna.972008>.

Fabbri M, Garzon R, Cimmino A, et al. MicroRNA-29 family reverts aberrant methylation in lung cancer by targeting DNA methyltransferases 3A and 3B. *Proc Natl Acad Sci U S A*. 2007;104:15805–15810. <https://doi.org/10.1073/pnas.0707628104>.

Garzon R, Liu S, Fabbri M, et al. MicroRNA-29b induces global DNA hypomethylation and tumor suppressor gene reexpression in acute myeloid leukemia by targeting directly DNMT3A and 3B and indirectly DNMT1. *Blood*. 2009;113:6411–6418. <https://doi.org/10.1182/blood-2008-07-170589>.

Xu Y, Chao L, Wang J, Sun Y. miRNA-148a regulates the expression of the estrogen receptor through DNMT1-mediated DNA methylation in breast cancer cells. *Oncol Lett*. 2017;14:4736–4740. <https://doi.org/10.3892/ol.2017.144736>.

- org/10.3892/ol.2017.6803.
- Roberts TC. The microRNA biology of the mammalian nucleus. *Mol Ther Nucleic Acids*. 2014;3:1–8. <https://doi.org/10.1038/mtna.2014.40>.
- Xiao M, Li J, Li W, et al. MicroRNAs activate gene transcription epigenetically as an enhancer trigger. *RNA Biol*. 2017;14:1326–1334. <https://doi.org/10.1080/15476286.2015.1112487>.
- Morlando M, Fatica A. Alteration of epigenetic regulation by long noncoding RNAs in cancer. *Int J Mol Sci*. 2018;19. <https://doi.org/10.3390/ijms19020570>.
- Guttman M, Amit I, Garber M, et al. Chromatin signature reveals over a thousand highly conserved large non-coding RNAs in mammals. *Nature*. 2009;457:223–227. <https://doi.org/10.1038/nature07672>.
- Wang KC, Chang HY. Molecular mechanisms of long noncoding RNAs. *Mol Cell*. 2011;43:904–914. <https://doi.org/10.1016/j.molcel.2011.08.018>.Molecular.
- Anko M-L, Neugebauer KM. Long noncoding RNAs add another layer to pre-mRNA splicing regulation. *Mol Cell*. 2010;39:833–834. <https://doi.org/10.1016/j.molcel.2010.09.003>.
- Lindholm ME, Marabita F, Gomez-Cabrero D, et al. An integrative analysis reveals coordinated reprogramming of the epigenome and the transcriptome in human skeletal muscle after training. *Epigenetics*. 2015;9:1557–1569. <https://doi.org/10.4161/15592294.2014.982445>.
- King-Himmelreich TS, Schramm S, Wolters MC, et al. The impact of endurance exercise on global and AMPK gene-specific DNA methylation. *Biochem Biophys Res Commun*. 2016;474:284–290. <https://doi.org/10.1016/j.bbrc.2016.04.078>.
- Duggan C, Xiao L, Terry MB, McTiernan A. No effect of weight loss on LINE-1 methylation levels in peripheral blood leukocytes from postmenopausal overweight women. *Obesity (Silver Spring)*. 2014;22:2091–2096. <https://doi.org/10.1002/oby.20806>.
- Lisanti S, Omar WAW, Tomaszewski B, et al. Comparison of methods for quantification of global DNA methylation in human cells and tissues. *PLoS One*. 2013;8:e79044. <https://doi.org/10.1371/journal.pone.0079044>.
- Rowlands DS, Page RA, Sukala WR, et al. Multi-omic integrated networks connect DNA methylation and miRNA with skeletal muscle plasticity to chronic exercise in Type 2 diabetic obesity. *Physiol Genomics*. 2014;46:747–765. <https://doi.org/10.1152/physiolgenomics.00024.2014>.
- Nitert MD, Dayeh T, Volkov P, et al. Impact of an exercise intervention on DNA methylation in skeletal muscle from first-degree relatives of patients with type 2 diabetes. *Diabetes*. 2012;61:3322–3332. <https://doi.org/10.2337/db11-1653>.
- McGee SL, Sparling D, Olson A-L, Hargreaves M. Exercise increases MEF2- and GEF DNA-binding activity in human skeletal muscle. *FASEB J*. 2006;20:348–349. <https://doi.org/10.1096/fj.05-4671fje>.
- Ventura-Clapier R, Garnier A, Veksler V. Transcriptional control of mitochondrial biogenesis: the central role of PGC-1alpha. *Cardiovasc Res*. 2008;79:208–217. <https://doi.org/10.1093/cvr/cvn098>.
- Rönn T, Volkov P, Davegårdh C, et al. A six months exercise intervention influences the genome-wide DNA methylation pattern in human adipose tissue. *PLoS Genet*. 2013;9. <https://doi.org/10.1371/journal.pgen.1003572>.
- Denham J, O'Brien B, Marques FZ, Charchar FJ. Changes in the leukocyte methylome and its effect on cardiovascular-related genes after exercise. *J Appl Physiol*. 2015;118:475–488. <https://doi.org/10.1152/jappphysiol.00878.2014>.
- Zhang Y, Hashimoto S, Fujii C, et al. NFκB2 gene as a novel candidate that epigenetically responds to interval walking training. *Int J Sports Med*. 2015;36:769–775. <https://doi.org/10.1055/s-0035-1547221>.
- Tak PP, Firestein GS. NF-kappaB: a key role in inflammatory diseases. *J Clin Invest*. 2001;107:7–11. <https://doi.org/10.1172/JCI11830>.
- Nakajima K, Takeoka M, Mori M, et al. Exercise effects on methylation of ASC. *Gene*. 2010;31:671–675.
- Alibegovic AC, Sonne MP, Højbjerg L, et al. Insulin resistance induced by physical inactivity is associated with multiple transcriptional changes in skeletal muscle in young men. *Am J Physiol Endocrinol Metab*. 2010;299:E752–

E763. <https://doi.org/10.1152/ajpendo.00590.2009>.

Witzak CA, Sharoff CG, Goodyear LJ. AMP-activated protein kinase in skeletal muscle: from structure and localization to its role as a master regulator of cellular metabolism. *Cell Mol Life Sci*. 2008;65:3737–3755. <https://doi.org/10.1007/s00018-008-8244-6>.

Quentin T, Kitz J, Steinmetz M, Poppe A, Bär K, Krätzner R. Different expression of the catalytic alpha subunits of the AMP activated protein kinase—an immunohistochemical study in human tissue. *Histol Histopathol*. 2011;26:589–596. <https://doi.org/10.14670/HH-26.589>.

Robson-Ansley PJ, Saini A, Toms C, et al. Dynamic changes in DNA methylation status in peripheral blood Mononuclear cells following an acute bout of exercise: potential impact of exercise-induced elevations in interleukin-6 concentration. *J Biol Regul Homeost Agents*. 2014;28:407–417. <http://www.ncbi.nlm.nih.gov/pubmed/25316129>.

Walshe I, Robson-Ansley P, Gibson ASC, Lawrence C, Thompson KG, Ansley L. The reliability of the IL-6, sIL-6R and sgp130 response to a preloaded time trial. *Eur J Appl Physiol*. 2010;110:619–625. <https://doi.org/10.1007/s00421-010-1548-x>.

Hunter DJ, James L, Hussey B, Wadley AJ, Lindley MR, Maštana SS. Impact of aerobic exercise and fatty acid supplementation on global and gene-specific DNA methylation. *Epigenetics*. 2019;14:294–309. <https://doi.org/10.1080/15592294.2019.1582276>.

da Silva IRV, de Araujo CLP, Dorneles GP, et al. Exercise-modulated epigenetic markers and inflammatory response in COPD individuals: a pilot study. *Respir Physiol Neurobiol*. 2017;242:89–95. <https://doi.org/10.1016/j.resp.2017.04.004>.

Atamaniuk J, Vidotto C, Tschan H, Bachtel N, Stuhlmeier KM, Müller MM. Increased concentrations of cell-free plasma DNA after exhaustive exercise. *Clin Chem*. 2004;50:1668–1670. <https://doi.org/10.1373/clinchem.2004.034553>.

Peake J, Nosaka K, Suzuki K. Characterization of inflammatory responses to eccentric exercise in humans. *Exerc Immunol Rev*. 2005;11:64–85.

Barrès R, Yan J, Egan B, et al. Acute exercise remodels promoter methylation in human skeletal muscle. *Cell Metab*. 2012;15:405–411. <https://doi.org/10.1016/j.cmet.2012.01.001>.

Egan B, Carson BP, Garcia-Roves PM, et al. Exercise intensity-dependent regulation of peroxisome proliferator-activated receptor coactivator-1 mRNA abundance is associated with differential activation of upstream signalling kinases in human skeletal muscle. *J Physiol*. 2010;588:1779–1790. <https://doi.org/10.1113/jphysiol.2010.188011>.

Bajpeyi S, Covington JD, Taylor EM, Stewart LK, Galgani JE, Henagan TM. Skeletal muscle PGC1 α -1 nucleosome position and -260 nt DNA methylation determine exercise response and prevent ectopic lipid accumulation in men. *Endocrinology*. 2017;158:2190–2199. <https://doi.org/10.1210/en.2017-00051>.

Dimauro I, Scalabrini M, Fantini C, et al. Resistance training and redox homeostasis: correlation with age-associated genomic changes. *Redox Biol*. 2016;10:34–44. <https://doi.org/10.1016/j.redox.2016.09.008>.

Denham J, Marques FZ, Bruns EL, O'Brien BJ, Charchar FJ. Epigenetic changes in leukocytes after 8 weeks of resistance exercise training. *Eur J Appl Physiol*. 2016;116:1245–1253. <https://doi.org/10.1007/s00421-016-3382-2>.

Seaborne RA, Strauss J, Cocks M, et al. Human skeletal muscle possesses an epigenetic memory of hypertrophy. *Sci Rep*. 2018;8:1–17. <https://doi.org/10.1038/s41598-018-20287-3>.

McGee SL, Fairlie E, Garnham AP, Hargreaves M. Exercise-induced histone modifications in human skeletal muscle. *J Physiol*. 2009;587:5951–5958. <https://doi.org/10.1113/jphysiol.2009.181065>.

Morris SA, Rao B, Garcia BA, et al. Identification of histone H3 lysine 36 acetylation as a highly conserved histone modification. *J Biol Chem*. 2007;282:7632–7640. <https://doi.org/10.1074/jbc.M607909200>.

Dorneles GP, Boeira MCR, Schipper LL, et al. Acute strenuous exercise induces an imbalance on histone H4 acetylation/histone deacetylase 2 and increases the proinflammatory profile of PBMC of obese individuals. 2017;2017. <https://doi.org/10.1155/2017/1530230>.

Zimmer P, Baumann FT, Bloch W, et al. Impact of exercise on pro inflammatory cytokine levels and epigenetic

modulations of tumor-competitive lymphocytes in non-Hodgkin-lymphoma patients-randomized controlled trial. *Eur J Haematol.* 2014;93:527–532. <https://doi.org/10.1111/ejh.12395>.

Lavratti C, Dorneles G, Pochmann D, et al. Exercise-induced modulation of histone H4 acetylation status and cytokines levels in patients with schizophrenia. *Physiol Behav.* 2017;168:84–90. <https://doi.org/10.1016/j.physbeh.2016.10.021>.

Denham J, O'Brien B, Harvey JT, Charchar FJ. Genome-wide sperm DNA methylation changes after 3 months of exercise training in humans. *Epigenomics.* 2015;7:717–731. <https://doi.org/10.2217/epi.15.29>.

Keller P, Vollaard NBJ, Gustafsson T, et al. A transcriptional map of the impact of endurance exercise training on skeletal muscle phenotype. *J Appl Physiol.* 2011;110:46–59. <https://doi.org/10.1152/jappphysiol.00634.2010>.

Russell AP, Lamon S, Boon H, et al. Regulation of miRNAs in human skeletal muscle following acute endurance exercise and short-term endurance training. *J Physiol.* 2013;591:4637–4653. <https://doi.org/10.1113/jphysiol.2013.255695>.

Nielsen S, Scheele C, Yfanti C, et al. Muscle specific microRNAs are regulated by endurance exercise in human skeletal muscle. *J Physiol.* 2010;588:4029–4037. <https://doi.org/10.1113/jphysiol.2010.189860>.

Kristensen MM, Davidsen PK, Vigelsø A, et al. miRNAs in human subcutaneous adipose tissue: effects of weight loss induced by hypocaloric diet and exercise. *Obesity (Silver Spring).* 2017;25:572–580. <https://doi.org/10.1002/oby.21765>.

Tsiloulis T, Pike J, Powell D, et al. Impact of endurance exercise training on adipocyte microRNA expression in overweight men. *FASEB J.* 2017;31:161–171. <https://doi.org/10.1096/fj.201600678R>.

Dias RG, Silva MSM, Duarte NE, et al. PBMCs express a transcriptome signature predictor of oxygen uptake responsiveness to endurance exercise training in men. *Physiol Genomics.* 2015;47:13–23. <https://doi.org/10.1152/physiolgenomics.00072.2014>.

Radom-Aizik S, Zaldivar FP, Haddad F, Cooper DM. Impact of brief exercise on circulating monocyte gene and microRNA expression: implications for atherosclerotic vascular disease. *Brain Behav Immun.* 2014;39:121–129. <https://doi.org/10.1016/j.bbi.2014.01.003>.

Radom-Aizik S, Zaldivar F, Haddad F, Cooper DM. Impact of brief exercise on peripheral blood NK cell gene and microRNA expression in young adults. *J Appl Physiol.* 2013;114:628–636. <https://doi.org/10.1152/jappphysiol.01341.2012>.

Radom-Aizik S, Zaldivar F, Oliver S, Galassetti P, Cooper DM. Evidence for microRNA involvement in exercise-associated neutrophil gene expression changes. *J Appl Physiol.* 2010;109:252–261. <https://doi.org/10.1152/jappphysiol.01291.2009>.

Radom-Aizik S, Zaldivar F, Leu S-Y, Adams GR, Oliver S, Cooper DM. Effects of exercise on microRNA expression in young males peripheral blood mononuclear cells. *Clin Transl Sci.* 2012;5:32–38. <https://doi.org/10.1111/j.1752-8062.2011.00384.x>.

Rönn T, Volkov P, Tornberg A, et al. Extensive changes in the transcriptional profile of human adipose tissue including genes involved in oxidative phosphorylation after a 6-month exercise intervention. *Acta Physiol (Oxf).* 2014;211:188–200. <https://doi.org/10.1111/apha.12247>.

Stanford KI, Goodyear LJ. Exercise regulation of adipose tissue. *Adipocyte.* 2016;5:153–162. <https://doi.org/10.1080/21623945.2016.1191307>.

Chen X, Liang H, Zhang J, Zen K, Zhang C-Y. Secreted microRNAs: a new form of intercellular communication. *Trends Cell Biol.* 2012;22:125–132. <https://doi.org/10.1016/j.tcb.2011.12.001>.

Reid G, Kirschner MB, van Zandwijk N. Circulating microRNAs: association with disease and potential use as biomarkers. *Crit Rev Oncol Hematol.* 2011;80:193–208. <https://doi.org/10.1016/j.critrevonc.2010.11.004>.

Sapp RM, Shill DD, Roth SM, Hagberg JM. Circulating microRNAs in acute and chronic exercise: more than mere biomarkers. *J Appl Physiol.* 2017;122:702–717. <https://doi.org/10.1152/jappphysiol.00982.2016>.

- Nielsen S, Åkerström T, Rinnov A, et al. The miRNA plasma signature in response to acute aerobic exercise and endurance training. *PLoS One*. 2014;9. <https://doi.org/10.1371/journal.pone.0087308>.
- Baggish AL, Park J, Min P-K, et al. Rapid upregulation and clearance of distinct circulating microRNAs after prolonged aerobic exercise. *J Appl Physiol*. 2014;116:522–531. <https://doi.org/10.1152/jappphysiol.01141.2013>.
- Mooren FC, Viereck J, Krüger K, Thum T. Circulating microRNAs as potential biomarkers of aerobic exercise capacity. *Am J Physiol Heart Circ Physiol*. 2014;306:H557–H563. <https://doi.org/10.1152/ajpheart.00711.2013>.
- Cui SF, Wang C, Yin X, et al. Similar responses of circulating microRNAs to acute high-intensity interval exercise and vigorous-intensity continuous exercise. *Front Physiol*. 2016;7:102. <https://doi.org/10.3389/fphys.2016.00102>.
- Wahl P, Wehmeier UF, Jansen FJ, et al. Acute effects of different exercise protocols on the circulating vascular microRNAs -16, -21, and -126 in trained subjects. *Front Physiol*. 2016;7:643. <https://doi.org/10.3389/fphys.2016.00643>.
- Ogasawara R, Akimoto T, Umeno T, Sawada S, Hamaoka T, Fujita S. MicroRNA expression profiling in skeletal muscle reveals different regulatory patterns in high and low responders to resistance training. *Physiol Genomics*. 2016;48:320–324. <https://doi.org/10.1152/physiolgenomics.00124.2015>.
- Davidson PK, Gallagher IJ, Hartman JW, et al. High responders to resistance exercise training demonstrate differential regulation of skeletal muscle microRNA expression. *J Appl Physiol*. 2011;110:309–317. <https://doi.org/10.1152/jappphysiol.00901.2010>.
- Drummond MJ, McCarthy JJ, Fry CS, Esser KA, Rasmussen BB. Aging differentially affects human skeletal muscle microRNA expression at rest and after an anabolic stimulus of resistance exercise and essential amino acids. *Am J Physiol Endocrinol Metab*. 2008;295:E1333–E1340. <https://doi.org/10.1152/ajpendo.90562.2008>.
- Rivas DA, Lessard SJ, Rice NP, et al. Diminished skeletal muscle microRNA expression with aging is associated with attenuated muscle plasticity and inhibition of IGF-1 signaling. *FASEB J*. 2014;28:4133–4147. <https://doi.org/10.1096/fj.14-254490>.
- Zhang T, Birbrair A, Wang Z-M, et al. Improved knee extensor strength with resistance training associates with muscle specific miRNAs in older adults. *Exp Gerontol*. 2015;62:7–13. <https://doi.org/10.1016/j.exger.2014.12.014>.
- Hu Z, Klein JD, Mitch WE, Zhang L, Martinez I, Wang XH. MicroRNA-29 induces cellular senescence in aging muscle through multiple signaling pathways. *Aging (Albany, NY)*. 2014;6:160–175. <https://doi.org/10.18632/aging.100643>.
- D'Souza RF, Markworth JF, Aasen KMM, Zeng N, Cameron-Smith D, Mitchell CJ. Acute resistance exercise modulates microRNA expression profiles: combined tissue and circulatory targeted analyses. *PLoS One*. 2017;12. <https://doi.org/10.1371/journal.pone.0181594>, e0181594.
- Margolis LM, Lessard SJ, Ezzyat Y, Fielding RA, Rivas DA. Circulating microRNA are predictive of aging and acute adaptive response to resistance exercise in men. *J Gerontol A Biol Sci Med Sci*. 2017;72:1319–1326. <https://doi.org/10.1093/gerona/glw243>.
- Kiss T. Small nucleolar RNAs: an abundant group of noncoding RNAs with diverse cellular functions. *Cell*. 2002;109:145–148. [https://doi.org/10.1016/s0092-8674\(02\)00718-3](https://doi.org/10.1016/s0092-8674(02)00718-3).
- Håkansson KEJ, Sollie O, Simons KH, Quax PHA, Jensen J, Nossent AY. Circulating small non-coding RNAs as biomarkers for recovery after exhaustive or repetitive exercise. *Front Physiol*. 2018;9:1–12. <https://doi.org/10.3389/fphys.2018.01136>.
- Valleron W, Laprevotte E, Gautier E-F, et al. Specific small nucleolar RNA expression profiles in acute leukemia. *Leukemia*. 2012;26:2052–2060. <https://doi.org/10.1038/leu.2012.111>.
- Zhu M, Liu J, Xiao J, et al. Lnc-mg is a long non-coding RNA that promotes myogenesis. *Nat Commun*. 2017;8:14718. <https://doi.org/10.1038/ncomms14718>.

Chapter 7

Adams PD, Jasper H, Rudolph KL. Aging-induced stem cell mutations as drivers for disease and cancer. *Cell Stem Cell*. 2015;16(6):601–612. <https://doi.org/10.1016/j.stem.2015.05.002>.

Gude NA, Broughton KM, Firouzi F, Sussman MA. Cardiac ageing: extrinsic and intrinsic factors in cellular renewal and senescence. *Nat Rev Cardiol*. 2018;15(9):523–542. <https://doi.org/10.1038/s41569-018-0061-5>.

Hou Y, Dan X, Babbar M, et al. Ageing as a risk factor for neurodegenerative disease. *Nat Rev Neurol*. 2019;15(10):565–581. <https://doi.org/10.1038/s41582-019-0244-7>.

Khosla S, Farr JN, Tchkonina T, Kirkland JL. The role of cellular senescence in ageing and endocrine disease. *Nat Rev Endocrinol*. 2020;16(5):263–275. <https://doi.org/10.1038/s41574-020-0335-y>.

Shaw AC, Goldstein DR, Montgomery RR. Age-dependent dysregulation of innate immunity. *Nat Rev Immunol*. 2013;13(12):875–887. <https://doi.org/10.1038/nri3547>.

United-Nations. *World Population Ageing 2019: Highlights*; 2020. Retrieved from: https://www.un.org/development/desa/pd/sites/www.un.org.development.desa.pd/files/files/documents/2020/Jan/un_2019_worldpopulationageing_report.pdf.

Martin GM, LaMarco K, Strauss E, Kelner KL. Research on aging: the end of the beginning. *Science*. 2003;299(5611):1339–1341. <https://doi.org/10.1126/science.299.5611.1339>.

Miller RA, Harper JM, Dysko RC, Durkee SJ, Austad SN. Longer life spans and delayed maturation in wild-derived mice. *Exp Biol Med*. 2002;227(7):500–508. <https://doi.org/10.1177/153537020222700715>.

Olshansky SJ, Carnes BA, Cassel C. In search of methuselah: estimating the upper limits to human longevity. *Science*. 1990;250(4981):634–640. <https://doi.org/10.1126/science.2237414>.

Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet*. 2012;380(9838):219–229. [https://doi.org/10.1016/S0140-6736\(12\)61031-9](https://doi.org/10.1016/S0140-6736(12)61031-9).

World Health Organization. *Global Health Risks: Mortality and Burden of Disease Attributable to Selected Major Risks*; 2009. Retrieved from Geneva, Switzerland http://www.who.int/healthinfo/global_burden_disease/GlobalHealthRisks_report_full.pdf.

Chakravarty EF, Hubert HB, Lingala VB, Fries JF. Reduced disability and mortality among aging runners: 21-year longitudinal study. *Arch Intern Med*. 2008;168(15):1638–1646. <https://doi.org/10.1001/archinte.168.15.1638>.

Duggal NA, Pollock RD, Lazarus NR, Harridge S, Lord JM. Major features of immunesenescence, including reduced thymic output, are ameliorated by high levels of physical activity in adulthood. *Aging Cell*. 2018;17(2). <https://doi.org/10.1111/acel.12750>.

Pollock RD, O'Brien KA, Daniels LJ, et al. Properties of the vastus lateralis muscle in relation to age and physiological function in master cyclists aged 55–79 years. *Aging Cell*. 2018;17(2). <https://doi.org/10.1111/acel.12735>.

Lee DC, Brellenthin AG, Thompson PD, Sui X, Lee IM, Lavie CJ. Running as a key lifestyle medicine for longevity. *Prog Cardiovasc Dis*. 2017;60(1):45–55. <https://doi.org/10.1016/j.pcad.2017.03.005>.

Moore SC, Patel AV, Matthews CE, et al. Leisure time physical activity of moderate to vigorous intensity and mortality: a large pooled cohort analysis. *PLoS Med*. 2012;9(11). <https://doi.org/10.1371/journal.pmed.1001335>, e1001335.

Barros SP, Offenbacher S. Epigenetics: connecting environment and genotype to phenotype and disease. *J Dent Res*. 2009;88(5):400–408. <https://doi.org/10.1177/0022034509335868>.

Rodenhiser D, Mann M. Epigenetics and human disease: translating basic biology into clinical applications. *Can Med Assoc J*. 2006;174(3):341–348. <https://doi.org/10.1503/cmaj.050774>.

van Dijk SJ, Tellam RL, Morrison JL, Muhlhausler BS, Molloy PL. Recent developments on the role of epigenetics

in obesity and metabolic disease. *Clin Epigenetics*. 2015;7:66. <https://doi.org/10.1186/s13148-015-0101-5>.

Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell*. 2013;153(6):1194–1217. <https://doi.org/10.1016/j.cell.2013.05.039>.

Rebello-Marques A, De Sousa Lages A, Andrade R, et al. Aging hallmarks: the benefits of physical exercise. *Front Endocrinol*. 2018;9:258. <https://doi.org/10.3389/fendo.2018.00258>.

Fransquet PD, Wrigglesworth J, Woods RL, Ernst ME, Ryan J. The epigenetic clock as a predictor of disease and mortality risk: a systematic review and meta-analysis. *Clin Epigenetics*. 2019;11(1):62. <https://doi.org/10.1186/s13148-019-0656-7>.

Ferrioli M, Zauli G, Maiorano P, Milani D, Mirandola P, Neri LM. Role of physical exercise in the regulation of epigenetic mechanisms in inflammation, cancer, neurodegenerative diseases, and aging process. *J Cell Physiol*. 2019;234(9):14852–14864. <https://doi.org/10.1002/jcp.28304>.

Haskell WL, Lee IM, Pate RR, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation*. 2007;116(9):1081–1093. <https://doi.org/10.1161/CIRCULATIONAHA.107.185649>.

Blair SN, Cheng Y, Scott Holder J. Is physical activity or physical fitness more important in defining health benefits? *Med Sci Sports Exerc*. 2001;33(6):S379–S399.

Williams PT. Physical fitness and activity as separate heart disease risk factors: a meta-analysis. *Med Sci Sports Exerc*. 2001;33(5):754–761.

Blair SN, Jackson AS. Physical fitness and activity as separate heart disease risk factors: a meta-analysis. *Med Sci Sports Exerc*. 2001;33(5):762–764.

Blair SN, Kohl HW, Barlow CE. Physical activity, physical fitness, and all-cause mortality in women: do women need to be active? *J Am Coll Nutr*. 1993;12(4):368–371.

Kampert JB, Blair SN, Barlow CE, Kohl HW. Physical activity, physical fitness, and all-cause and cancer mortality: a prospective study of men and women. *Ann Epidemiol*. 1996;6(5):452–457. [https://doi.org/10.1016/S1047-2797\(96\)00059-2](https://doi.org/10.1016/S1047-2797(96)00059-2).

Kodama S, Saito K, Tanaka S, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA*. 2009;301(19):2024–2035. <https://doi.org/10.1001/jama.2009.681>.

Lakka TA, Venalainen JM, Rauramaa R, Salonen R, Tuomilehto J, Salonen JT. Relation of leisure-time physical activity and cardiorespiratory fitness to the risk of acute myocardial infarction in men. *N Engl J Med*. 1994;330(22):1549–1554. <https://doi.org/10.1056/NEJM199406023302201>.

Myers J, Kaykha A, George S, et al. Fitness versus physical activity patterns in predicting mortality in men. *Am J Med*. 2004;117(12):912–918. <https://doi.org/10.1016/j.amjmed.2004.06.047>.

Park MS, Chung SY, Chang Y, Kim K. Physical activity and physical fitness as predictors of all-cause mortality in Korean men. *J Korean Med Sci*. 2009;24(1):13–19. <https://doi.org/10.3346/jkms.2009.24.1.13>.

Sui X, LaMonte MJ, Laditka JN, et al. Cardiorespiratory fitness and adiposity as mortality predictors in older adults. *JAMA*. 2007;298(21):2507–2516.

Villeneuve PJ, Morrison HI, Craig CL, Schaubel DE. Physical activity, physical fitness, and risk of dying. *Epidemiology*. 1998;9(6):626–631.

Wei M, Gibbons LW, Kampert JB, Nichaman MZ, Blair SN. Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. *Ann Intern Med*. 2000;132(8):605–611.

Paffenbarger RS, Hyde RT, Wing AL, Hsieh CC. Physical activity, all-cause mortality, and longevity of college alumni. *New Engl J Med*. 1986;314(10):605–613.

Paffenbarger Jr RS, Hyde RT, Wing AL, Steinmetz CH. A natural history of athleticism and cardiovascular health. *JAMA*. 1984;252(4):491–495. <https://doi.org/10.1001/jama.1984.03350040021015>.

- Lee D-c, Pate RR, Lavie CJ, Sui X, Church TS, Blair SN. Leisure-time running reduces all-cause and cardiovascular mortality risk. *J Am Coll Cardiol*. 2014;64(5):472–481. <https://doi.org/10.1016/j.jacc.2014.04.058>.
- Blair SN, Kohl III HW, Paffenbarger Jr RS, Clark DG, Gibbons LW. Physical fitness and all-cause mortality: prospective study of healthy men and women. *JAMA*. 1989;262(17):2395–2401. <https://doi.org/10.1001/jama.1989.03430170057028>.
- Gulati M, Black HR, Shaw LJ, et al. The prognostic value of a nomogram for exercise capacity in women. *N Engl J Med*. 2005;353(5):468–475. <https://doi.org/10.1056/NEJMoa044154>.
- Kokkinos P. Physical activity and cardiovascular disease prevention: current recommendations. *Angiology*. 2008. <https://doi.org/10.1177/0003319708318582>.
- Mora S, Redberg RF, Cui Y, et al. Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women. *JAMA*. 2003;290(12):1600–1607. <https://doi.org/10.1001/jama.290.12.1600>.
- Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med*. 2002;346(11):793–801. <https://doi.org/10.1056/NEJMoa011858>.
- Sandvik L, Erikssen J, Thaulow E, Erikssen G, Mundal R, Rodahl K. Physical fitness as a predictor of mortality among healthy, middle-aged Norwegian men. *N Engl J Med*. 1993;328(8):533–537. <https://doi.org/10.1056/NEJM199302253280803>.
- McDonagh MJ, Davies CT. Adaptive response of mammalian skeletal muscle to exercise with high loads. *Eur J Appl Physiol Occup Physiol*. 1984;52(2):139–155.
- Laufs U, Werner N, Link A, et al. Physical training increases endothelial progenitor cells, inhibits neointima formation, and enhances angiogenesis. *Circulation*. 2004;109(2):220–226. <https://doi.org/10.1161/01.CIR.0000109141.48980.37>.
- Sipola P, Heikkinen J, Laaksonen DE, Kettunen R. Influence of 12 weeks of jogging on magnetic resonance-determined left ventricular characteristics in previously sedentary subjects free of cardiovascular disease. *Am J Cardiol*. 2009;103(4):567–571. <https://doi.org/10.1016/j.amjcard.2008.10.020>.
- Sato Y, Nagasaki M, Nakai N, Fushimi T. Physical exercise improves glucose metabolism in lifestyle-related diseases. *Exp Biol Med*. 2003;228(10):1208–1212. <https://doi.org/10.1177/153537020322801017>.
- Nieman DC, Henson DA. Role of endurance exercise in immune senescence. *Med Sci Sports Exerc*. 1994;26(2):172–181.
- Joyner MJ, Green DJ. Exercise protects the cardiovascular system: effects beyond traditional risk factors. *J Physiol*. 2009;587(23):5551–5558. <https://doi.org/10.1113/jphysiol.2009.179432>.
- Neufer PD, Bamman MM, Muoio DM, et al. Understanding the cellular and molecular mechanisms of physical activity-induced health benefits. *Cell Metab*. 2015;22(1):4–11. <https://doi.org/10.1016/j.cmet.2015.05.011>.
- Mora S, Cook N, Buring JE, Ridker PM, Lee IM. Physical activity and reduced risk of cardiovascular events: potential mediating mechanisms. *Circulation*. 2007;116(19):2110–2118. <https://doi.org/10.1161/CIRCULATIONHA.107.729939>.
- Monroy-Jaramillo N, Vázquez-Martínez ER. Epigenetics and ageing. In: Gomez-Verjan JC, RiveroSegura NA, eds. *Clinical Genetics and Genomics of Aging*. Cham: Springer International Publishing; 2020:141–166.
- Jones MJ, Goodman SJ, Kobor MS. DNA methylation and healthy human aging. *Aging Cell*. 2015;14(6):924–932. <https://doi.org/10.1111/accel.12349>.
- Xiao FH, Kong QP, Perry B, He YH. Progress on the role of DNA methylation in aging and longevity. *Brief Funct Genom*. 2016;15(6):454–459. <https://doi.org/10.1093/bfgp/ewl009>.
- Heyn H, Li N, Ferreira HJ, et al. Distinct DNA methylomes of newborns and centenarians. *Proc Natl Acad Sci*. 2012;109(26):10522–10527. <https://doi.org/10.1073/pnas.1120658109>.
- Jylhävä J, Pedersen NL, Hägg S. Biological age predictors. *EBioMedicine*. 2017;21:29–36. <https://doi.org/10.1016/j.ebiom.2017.05.011>.

org/10.1016/j.ebiom.2017.03.046.

Lee HY, Lee SD, Shin K-J. Forensic DNA methylation profiling from evidence material for investigative leads. *BMB Rep.* 2016;49(7):359–369. <https://doi.org/10.5483/bmbrep.2016.49.7.070>.

Chen L-L. The biogenesis and emerging roles of circular RNAs. *Nat Rev Mol Cell Biol.* 2016;17(4):205.

Griñán-Ferré C, Izquierdo V, Otero E, et al. Environmental enrichment improves cognitive deficits, AD hallmarks and epigenetic alterations presented in 5xFAD mouse model. *Front Cell Neurosci.* 2018;12:224. <https://doi.org/10.3389/fncel.2018.00224>.

Obeid R, Schadt A, Dillmann U, Kostopoulos P, Fassbender K, Herrmann W. Methylation status and neurodegenerative markers in Parkinson disease. *Clin Chem.* 2009;55(10):1852–1860. <https://doi.org/10.1373/clinchem.2009.125021>.

Glezeva N, Moran B, Collier P, et al. Targeted DNA methylation profiling of human cardiac tissue reveals novel epigenetic traits and gene deregulation across different heart failure patient subtypes. *Circ Heart Fail.* 2019;12(3). <https://doi.org/10.1161/circheartfailure.118.005765>, e005765.

Movassagh M, Choy M-K, Goddard M, Bennett MR, Down TA, Foo RSY. Differential DNA methylation correlates with differential expression of angiogenic factors in human heart failure. *PLoS One.* 2010;5(1):e8564. <https://doi.org/10.1371/journal.pone.0008564>.

Gensous N, Bacalini MG, Pirazzini C, et al. The epigenetic landscape of age-related diseases: the geroscience perspective. *Biogerontology.* 2017;18(4):549–559. <https://doi.org/10.1007/s10522-017-9695-7>.

You JS, Jones PA. Cancer genetics and epigenetics: two sides of the same coin? *Cancer Cell.* 2012;22(1):9–20. <https://doi.org/10.1016/j.ccr.2012.06.008>.

So K, Tamura G, Honda T, et al. Multiple tumor suppressor genes are increasingly methylated with age in non-neoplastic gastric epithelia. *Cancer Sci.* 2006;97(11):1155–1158. <https://doi.org/10.1111/j.1349-7006.2006.00302.x>.

Baylin SB, Jones PA. A decade of exploring the cancer epigenome—biological and translational implications. *Nat Rev Cancer.* 2011;11(10):726–734. <https://doi.org/10.1038/nrc3130>.

Song S, Johnson FB. Epigenetic mechanisms impacting aging: a focus on histone levels and telomeres. *Genes.* 2018;9(4):201. <https://doi.org/10.3390/genes9040201>.

Scaffidi P, Misteli TJS. Lamin A-dependent nuclear defects in human. *Aging.* 2006;312(5776):1059–1063.

Shumaker DK, Dechat T, Kohlmaier A, et al. Mutant nuclear lamin A leads to progressive alterations of epigenetic control in premature aging. *Proc Natl Acad Sci U S A.* 2006;103(23):8703–8708.

Lander ES, Linton LM, Birren B, et al. Initial sequencing and analysis of the human genome. *Nature.* 2001;409.

Tian X, Firsanov D, Zhang Z, et al. SIRT6 is responsible for more efficient DNA double-strand break repair in long-lived species. *Cell.* 2019;177(3):622–638.e622.

Barski A, Cuddapah S, Cui K, et al. High-resolution profiling of histone methylations in the human genome. *Cell.* 2007;129(4):823–837.

Benevolenskaya EV. Histone H3K4 demethylases are essential in development and differentiation. *Biochem Cell Biol.* 2007;85(4):435–443.

Klose RJ, Zhang Y. Regulation of histone methylation by demethylimination and demethylation. *Nat Rev Mol Cell Biol.* 2007;8(4):307–318.

Fraga MF, Esteller M. Epigenetics and aging: the targets and the marks. *Trends Genet.* 2007;23(8):413–418.

Han S, Brunet A. Histone methylation makes its mark on longevity. *Trends Cell Biol.* 2012;22(1):42–49. <https://doi.org/10.1016/j.tcb.2011.11.001>.

Ahuja G, Bartsch D, Yao W, et al. Loss of genomic integrity induced by lysosphingolipid imbalance drives ageing in the heart. *EMBO Rep.* 2019;20(4), e47407.

El Mansouri FE, Chabane N, Zayed N, et al. Contribution of H3K4 methylation by SET-1A to interleukin-1-induced cyclooxygenase 2 and inducible nitric oxide synthase expression in human osteoarthritis chondrocytes. *Arthritis Rheum.* 2011;63(1):168–179.

- Narayan P, Dragunow M. Alzheimer's disease and histone code alterations. In: *Neuroepigenomics in Aging and Disease*. Springer; 2017:321–336.
- Portela A, Esteller M. Epigenetic modifications and human disease. *Nat Biotechnol*. 2010;28(10):1057.
- Kouzarides T. Chromatin modifications and their function. *Cell*. 2007;128(4):693–705.
- Mosammamapař N, Shi Y. Reversal of histone methylation: biochemical and molecular mechanisms of histone demethylases. *Annu Rev Biochem*. 2010;79:155–179.
- Bradbury C, Khanim F, Hayden R, et al. Histone deacetylases in acute myeloid leukaemia show a distinctive pattern of expression that changes selectively in response to deacetylase inhibitors. *Leukemia*. 2005;19(10):1751–1759.
- Chen WY, Wang DH, Yen RC, Luo J, Gu W, Baylin SB. Tumor suppressor HIC1 directly regulates SIRT1 to modulate p53-dependent DNA-damage responses. *Cell*. 2005;123(3):437–448.
- Engel N, Mahlknecht U. Aging and anti-aging: unexpected side effects of everyday medication through sirtuin1 modulation. *Int J Mol Med*. 2008;21(2):223–232.
- Chandra T, Kirschner K, Thuret J-Y, et al. Independence of repressive histone marks and chromatin compaction during senescent heterochromatic layer formation. *Mol Cell*. 2012;47(2):203–214.
- Narita M, Nuñez S, Heard E, et al. Rb-mediated heterochromatin formation and silencing of E2F target genes during cellular senescence. *Cell*. 2003;113(6):703–716.
- Hu W, Wang T, Xu J, Li H. MicroRNA mediates DNA methylation of target genes. *Biochem Biophys Res Commun*. 2014;444(4):676–681.
- Zhang Z, Zhang MQ. Histone modification profiles are predictive for tissue/cell-type specific expression of both protein-coding and microRNA genes. *BMC Bioinform*. 2011;12(1):155.
- Gomez-Verjan J, Vazquez-Martinez E, Rivero-Segura N, Medina-Campos R. The RNA world of human ageing. *Hum Genet*. 2018;137(11–12):865–879.
- Braga DL, Mousovich-Neto F, Tonon-da-Silva G, Salgueiro WG, Mori MA. Epigenetic changes during ageing and their underlying mechanisms. *Biogerontology*. 2020;21.
- De Lencastre A, Pincus Z, Zhou K, Kato M, Lee SS, Slack FJ. MicroRNAs both promote and antagonize longevity in *C. elegans*. *Curr Biol*. 2010;20(24):2159–2168.
- Kato M, Chen X, Inukai S, Zhao H, Slack FJ. Age-associated changes in expression of small, noncoding RNAs, including microRNAs, in *C. elegans*. *RNA*. 2011;17(10):1804–1820.
- Mori MA, Raghavan P, Thomou T, et al. Role of microRNA processing in adipose tissue in stress defense and longevity. *Cell Metab*. 2012;16(3):336–347.
- ElSharawy A, Keller A, Flachsbart F, et al. Genome-wide miRNA signatures of human longevity. *Aging Cell*. 2012;11(4):607–616.
- Balzano F, Deiana M, Dei Giudici S, et al. MicroRNA expression analysis of centenarians and rheumatoid arthritis patients reveals a common expression pattern. *Int J Med Sci*. 2017;14(7):622.
- Gombar S, Jung HJ, Dong F, et al. Comprehensive microRNA profiling in B-cells of human centenarians by massively parallel sequencing. *BMC Genomics*. 2012;13(1):353.
- Gudmundsson H, Gudbjartsson DF, Kong A, et al. Inheritance of human longevity in Iceland. *Eur J Hum Genet*. 2000;8(10):743–749.
- Hooten NN, Abdelmohsen K, Gorospe M, Ejiogu N, Zonderman AB, Evans MK. microRNA expression patterns reveal differential expression of target genes with age. *PLoS One*. 2010;5(5), e10724.
- Jung HJ, Suh Y. Circulating miRNAs in ageing and ageing-related diseases. *J Genet Genom*. 2014;41(9):465–472.
- Kumar S, Vijayan M, Bhatti J, Reddy PH. MicroRNAs as peripheral biomarkers in aging and age-related diseases. In: *Progress in Molecular Biology and Translational Science*. Vol. 146. Elsevier; 2017:47–94.
- de Lucia C, Komici K, Borghetti G, et al. microRNA in cardiovascular aging and age-related cardiovascular diseases. *Front Med*. 2017;4:74.

Hadar A, Milanesi E, Walczak M, et al. SIRT1, miR-132 and miR-212 link human longevity to Alzheimer's disease. *Sci Rep.* 2018;8(1):1–10.

Mori MA, Ludwig RG, Garcia-Martin R, Brandão BB, Kahn CR. Extracellular miRNAs: from biomarkers to mediators of physiology and disease. *Cell Metab.* 2019;30(4):656–673.

Barnes PJ. Senescence in COPD and its comorbidities. *Annu Rev Physiol.* 2017;79:517–539.

Capri M, Olivieri F, Lanzarini C, et al. Identification of miR-31-5p, miR-141-3p, miR-200c-3p, and GLT 1 as human liver aging markers sensitive to donor–recipient age-mismatch in transplants. *Aging Cell.* 2017;16(2):262–272.

Marini F, Cianferotti L, Brandi ML. Epigenetic mechanisms in bone biology and osteoporosis: can they drive therapeutic choices? *Int J Mol Sci.* 2016;17(8):1329.

Pourrajab F, Zarch AV, Hekmatimoghaddam S, Zare-Khormizi MR. The master switchers in the aging of cardiovascular system, reverse senescence by microRNA signatures; as highly conserved molecules. *Prog Biophys Mol Biol.* 2015;119(2):111–128.

Toutfaire M, Bauwens E, Debacq-Chainiaux F. The impact of cellular senescence in skin ageing: a notion of mosaic and therapeutic strategies. *Biochem Pharmacol.* 2017;142:1–12.

Dinami R, Ercolani C, Petti E, et al. miR-155 drives telomere fragility in human breast cancer by targeting TRF1. *Cancer Res.* 2014;74(15):4145–4156.

Xu T, Liu Q, Yao J, Dai Y, Wang H, Xiao J. Circulating microRNAs in response to exercise. *Scand J Med Sci Sports.* 2015;25(2):e149–e154. <https://doi.org/10.1111/sms.12421>.

Xu X, Chen W, Miao R, et al. miR-34a induces cellular senescence via modulation of telomerase activity in human hepatocellular carcinoma by targeting FoxM1/c-Myc pathway. *Oncotarget.* 2015;6(6):3988.

Elling R, Chan J, Fitzgerald KA. Emerging role of long noncoding RNAs as regulators of innate immune cell development and inflammatory gene expression. *Eur J Immunol.* 2016;46(3):504–512.

Inamura K. Major tumor suppressor and oncogenic non-coding RNAs: clinical relevance in lung cancer. *Cell.* 2017;6(2):12.

Di Gesualdo F, Capaccioli S, Lulli M. A pathophysiological view of the long non-coding RNA world. *Oncotarget.* 2014;5(22):10976.

Fu VX, Dobosy JR, Desotelle JA, et al. Aging and cancer-related loss of insulin-like growth factor 2 imprinting in the mouse and human prostate. *Cancer Res.* 2008;68(16):6797–6802.

Prensner JR, Chinnaiyan AM. The emergence of lncRNAs in cancer biology. *Cancer Discov.* 2011;1(5):391–407.

Liang S, Gong X, Zhang G, Huang G, Lu Y, Li Y. The lncRNA XIST interacts with miR-140/miR-124/ iASPP axis to promote pancreatic carcinoma growth. *Oncotarget.* 2017;8(69), 113701.

Yoon J-H, Abdelmohsen K, Kim J, et al. Scaffold function of long non-coding RNA HOTAIR in protein ubiquitination. *Nat Commun.* 2013;4(1):1–14.

He J, Tu C, Liu Y. Role of lncRNAs in aging and age-related diseases. *Aging Med.* 2018;1(2):158–175.

Jain S, Thakkar N, Chhatai J, Pal Bhadra M, Bhadra U. Long non-coding RNA: functional agent for disease traits. *RNA Biol.* 2017;14(5):522–535.

Akerman I, Tu Z, Beucher A, et al. Human pancreatic β cell lncRNAs control cell-specific regulatory networks. *Cell Metab.* 2017;25(2):400–411.

Liu Y, Ferguson JF, Xue C, et al. Tissue-specific RNA-Seq in human evoked inflammation identifies blood and adipose LincRNA signatures of cardiometabolic diseases. *Arterioscler Thromb Vasc Biol.* 2014;34(4):902–912.

Simion V, Haemmig S, Feinberg MW. LncRNAs in vascular biology and disease. *Vasc Pharmacol.* 2019;114:145–156.

Sanger HL, Klotz G, Riesner D, Gross HJ, Kleinschmidt AK. Viroids are single-stranded covalently closed circular RNA molecules existing as highly base-paired rod-like structures. *Proc Natl Acad Sci U S A.* 1976;73(11):3852–3856.

Yu C-Y, Kuo H-C. The emerging roles and functions of circular RNAs and their generation. *J Biomed Sci.*

2019;26(1):29.

Enuka Y, Lauriola M, Feldman ME, Sas-Chen A, Ulitsky I, Yarden Y. Circular RNAs are long-lived and display only minimal early alterations in response to a growth factor. *Nucleic Acids Res.* 2016;44(3):1370–1383.

Jeck WR, Sorrentino JA, Wang K, et al. Circular RNAs are abundant, conserved, and associated with ALU repeats. *RNA.* 2013;19(2):141–157.

Li Z, Huang C, Bao C, et al. Exon-intron circular RNAs regulate transcription in the nucleus. *Nat Struct Mol Biol.* 2015;22(3):256.

Hansen TB, Jensen TI, Clausen BH, et al. Natural RNA circles function as efficient microRNA sponges. *Nature.* 2013;495(7441):384–388.

Conn SJ, Pillman KA, Toubia J, et al. The RNA binding protein quaking regulates formation of circRNAs. *Cell.* 2015;160(6):1125–1134.

Legnini I, Di Timoteo G, Rossi F, et al. Circ-ZNF609 is a circular RNA that can be translated and functions in myogenesis. *Mol Cell.* 2017;66(1):22–37.e29.

Guo M, Qiu J, Shen F, et al. Comprehensive analysis of circular RNA profiles in skeletal muscles of aging mice and after aerobic exercise intervention. *Aging (Albany NY).* 2020;12(6):5071.

Meinecke A, Mitzka S, Juřt A, Cushman S, Stojanović SD, Xiao K. Cardiac endurance training alters plasma profiles of circular RNA MBOAT2. *Am J Physiol Heart Circ Physiol.* 2020;319.

Maiese K. Disease onset and aging in the world of circular RNAs. *J Transl Sci.* 2016;2(6):327.

Jiang G, Ma Y, An T, et al. Relationships of circular RNA with diabetes and depression. *Sci Rep.* 2017;7(1):1–8.

Kumar L, Haque R, Baghel T, Nazir A. Circular RNAs: the emerging class of non-coding RNAs and their potential role in human neurodegenerative diseases. *Mol Neurobiol.* 2017;54(9):7224–7234.

Shan K, Liu C, Liu B-H, et al. Circular noncoding RNA HIPK3 mediates retinal vascular dysfunction in diabetes mellitus. *Circulation.* 2017;136(17):1629–1642.

Zhou R, Wu Y, Wang W, et al. Circular RNAs (circRNAs) in cancer. *Cancer Lett.* 2018;425:134–142.

Du WW, Yang W, Chen Y, et al. Foxo3 circular RNA promotes cardiac senescence by modulating multiple factors associated with stress and senescence responses. *Eur Heart J.* 2017;38(18):1402–1412.

Du WW, Yang W, Liu E, Yang Z, Dhaliwal P, Yang BB. Foxo3 circular RNA retards cell cycle progression via forming ternary complexes with p21 and CDK2. *Nucleic Acids Res.* 2016;44(6):2846–2858.

Holdt LM, Stahringer A, Sass K, et al. Circular non-coding RNA ANRIL modulates ribosomal RNA maturation and atherosclerosis in humans. *Nat Commun.* 2016;7(1):1–14.

Wang K, Long B, Liu F, et al. A circular RNA protects the heart from pathological hypertrophy and heart failure by targeting miR-223. *Eur Heart J.* 2016;37(33):2602–2611.

Pareja-Galeano H, Sanchis-Gomar F, García-Giménez JL. Physical exercise and epigenetic modulation: elucidating intricate mechanisms. *Sports Med.* 2014;44(4):429–436. <https://doi.org/10.1007/s40279-013-0138-6>.

Sanchis-Gomar F, Garcia-Gimenez JL, Perez-Quilis C, Gomez-Cabrera MC, Pallardo FV, Lippi G. Physical exercise as an epigenetic modulator: eustress, the “positive stress” as an effector of gene expression. *J Strength Cond Res.* 2012;26(12):3469–3472. <https://doi.org/10.1519/JSC.0b013e31825bb594>.

Santos-Rebouças CB, Pimentel MM. Implication of abnormal epigenetic patterns for human diseases. *Eur J Hum Genet.* 2007;15(1):10–17. <https://doi.org/10.1038/sj.ejhg.5201727>.

Ling C, Rönn T. Epigenetic adaptation to regular exercise in humans. *Drug Discov Today.* 2014;19(7):1015–1018.

Alibegovic AC, Sonne MP, Højbjørre L, et al. Insulin resistance induced by physical inactivity is associated with multiple transcriptional changes in skeletal muscle in young men. *Am J Physiol Endocrinol Metab.* 2010;299(5):E752–E763. <https://doi.org/10.1152/ajpendo.00590.2009>.

Barrès R, Yan J, Egan B, et al. Acute exercise remodels promoter methylation in human skeletal muscle. *Cell Metab.* 2012;15(3):405–411. <https://doi.org/10.1016/j.cmet.2012.01.001>.

Ntanasis-Stathopoulos J, Tzanninis JG, Philippou A, Koutsilieris M. Epigenetic regulation on gene expression induced by physical exercise. *J Musculoskelet Neuronal Interact.* 2013;13(2):133–146.

Nitert MD, Dayeh T, Volkov P, et al. Impact of an exercise intervention on DNA methylation in skeletal muscle from first-degree relatives of patients with type 2 diabetes. *Diabetes.* 2012;61(12):3322–3332.

Rönn T, Volkov P, Davegårdh C, et al. A six months exercise intervention influences the genome-wide DNA methylation pattern in human adipose tissue. *PLoS Genet.* 2013;9(6). <https://doi.org/10.1371/journal.pgen.1003572>, e1003572.

Rowlands DS, Page RA, Sukala WR, et al. Multi-omic integrated networks connect DNA methylation and miRNA with skeletal muscle plasticity to chronic exercise in Type 2 diabetic obesity. *Physiol Genomics.* 2014;46(20):747–765. <https://doi.org/10.1152/physiolgenomics.00024.2014>.

Brown WM. Exercise-associated DNA methylation change in skeletal muscle and the importance of imprinted genes: a bioinformatics meta-analysis. *Br J Sports Med.* 2015;49(24):1567–1578. <https://doi.org/10.1136/bjsports-2014-094073>.

Landen S, Voisin S, Craig JM, McGee SL, Lamon S, Eynon N. Genetic and epigenetic sex-specific adaptations to endurance exercise. *Epigenetics.* 2019;14(6):523–535. <https://doi.org/10.1080/15592294.2019.1603961>.

Ohsawa I, Konno R, Masuzawa R, Kawano F. Amount of daily exercise is an essential stimulation to alter the epigenome of skeletal muscle in rats. *J Appl Physiol (1985).* 2018;125(4):1097–1104. <https://doi.org/10.1152/jap-physiol.00074.2018>.

Smith JAH, Kohn TA, Chetty AK, Ojuka EO. CaMK activation during exercise is required for histone hyperacetylation and MEF2A binding at the MEF2 site on the Glut4 gene. *Am J Physiol Endocrinol Metab.* 2008;295(3):E698–E704. <https://doi.org/10.1152/ajpendo.00747.2007>.

Joseph JS, Ayeleso AO, Mukwevho E. Exercise increases hyper-acetylation of histones on the Cis-element of NRF-1 binding to the Mef2a promoter: implications on type 2 diabetes. *Biochem Biophys Res Commun.* 2017;486(1):83–87. <https://doi.org/10.1016/j.bbrc.2017.03.002>.

Lochmann TL, Thomas RR, Bennett Jr JP, Taylor SM. Epigenetic modifications of the PGC-1 α promoter during exercise induced expression in mice. *PLoS One.* 2015;10(6):e0129647. <https://doi.org/10.1371/journal.pone.0129647>.

Masuzawa R, Konno R, Ohsawa I, Watanabe A, Kawano F. Muscle type-specific RNA polymerase II recruitment during PGC-1 α gene transcription after acute exercise in adult rats. *J Appl Physiol (1985).* 2018. <https://doi.org/10.1152/jap-physiol.00202.2018>.

Gomez-Pinilla F, Zhuang Y, Feng J, Ying Z, Fan G. Exercise impacts brain-derived neurotrophic factor plasticity by engaging mechanisms of epigenetic regulation. *Eur J Neurosci.* 2011;33(3):383–390. <https://doi.org/10.1111/j.1460-9568.2010.07508.x>.

Chandramohan Y, Droste SK, Arthur JSC, Reul JMHM. The forced swimming-induced behavioural immobility response involves histone H3 phospho-acetylation and c-Fos induction in dentate gyrus granule neurons via activation of the N-methyl-D-aspartate/extracellular signal-regulated kinase/mitogen- and stress-activated kinase signalling pathway. *Eur J Neurosci.* 2008;27(10):2701–2713. <https://doi.org/10.1111/j.1460-9568.2008.06230.x>.

Pattamaprapanont P, Garde C, Fabre O, Barrès R. Muscle contraction induces acute hydroxymethylation of the exercise-responsive gene Nr4a3. *Front Endocrinol (Lausanne).* 2016;7:165. <https://doi.org/10.3389/fendo.2016.00165>.

McGee SL, Fairlie E, Garnham AP, Hargreaves M. Exercise-induced histone modifications in human skeletal muscle. *J Physiol.* 2009;587(Pt 24):5951–5958. <https://doi.org/10.1113/jphysiol.2009.181065>.

Yu M, Stepto NK, Chibalin AV, et al. Metabolic and mitogenic signal transduction in human skeletal muscle after intense cycling exercise. *J Physiol.* 2003;546(Pt 2):327–335. <https://doi.org/10.1113/jphysiol.2002.034223>.

Lim C, Shimizu J, Kawano F, Kim HJ, Kim CK. Adaptive responses of histone modifications to resistance exercise in human skeletal muscle. *PLoS One.* 2020;15(4):e0231321. <https://doi.org/10.1371/journal.pone.0231321>.

Widmann M, Nieß AM, Munz B. Physical exercise and epigenetic modifications in skeletal muscle. *Sports Med.*

2019;49(4):509–523. <https://doi.org/10.1007/s40279-019-01070-4>.

Davidson PK, Gallagher IJ, Hartman JW, et al. High responders to resistance exercise training demonstrate differential regulation of skeletal muscle microRNA expression. *J Appl Physiol*. 2011;110(2):309–317. <https://doi.org/10.1152/jappphysiol.00901.2010>.

McCarthy JJ, Esser KA. MicroRNA-1 and microRNA-133a expression are decreased during skeletal muscle hypertrophy. *J Appl Physiol*. 2007;102(1):306–313. <https://doi.org/10.1152/jappphysiol.00932.2006>.

Fernandes T, Hashimoto NY, Magalhães FC, et al. Aerobic exercise training-induced left ventricular hypertrophy involves regulatory microRNAs, decreased angiotensin-converting enzyme-angiotensin II, and synergistic regulation of angiotensin-converting enzyme 2-angiotensin (1-7). *Hypertension*. 2011;58(2):182–189. <https://doi.org/10.1161/hypertensionaha.110.168252>.

Ma Z, Qi J, Meng S, Wen B, Zhang J. Swimming exercise training-induced left ventricular hypertrophy involves microRNAs and synergistic regulation of the PI3K/AKT/mTOR signaling pathway. *Eur J Appl Physiol*. 2013;113(10):2473–2486. <https://doi.org/10.1007/s00421-013-2685-9>.

Melo SFS, Fernandes T, Baraúna V, et al. Expression of microRNA-29 and collagen in cardiac muscle after swimming training in myocardial-infarcted rats. *Cell Physiol Biochem*. 2014;33(3):657–669. <https://doi.org/10.1159/000358642>.

Soci UP, Fernandes T, Hashimoto NY, et al. MicroRNAs 29 are involved in the improvement of ventricular compliance promoted by aerobic exercise training in rats. *Physiol Genomics*. 2011;43(11):665–673. <https://doi.org/10.1152/physiolgenomics.00145.2010>.

Da Silva Jr ND, Fernandes T, Soci UP, Monteiro AW, Phillips MI, De Oliveira EM. Swimming training in rats increases cardiac microRNA-126 expression and angiogenesis. *Med Sci Sports Exerc*. 2012;44(8):1453–1462. <https://doi.org/10.1249/MSS.0b013e31824e8a36>.

Fernandes T, Magalhães FC, Roque FR, Phillips MI, Oliveira EM. Exercise training prevents the microvascular rarefaction in hypertension balancing angiogenic and apoptotic factors: role of microRNAs-16, -21, and -126. *Hypertension*. 2012;59(2):513–520. <https://doi.org/10.1161/HYPERTENSIONAHA.111.185801>.

Liu F-J, Wen T, Liu L. MicroRNAs as a novel cellular senescence regulator. *Ageing Res Rev*. 2012;11(1):41–50. <https://doi.org/10.1016/j.arr.2011.06.001>.

Radom-Aizik S, Zaldivar Jr FP, Haddad F, Cooper DM. Impact of brief exercise on circulating monocyte gene and microRNA expression: implications for atherosclerotic vascular disease. *Brain Behav Immun*. 2014;39:121–129. <https://doi.org/10.1016/j.bbi.2014.01.003>.

Aoi W, Naito Y, Mizushima K, et al. The microRNA miR-696 regulates PGC-1 α in mouse skeletal muscle in response to physical activity. *Am J Physiol Endocrinol Metab*. 2010;298(4):E799–E806. <https://doi.org/10.1152/ajpendo.00448.2009>.

Bye A, Røsjø H, Aspenes ST, Condorelli G, Omland T, Wisløff U. Circulating microRNAs and aerobic fitness—the HUNT-study. *PLoS One*. 2013;8(2):e57496. <https://doi.org/10.1371/journal.pone.0057496>.

Mooren FC, Viereck J, Krüger K, Thum T. Circulating microRNAs as potential biomarkers of aerobic exercise capacity. *Am J Phys Heart Circ Phys*. 2014;306(4):H557–H563. <https://doi.org/10.1152/ajpheart.00711.2013>.

Baggish AL, Hale A, Weiner RB, et al. Dynamic regulation of circulating microRNA during acute exhaustive exercise and sustained aerobic exercise training. *J Physiol*. 2011;589(16):3983–3994. <https://doi.org/10.1113/jphysiol.2011.213363>.

Radom-Aizik S, Zaldivar F, Oliver S, Galassetti P, Cooper DM. Evidence for microRNA involvement in exercise-associated neutrophil gene expression changes. *J Appl Physiol*. 2010;109(1):252–261. <https://doi.org/10.1152/jappphysiol.01291.2009>.

Russell AP, Lamon S, Boon H, et al. Regulation of miRNAs in human skeletal muscle following acute endurance exercise and short-term endurance training. *J Physiol*. 2013;591(18):4637–4653. <https://doi.org/10.1113/jphysiol.2013.255695>.

Safdar A, Abadi A, Akhtar M, Hettinga BP, Tarnopolsky MA. miRNA in the regulation of skeletal muscle adaptation to acute endurance exercise in C57Bl/6J male mice. *PLoS One*. 2009;4(5):e5610. <https://doi.org/10.1371/journal.pone.0005610>.

Aoi W, Ichikawa H, Mune K, et al. Muscle-enriched microRNA miR-486 decreases in circulation in response to exercise in young men. *Front Physiol*. 2013;4:80. <https://doi.org/10.3389/fphys.2013.00080>.

Nielsen S, Åkerström T, Rinnov A, et al. The miRNA plasma signature in response to acute aerobic exercise and endurance training. *PLoS One*. 2014;9(2):e87308. <https://doi.org/10.1371/journal.pone.0087308>.

Nielsen S, Scheele C, Yfanti C, et al. Muscle specific microRNAs are regulated by endurance exercise in human skeletal muscle. *J Physiol*. 2010;588(20):4029–4037. <https://doi.org/10.1113/jphysiol.2010.189860>.

Radom-Aizik S, Zaldivar Jr F, Leu SY, Adams GR, Oliver S, Cooper DM. Effects of exercise on microRNA expression in young males peripheral blood mononuclear cells. *Clin Transl Sci*. 2012;5(1):32–38. <https://doi.org/10.1111/j.1752-8062.2011.00384.x>.

Dias RG, Silva MSM, Duarte NE, et al. PBMCs express a transcriptome signature predictor of oxygen uptake responsiveness to endurance exercise training in men. *Physiol Genomics*. 2015;47(2):13–23. <https://doi.org/10.1152/physiolgenomics.00072.2014>.

Denham J, Prestes PR. Muscle-enriched microRNAs isolated from whole blood are regulated by exercise and are potential biomarkers of cardiorespiratory fitness. *Front Genet*. 2016;7:196. <https://doi.org/10.3389/fgene.2016.00196>.

Radom-Aizik S, Zaldivar F, Haddad F, Cooper DM. Impact of brief exercise on peripheral blood NK cell gene and microRNA expression in young adults. *J Appl Physiol*. 2013;114(5):628–636. <https://doi.org/10.1152/jappphysiol.01341.2012>.

Taurino C, Miller WH, McBride MW, et al. Gene expression profiling in whole blood of patients with coronary artery disease. *Clin Sci*. 2010;119(8):335–343. <https://doi.org/10.1042/cs20100043>.

Tonevitsky AG, Maltseva DV, Abbasi A, et al. Dynamically regulated miRNA-mRNA networks revealed by exercise. *BMC Physiol*. 2013;13:9. <https://doi.org/10.1186/1472-6793-13-9>.

Li Y, Yao M, Zhou Q, et al. Dynamic regulation of circulating microRNAs during acute exercise and longterm exercise training in basketball athletes. *Front Physiol*. 2018;9:282.

Zhou Q, Shi C, Lv Y, Zhao C, Jiao Z, Wang T. Circulating microRNAs in response to exercise training in healthy adults. *Front Genet*. 2020;11:256. <https://doi.org/10.3389/fgene.2020.00256>.

Just J, Yan Y, Farup J, et al. Blood flow-restricted resistance exercise alters the surface profile, miRNA cargo and functional impact of circulating extracellular vesicles. *Sci Rep*. 2020;10(1):5835. <https://doi.org/10.1038/s41598-020-62456-3>.

Lovett JAC, Durcan PJ, Myburgh KH. Investigation of circulating extracellular vesicle microRNA following two consecutive bouts of muscle-damaging exercise. *Front Physiol*. 2018;9:1149. <https://doi.org/10.3389/fphys.2018.01149>.

Nair VD, Ge Y, Li S, et al. Sedentary and trained older men have distinct circulating exosomal microRNA profiles at baseline and in response to acute exercise. *Front Physiol*. 2020;11:605. <https://doi.org/10.3389/fphys.2020.00605>.

Zaidi SK, Van Wijnen AJ, Lian JB, Stein JL, Stein GS. Targeting deregulated epigenetic control in cancer. *J Cell Physiol*. 2013;228(11):2103–2108. <https://doi.org/10.1002/jcp.24387>.

Coyle YM, Xie XJ, Lewis CM, Bu D, Milchgrub S, Euhus DM. Role of physical activity in modulating breast cancer risk as defined by APC and RASSF1A promoter hypermethylation in nonmalignant breast tissue. *Cancer Epidemiol Biomark Prev*. 2007;16(2):192–196. <https://doi.org/10.1158/1055-9965.Epi-06-0700>.

Zeng H, Irwin ML, Lu L, et al. Physical activity and breast cancer survival: an epigenetic link through reduced methylation of a tumor suppressor gene L3MBTL1. *Breast Cancer Res Treat*. 2012;133(1):127–135. <https://doi.org/10.1007/s10549-011-1716-7>.

Bryan AD, Magnan RE, Hooper AE, Harlaar N, Hutchison KE. Physical activity and differential methylation of breast cancer genes assayed from saliva: a preliminary investigation. *Ann Behav Med*. 2013;45(1):89–98. <https://doi.org/10.1007/s10549-011-1716-7>.

org/10.1007/s12160-012-9411-4.

Grazioli E, Dimauro I, Mercatelli N, et al. Physical activity in the prevention of human diseases: role of epigenetic modifications. *BMC Genomics*. 2017;18(8):802. <https://doi.org/10.1186/s12864-017-4193-5>.

Zimmer P, Baumann FT, Bloch W, et al. Impact of exercise on pro inflammatory cytokine levels and epigenetic modulations of tumor-competitive lymphocytes in non-Hodgkin-lymphoma patients-randomized controlled trial. *Eur J Haematol*. 2014;93(6):527–532. <https://doi.org/10.1111/ejh.12395>.

Franceschi C, Bonafè M, Valensin S. Human immunosenescence: the prevailing of innate immunity, the failing of clonotypic immunity, and the filling of immunological space. *Vaccine*. 2000;18(16):1717–1720. [https://doi.org/10.1016/S0264-410X\(99\)00513-7](https://doi.org/10.1016/S0264-410X(99)00513-7).

Franceschi C, Capri M, Monti D, et al. Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. *Mech Ageing Dev*. 2007;128(1):92–105. <https://doi.org/10.1016/j.mad.2006.11.016>.

Campisi J. Replicative senescence and immortalization. In: *The Molecular Basis of Cell Cycle and Growth Control*; 1999:348–373.

Fulop T, Larbi A, Dupuis G, et al. Immunosenescence and inflamm-aging as two sides of the same coin: friends or foes? *Front Immunol*. 2018;8:1960. <https://doi.org/10.3389/fimmu.2017.01960>.

Chung HY, Lee EK, Choi YJ, et al. Molecular inflammation as an underlying mechanism of the aging process and age-related diseases. *J Dent Res*. 2011;90(7):830–840. <https://doi.org/10.1177/0022034510387794>.

Brunnsgaard H, Ladelund S, Pedersen AN, Schroll M, Jørgensen T, Pedersen BK. Predicting death from tumour necrosis factor- α and interleukin-6 in 80-year-old people. *Clin Exp Immunol*. 2003;132. <https://doi.org/10.1046/j.1365-2249.2003.02137.x>.

Herrero C, Marques L, Lloberas J, Celada A. IFN- γ -dependent transcription of MHC class II IA is impaired in macrophages from aged mice. *J Clin Invest*. 2001;107.

Ponnappan S, Ponnappan U. Aging and immune function: molecular mechanisms to interventions. *Antioxid Redox Signal*. 2011;14. <https://doi.org/10.1089/ars.2010.3228>.

van Deursen JM. The role of senescent cells in ageing. *Nature*. 2014;509(7501):439–446. <https://doi.org/10.1038/nature13193>.

Nakajima K, Takeoka M, Mori M, et al. Exercise effects on methylation of ASC gene. *Int J Sports Med*. 2010;31(9):671–675.

Bopp T, Radsak M, Schmitt E, Schild H. New strategies for the manipulation of adaptive immune responses. *Cancer Immunol Immunother*. 2010;59(9):1443–1448. <https://doi.org/10.1007/s00262-010-0851-z>.

Davidson-Moncada J, Papavasiliou FN, Tam W. MicroRNAs of the immune system. *Ann N Y Acad Sci*. 2010;1183(1):183–194. <https://doi.org/10.1111/j.1749-6632.2009.05121.x>.

Ellison GM, Waring CD, Vicinanza C, Torella D. Physiological cardiac remodelling in response to endurance exercise training: cellular and molecular mechanisms. *Heart*. 2012;98(1):5–10. <https://doi.org/10.1136/heartjnl-2011-300639>.

Fernandes T, Baraúna VG, Negrão CE, Phillips MI, Oliveira EM. Aerobic exercise training promotes physiological cardiac remodeling involving a set of microRNAs. *Am J Physiol Heart Circ Physiol*. 2015;309(4):H543–H552. <https://doi.org/10.1152/ajpheart.00899.2014>.

Tao L, Bei Y, Lin S, et al. Exercise training protects against acute myocardial infarction via improving myocardial energy metabolism and mitochondrial biogenesis. *Cell Physiol Biochem*. 2015;37(1):162–175.

<https://doi.org/10.1159/000430342>.

Care A, Catalucci D, Felicetti F, et al. MicroRNA-133 controls cardiac hypertrophy. *Nat Med*. 2007;13(5):613–618. http://www.nature.com/nm/journal/v13/n5/suppinfo/nm1582_S1.html.

Liu X, Xiao J, Zhu H, et al. miR-222 is necessary for exercise-induced cardiac growth and protects against patho-

logical cardiac remodeling. *Cell Metab.* 2015;21(4):584–595. <https://doi.org/10.1016/j.cmet.2015.02.014>.

Shi J, Bei Y, Kong X, et al. miR-17-3p contributes to exercise-induced cardiac growth and protects against myocardial ischemia-reperfusion injury. *Theranostics.* 2017;7(3):664–676. <https://doi.org/10.7150/thno.15162>.

Soci UPR, Fernandes T, Barauna VG, et al. Epigenetic control of exercise training-induced cardiac hypertrophy by miR-208. *Clin Sci (Lond).* 2016;130(22):2005–2015. <https://doi.org/10.1042/cs20160480>.

van Rooij E, Sutherland LB, Thatcher JE, et al. Dysregulation of microRNAs after myocardial infarction reveals a role of miR-29 in cardiac fibrosis. *Proc Natl Acad Sci U S A.* 2008;105(35):13027–13032. <https://doi.org/10.1073/pnas.0805038105>.

Fish JE, Santoro MM, Morton SU, et al. miR-126 regulates angiogenic signaling and vascular integrity. *Dev Cell.* 2008;15(2):272–284. <https://doi.org/10.1016/j.devcel.2008.07.008>.

Mackay CP, Kuys SS, Brauer SG. The effect of aerobic exercise on brain-derived neurotrophic factor in people with neurological disorders: a systematic review and meta-analysis. *Neural Plast.* 2017;2017:4716197. <https://doi.org/10.1155/2017/4716197>.

Szuhany KL, Bugatti M, Otto MW. A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor. *J Psychiatr Res.* 2015;60:56–64. <https://doi.org/10.1016/j.jpsychires.2014.10.003>.

Abel JL, Rissman EF. Running-induced epigenetic and gene expression changes in the adolescent brain. *Int J Dev Neurosci.* 2013;31(6):382–390. <https://doi.org/10.1016/j.ijdevneu.2012.11.002>.

Elsner VR, Lovatel GA, Bertoldi K, et al. Effect of different exercise protocols on histone acetyltransferases and histone deacetylases activities in rat hippocampus. *Neuroscience.* 2011;192:580–587. <https://doi.org/10.1016/j.neuroscience.2011.06.066>.

Sølvsten CAE, de Paoli F, Christensen JH, Nielsen AL. Voluntary physical exercise induces expression and epigenetic remodeling of VegfA in the rat hippocampus. *Mol Neurobiol.* 2018;55(1):567–582. <https://doi.org/10.1007/s12035-016-0344-y>.

Coppedè F. Genetics and epigenetics of Parkinson's disease. *Sci World J.* 2012;2012. <https://doi.org/10.1100/2012/489830>, 489830.

Srinageshwar B, Maiti P, Dunbar GL, Rossignol J. Role of epigenetics in stem cell proliferation and differentiation: implications for treating neurodegenerative diseases. *Int J Mol Sci.* 2016;17(2). <https://doi.org/10.3390/ijms17020199>.

Yao Y, Zhang X, Chen H-P, et al. MicroRNA-186 promotes macrophage lipid accumulation and secretion of pro-inflammatory cytokines by targeting cystathionine γ -lyase in THP-1 macrophages. *Atherosclerosis.* 2016;250(Supplement C):122–132. <https://doi.org/10.1016/j.atherosclerosis.2016.04.030>.

Lavratti C, Dorneles G, Pochmann D, et al. Exercise-induced modulation of histone H4 acetylation status and cytokines levels in patients with schizophrenia. *Physiol Behav.* 2017;168:84–90. <https://doi.org/10.1016/j.physbeh.2016.10.021>.

Fabre O, Ingerslev LR, Garde C, Donkin I, Simar D, Barrès R. Exercise training alters the genomic response to acute exercise in human adipose tissue. *Epigenomics.* 2018;10(8):1033–1050. <https://doi.org/10.2217/epi-2018-0039>.

Dimauro I, Paronetto MP, Caporossi D. Exercise, redox homeostasis and the epigenetic landscape. *Redox Biol.* 2020;35, 101477.

Kanzleiter T, Jähnert M, Schulze G, et al. Exercise training alters DNA methylation patterns in genes related to muscle growth and differentiation in mice. *Am J Physiol Endocrinol Metab.* 2015;308(10):E912–E920.

Blackburn EH. Telomeres and telomerase. *Keio J Med.* 2000;49(2):59–65. <https://doi.org/10.2302/kjm.49.59>.

Rhodes D, Fairall L, Simonsson T, Court R, Chapman L. Telomere architecture. *EMBO Rep.* 2002;3(12):1139–1145. <https://doi.org/10.1093/embo-reports/kvf246>.

de Lange T. Shelterin: the protein complex that shapes and safeguards human telomeres. *Genes Dev.* 2005;19. <https://doi.org/10.1101/gad.1346005>.

Chan SRWL, Blackburn EH. Telomeres and telomerase. *Philos Trans R Soc Lond Ser B Biol Sci.* 2004;359:109–

122. <https://doi.org/10.1098/rstb.2003.1370>.

Griffith JD, Comeau L, Rosenfield S, et al. Mammalian telomeres end in a large duplex loop. *Cell*. 1999;97(4):503–514. [https://doi.org/10.1016/S0092-8674\(00\)80760-6](https://doi.org/10.1016/S0092-8674(00)80760-6).

Deng Y, Chang S. Role of telomeres and telomerase in genomic instability, senescence and cancer. *Lab Invest*. 2007;87(11):1071–1076. <https://doi.org/10.1038/labinvest.3700673>.

Miyake Y, Nakamura M, Nabetani A, et al. RPA-like mammalian Ctc1-Stn1-Ten1 complex binds to single-stranded DNA and protects telomeres independently of the Pot1 pathway. *Mol Cell*. 2009;36(2):193–206. <https://doi.org/10.1016/j.molcel.2009.08.009>.

Greider CW, Blackburn EH. The telomere terminal transferase of Tetrahymena is a ribonucleoprotein enzyme with two kinds of primer specificity. *Cell*. 1987;51:887–898.

Oeseburg H, de Boer RA, van Gilst WH, van der Harst P. Telomere biology in healthy aging and disease. *Pflügers Arch - Eur J Physiol*. 2009;459(2):259–268. <https://doi.org/10.1007/s00424-009-0728-1>.

Blackburn EH, Greider CW, Henderson E, Lee MS, Shampay J, Shippen-Lentz D. Recognition and elongation of telomeres by telomerase. *Genome*. 1989;31(2):553–560. <https://doi.org/10.1139/g89-104>.

Dlouha D, Maluskova J, Kralova Lesna I, Lanska V, Hubacek JA. Comparison of the relative telomere length measured in leukocytes and eleven different human tissues. *Physiol Res*. 2014;63(Suppl 3):S343–S350.

Friedrich U, Griese E, Schwab M, Fritz P, Thon K, Klotz U. Telomere length in different tissues of elderly patients. *Mech Ageing Dev*. 2000;119. [https://doi.org/10.1016/s0047-6374\(00\)00173-1](https://doi.org/10.1016/s0047-6374(00)00173-1).

Gardner JP, Kimura M, Chai W, et al. Telomere dynamics in macaques and humans. *J Gerontol Ser A Biol Sci Med Sci*. 2007;62(4):367–374. <https://doi.org/10.1093/gerona/62.4.367>.

Wilson WRW, Herbert KE, Mištry Y, et al. Blood leucocyte telomere DNA content predicts vascular telomere DNA content in humans with and without vascular disease. *Eur Heart J*. 2008;29(21):2689–2694. <https://doi.org/10.1093/eurheartj/ehn386>.

Takubo K, Izumiya-Shimomura N, Honma N, et al. Telomere lengths are characteristic in each human individual. *Exp Gerontol*. 2002;37(4):523–531. [https://doi.org/10.1016/S0531-5565\(01\)00218-2](https://doi.org/10.1016/S0531-5565(01)00218-2).

Sidorov I, Kimura M, Yashin A, Aviv A. Leukocyte telomere dynamics and human hematopoietic stem cell kinetics during somatic growth. *Exp Hematol*. 2009;37(4):514–524. <https://doi.org/10.1016/j.exphem.2008.11.009>.

von Zglinicki T, Martin-Ruiz C. Telomeres as biomarkers for ageing and age-related diseases. *Curr Mol Med*. 2005;5(2):197–203. <https://doi.org/10.2174/1566524053586545>.

Olovnikov AM. Principle of marginotomy in template synthesis of polynucleotides. *Dokl Akad Nauk SSSR*. 1971;201(6):1496–1499.

Watson JD. Origin of concatemeric T7 DNA. *Nat New Biol*. 1972;239(94):197–201.

Fagagna FdAd, Reaper PM, Clay-Farrace L, et al. A DNA damage checkpoint response in telomere-initiated senescence. *Nature*. 2003;426(6963):194–198. <https://doi.org/10.1038/nature02118>.

Takai H, Smogorzewska A, de Lange T. DNA damage foci at dysfunctional telomeres. *Curr Biol*. 2003;13(17):1549–1556. [https://doi.org/10.1016/S0960-9822\(03\)00542-6](https://doi.org/10.1016/S0960-9822(03)00542-6).

Von Zglinicki T. Role of oxidative stress in telomere length regulation and replicative senescence. *Ann N Y Acad Sci*. 2000;908:99–110. <https://doi.org/10.1111/j.1749-6632.2000.tb06639.x>.

Bekaert S, De Meyer T, Rietzschel ER, et al. Telomere length and cardiovascular risk factors in a middle-aged population free of overt cardiovascular disease. *J Anat*. 2007;6(5):639–647. <https://doi.org/10.1111/j.1474-9726.2007.00321.x>.

Vasan RS, Demissie S, Kimura M, et al. Association of leukocyte telomere length with circulating biomarkers of the renin-angiotensin-aldosterone system: the Framingham heart study. *Circulation*. 2008;117(9):1138–1144. <https://doi.org/10.1161/CIRCULATIONAHA.107.731794>.

Valdes AM, Andrew T, Gardner JP, et al. Obesity, cigarette smoking, and telomere length in women. *Lancet*.

2005;366(9486):662–664. [https://doi.org/10.1016/S0140-6736\(05\)66630-5](https://doi.org/10.1016/S0140-6736(05)66630-5).

Harris SE, Deary IJ, MacIntyre A, et al. The association between telomere length, physical health, cognitive ageing, and mortality in non-demented older people. *Neurosci Lett*. 2006;406(3):260–264. <https://doi.org/10.1016/j.neulet.2006.07.055>.

Puterman E, Lin J, Blackburn E, O'Donovan A, Adler N, Epel E. The power of exercise: buffering the effect of chronic stress on telomere length. *PLoS One*. 2010;5(5):e10837. <https://doi.org/10.1371/journal.pone.0010837>.

Cherkas LF, Hunkin JL, Kato BS, et al. The association between physical activity in leisure time and leukocyte telomere length. *Arch Intern Med*. 2008;168(2):154–158. <https://doi.org/10.1001/archinternmed.2007.39>.

Ludlow AT, Ludlow LW, Roth SM. Do telomeres adapt to physiological stress? Exploring the effect of exercise on telomere length and telomere-related proteins. *Biomed Res Int*. 2013;2013:15. <https://doi.org/10.1155/2013/601368>.

Fumagalli M, Rossiello F, Clerici M, et al. Telomeric DNA damage is irreparable and causes persistent DNA-damage-response activation. *Nat Cell Biol*. 2012;14(4):355–365. <https://doi.org/10.1038/ncb2466>.

Hackett JA, Greider CW. Balancing instability: dual roles for telomerase and telomere dysfunction in tumorigenesis. *Oncogene*. 2002;21(4):619–626. <https://doi.org/10.1038/sj.onc.1205061>.

Hewitt G, Jurk D, Marques F, et al. Telomeres are favoured targets of a persistent DNA damage response in ageing and stress-induced senescence. *Nat Commun*. 2012;3. <https://doi.org/10.1038/ncomms1708>.

d'Adda di Fagagna F. Living on a break: cellular senescence as a DNA-damage response. *Nat Rev Cancer*. 2008;8(7):512–522. <https://doi.org/10.1038/nrc2440>.

Bhatia-Dey N, Kanherkar RR, Stair SE, Makarev EO, Csoka AB. Cellular senescence as the causal nexus of aging. *Front Genet*. 2016;7(13). <https://doi.org/10.3389/fgene.2016.00013>.

Fathi E, Charoudeh HN, Sanaat Z, Farahzadi R. Telomere shortening as a hallmark of stem cell senescence. *Stem Cell Investig*. 2019;6:7. <https://doi.org/10.21037/sci.2019.02.04>.

Sharpless NE, DePinho RA. How stem cells age and why this makes us grow old. *Nat Rev Mol Cell Biol*. 2007;8(9):703–713. <https://doi.org/10.1038/nrm2241>.

Sahin E, Colla S, Liesa M, et al. Telomere dysfunction induces metabolic and mitochondrial compromise. *Nature*. 2011;470. <https://doi.org/10.1038/nature09787>.

Vitorelli S, Passos JF. Telomeres and cell senescence—size matters not. *EBioMedicine*. 2017;21:14–20. <https://doi.org/10.1016/j.ebiom.2017.03.027>.

Passos JF, Saretzki G, Ahmed S, et al. Mitochondrial dysfunction accounts for the stochastic heterogeneity in telomere-dependent senescence. *PLoS Biol*. 2007;5. <https://doi.org/10.1371/journal.pbio.0050110>.

Gottschling DE, Aparicio OM, Billington BL, Zakian VA. Position effect at *S. cerevisiae* telomeres: reversible repression of Pol II transcription. *Cell*. 1990;63(4):751–762. [https://doi.org/10.1016/0092-8674\(90\)90141-z](https://doi.org/10.1016/0092-8674(90)90141-z).

Tham WH, Zakian VA. Transcriptional silencing at *saccharomyces* telomeres: implications for other organisms. *Oncogene*. 2002;21(4):512–521. <https://doi.org/10.1038/sj.onc.1205078>.

Blasco MA. The epigenetic regulation of mammalian telomeres. *Nat Rev Genet*. 2007;8(4):299–309. <https://doi.org/10.1038/nrg2047>.

Blasco MA. Telomere length, stem cells and aging. *Nat Chem Biol*. 2007;3(10):640–649. <https://doi.org/10.1038/nchembio.2007.38>.

Kulkarni A, Zschenker O, Reynolds G, Miller D, Murnane JP. Effect of telomere proximity on telomere position effect, chromosome healing, and sensitivity to DNA double-strand breaks in a human tumor cell line. *Mol Cell Biol*. 2010;30(3):578–589. <https://doi.org/10.1128/mcb.01137-09>.

Robin JD, Ludlow AT, Batten K, et al. Telomere position effect: regulation of gene expression with progressive telomere shortening over long distances. *Genes Dev*. 2014;28(22):2464–2476. <https://doi.org/10.1101/gad.251041.114>.

Müzeczinler A, Zaineddin AK, Brenner H. A systematic review of leukocyte telomere length and age in adults. *Ageing Res Rev*. 2013;12(2):509–519. <https://doi.org/10.1016/j.arr.2013.01.003>.

- Rode L, Nordestgaard BG, Bojesen SE. Peripheral blood leukocyte telomere length and mortality among 64,637 individuals from the general population. *J Natl Cancer Inst.* 2015;107(6). <https://doi.org/10.1093/jnci/djv074>, djv074.
- Tucker LA. Physical activity and telomere length in U.S. men and women: an NHANES investigation. *Prev Med.* 2017;100:145–151. <https://doi.org/10.1016/j.ypmed.2017.04.027>.
- Marioni RE, Harris SE, Shah S, et al. The epigenetic clock and telomere length are independently associated with chronological age and mortality. *Int J Epidemiol.* 2016. <https://doi.org/10.1093/ije/dyw041>.
- Crabbe L, Jauch A, Naeger CM, Holtgreve-Grez H, Karlseder J. Telomere dysfunction as a cause of genomic instability in Werner syndrome. *Proc Natl Acad Sci.* 2007;104(7):2205–2210. <https://doi.org/10.1073/pnas.0609410104>.
- Decker ML, Chavez E, Vulto I, Lansdorp PM. Telomere length in Hutchinson-Gilford progeria syndrome. *Mech Ageing Dev.* 2009;130(6):377–383. <https://doi.org/10.1016/j.mad.2009.03.001>.
- Honig LS, Kang MS, Schupf N, Lee JH, Mayeux R. Association of shorter leukocyte telomere repeat length with dementia and mortality. *Arch Neurol.* 2012;69(10):1332–1339. <https://doi.org/10.1001/archneurol.2012.1541>.
- Martin-Ruiz C, Dickinson HO, Keys B, Rowan E, Kenny RA, Von Zglinicki T. Telomere length predicts poststroke mortality, dementia, and cognitive decline. *Ann Neurol.* 2006;60(2):174–180. <https://doi.org/10.1002/ana.20869>.
- Kim JH, Ko JH, Lee DC, Lim I, Bang H. Habitual physical exercise has beneficial effects on telomere length in postmenopausal women. *Menopause.* 2012;19. <https://doi.org/10.1097/gme.0b013e3182503e97>.
- Weischer M, Bojesen SE, Nordestgaard BG. Telomere shortening unrelated to smoking, body weight, physical activity, and alcohol intake: 4,576 general population individuals with repeat measurements 10 years apart. *PLoS Genet.* 2014;10(3). <https://doi.org/10.1371/journal.pgen.1004191>, e1004191.
- Astrup AS, Tarnow L, Jorsal A, et al. Telomere length predicts all-cause mortality in patients with type 1 diabetes. *Diabetologia.* 2010;53(1):45–48. <https://doi.org/10.1007/s00125-009-1542-1>.
- Bakaysa SL, Mucci LA, Slagboom PE, et al. Telomere length predicts survival independent of genetic influences. *Aging Cell.* 2007;6(6):769–774. <https://doi.org/10.1111/j.1474-9726.2007.00340.x>.
- Cawthon RM, Smith KR, O'Brien E, Sivatchenko A, Kerber RA. Association between telomere length in blood and mortality in people aged 60 years or older. *Lancet.* 2003;361(9355):393–395. [https://doi.org/10.1016/S0140-6736\(03\)12384-7](https://doi.org/10.1016/S0140-6736(03)12384-7).
- Deelen J, Beekman M, Codd V, et al. Leukocyte telomere length associates with prospective mortality independent of immune-related parameters and known genetic markers. *Int J Epidemiol.* 2014;43(3):878–886. <https://doi.org/10.1093/ije/dyt267>.
- Ehrlenbach S, Willeit P, Kiechl S, et al. Influences on the reduction of relative telomere length over 10 years in the population-based Bruneck Study: introduction of a well-controlled high-throughput assay. *Int J Epidemiol.* 2009;38(6):1725–1734. <https://doi.org/10.1093/ije/dyp273>.
- Glei DA, Goldman N, Weinstein M, Rises RA. Shorter ends, faster end? Leukocyte telomere length and mortality among older Taiwanese. *J Gerontol A Biol Sci Med Sci.* 2015;70(12):1490–1498. <https://doi.org/10.1093/geron/glu191>.
- Lee J, Sandford AJ, Connett JE, et al. The relationship between telomere length and mortality in chronic obstructive pulmonary disease (COPD). *PLoS One.* 2012;7(4):e35567. <https://doi.org/10.1371/journal.pone.0035567>.
- Rehkopf DH, Dow WH, Rosero-Bixby L, Lin J, Epel ES, Blackburn EH. Longer leukocyte telomere length in Costa Rica's Nicoya Peninsula: a population-based study. *Exp Gerontol.* 2013;48(11):1266–1273. <https://doi.org/10.1016/j.exger.2013.08.005>.
- Strandberg TE, Saijonmaa O, Tilvis RS, et al. Association of telomere length in older men with mortality and midlife body mass index and smoking. *J Gerontol A Biol Sci Med Sci.* 2011;66(7):815–820. <https://doi.org/10.1093/geron/glr064>.
- Fitzpatrick AL, Kronmal RA, Kimura M, et al. Leukocyte telomere length and mortality in the Cardiovascular Health Study. *J Gerontol A Biol Sci Med Sci.* 2011;66(4):421–429. <https://doi.org/10.1093/geron/glr224>.

- Boonekamp JJ, Simons MJP, Hemerik L, Verhulst S. Telomere length behaves as biomarker of somatic redundancy rather than biological age. *Aging Cell*. 2013;12(2):330–332. <https://doi.org/10.1111/accel.12050>.
- Bischoff C, Petersen HC, Graakjaer J, et al. No association between telomere length and survival among the elderly and oldest old. *Epidemiology*. 2006;17(2):190–194. <https://doi.org/10.1097/01.ede.0000199436.55248.10>.
- Martin-Ruiz CM, Gussekloo J, van Heemst D, von Zglinicki T, Westendorp RGJ. Telomere length in white blood cells is not associated with morbidity or mortality in the oldest old: a population-based study. *Aging Cell*. 2005;4(6):287–290. <https://doi.org/10.1111/j.1474-9726.2005.00171.x>.
- Heidinger BJ, Blount JD, Boner W, Griffiths K, Metcalfe NB, Monaghan P. Telomere length in early life predicts lifespan. *Proc Natl Acad Sci U S A*. 2012;109(5):1743–1748. <https://doi.org/10.1073/pnas.1113306109>.
- Epel ES, Merkin SS, Cawthon R, et al. The rate of leukocyte telomere shortening predicts mortality from cardiovascular disease in elderly men. *Aging (Albany NY)*. 2009;1(1):81–88. <https://doi.org/10.18632/aging.100007>.
- Fitzpatrick AL, Kronmal RA, Gardner JP, et al. Leukocyte telomere length and cardiovascular disease in the cardiovascular health study. *Am J Epidemiol*. 2007;165(1):14–21. <https://doi.org/10.1093/aje/kw346>.
- Arai Y, Martin-Ruiz CM, Takayama M, et al. Inflammation, but not telomere length, predicts successful ageing at extreme old age: a longitudinal study of semi-supercentenarians. *EBioMedicine*. 2015;2(10):1549–1558. <https://doi.org/10.1016/j.ebiom.2015.07.029>.
- Bendix L, Thinggaard M, Fenger M, et al. Longitudinal changes in leukocyte telomere length and mortality in humans. *J Gerontol A Biol Sci Med Sci*. 2014;69(2):231–239. <https://doi.org/10.1093/gerona/glt153>.
- Houben JMJ, Giltay EJ, Rius-Ottenheim N, Hageman GJ, Kromhout D. Telomere length and mortality in elderly men: the Zutphen Elderly Study. *J Gerontol A Biol Sci Med Sci*. 2011;66(1):38–44. <https://doi.org/10.1093/gerona/glq164>.
- Kimura M, Hjelmborg JVB, Gardner JP, et al. Telomere length and mortality: a study of leukocytes in elderly Danish twins. *Am J Epidemiol*. 2008;167(7):799–806. <https://doi.org/10.1093/aje/kwm380>.
- Njajou OT, Hsueh W-C, Blackburn EH, et al, Health ABC Study. Association between telomere length, specific causes of death, and years of healthy life in health, aging, and body composition, a populationbased cohort study. *J Gerontol A Biol Sci Med Sci*. 2009;64(8):860–864. <https://doi.org/10.1093/gerona/glp061>.
- Svensson J, Karlsson MK, Ljunggren Ö, Tivesten Å, Mellström D, Movérare-Skrttic S. Leukocyte telomere length is not associated with mortality in older men. *Exp Gerontol*. 2014;57:6–12. <https://doi.org/10.1016/j.exger.2014.04.013>.
- Glei DA, Goldman N, Risques RA, et al. Predicting survival from telomere length versus conventional predictors: a multinational population-based cohort study. *PLoS One*. 2016;11(4):e0152486. <https://doi.org/10.1371/journal.pone.0152486>.
- Njajou OT, Cawthon RM, Damcott CM, et al. Telomere length is paternally inherited and is associated with parental lifespan. *Proc Natl Acad Sci U S A*. 2007;104(29):12135–12139. <https://doi.org/10.1073/pnas.0702703104>.
- Soerensen M, Thinggaard M, Nygaard M, et al. Genetic variation in TERT and TERC and human leukocyte telomere length and longevity: a cross-sectional and longitudinal analysis. *Aging Cell*. 2012;11(2):223–227. <https://doi.org/10.1111/j.1474-9726.2011.00775.x>.
- Mortimer RK, Johnston JR. Life span of individual yeast cells. *Nature*. 1959;183(4677):1751–1752. <https://doi.org/10.1038/1831751a0>.
- Morgan RG, Donato AJ, Walker AE. Telomere uncapping and vascular aging. *Am J Phys Heart Circ Phys*. 2018;315(1):H1–H5. <https://doi.org/10.1152/ajpheart.00008.2018>.
- Acosta JC, Banito A, Wuestefeld T, et al. A complex secretory program orchestrated by the inflammasome controls paracrine senescence. *Nat Cell Biol*. 2013;15:978. <https://doi.org/10.1038/ncb2784>.
- Minamino T, Orimo M, Shimizu I, et al. A crucial role for adipose tissue p53 in the regulation of insulin resistance. *Nat Med*. 2009;15(9):1082–1087. <https://doi.org/10.1038/nm.2014>.
- Shimizu I, Yoshida Y, Katsuno T, et al. p53-induced adipose tissue inflammation is critically involved in the develop-

ment of insulin resistance in heart failure. *Cell Metab.* 2012;15(1):51–64. <https://doi.org/10.1016/j.cmet.2011.12.006>.

Minamino T, Komuro I. Vascular cell senescence: contribution to atherosclerosis. *Circ Res.* 2007;100(1):15–26. <https://doi.org/10.1161/01.RES.0000256837.40544.4a>.

Zhou X, Perez F, Han K, Jurivich DA. Clonal senescence alters endothelial ICAM-1 function. *Mech Ageing Dev.* 2006;127(10):779–785. <https://doi.org/10.1016/j.mad.2006.07.003>.

Thangavel C, Dean JL, Ertel A, et al. Therapeutically activating RB: reestablishing cell cycle control in endocrine therapy-resistant breast cancer. *Endocr Relat Cancer.* 2011;18(3):333–345. <https://doi.org/10.1530/erc-10-0262>.

Liton PB, Challa P, Stinnett S, Luna C, Epstein DL, Gonzalez P. Cellular senescence in the glaucomatous outflow pathway. *Exp Gerontol.* 2005;40(8):745–748. <https://doi.org/10.1016/j.exger.2005.06.005>.

Martin JA, Brown TD, Heiner AD, Buckwalter JA. Chondrocyte senescence, joint loading and osteoarthritis. *Clin Orthop Relat Res.* 2004;427:S96–S103. <https://doi.org/10.1097/01.blo.0000143818.74887.b1>.

Castle SC, Uyemuraabc K, Crawford W, Wongab W, Klausermeyer WB, Makinodan T. Age-related impaired proliferation of peripheral blood mononuclear cells is associated with an increase in both IL-10 and IL-12. *Exp Gerontol.* 1999;34(2):243–252. [https://doi.org/10.1016/S0531-5565\(98\)00064-3](https://doi.org/10.1016/S0531-5565(98)00064-3).

Froelich CJ, Burkett JS, Guiffaut S, Kingsland R, Brauner D. Phytohemagglutinin induced proliferation by aged lymphocytes: reduced expression of high affinity interleukin-2 receptors and interleukin-2 secretion. *Life Sci.* 1988;43(20):1583–1590. [https://doi.org/10.1016/0024-3205\(88\)90529-2](https://doi.org/10.1016/0024-3205(88)90529-2).

Franceschi C, Bonafe M, Valensin S, et al. Inflamm-aging: an evolutionary perspective on immunosenescence. *Ann N Y Acad Sci.* 2000;908(1):244–254. <https://doi.org/10.1111/j.1749-6632.2000.tb06651.x>.

Targonski PV, Jacobson RM, Poland GA. Immunosenescence: role and measurement in influenza vaccine response among the elderly. *Vaccine.* 2007;25(16):3066–3069. <https://doi.org/10.1016/j.vaccine.2007.01.025>.

Effros RB, Allsopp R, Chiu CP, et al. Shortened telomeres in the expanded CD28-CD8+ cell subset in HIV disease implicate replicative senescence in HIV pathogenesis. *AIDS.* 1996;10(8):F17–F22.

Huzen J, de Boer RA, van Veldhuisen DJ, van Gilst WH, van der Harst P. The emerging role of telomere biology in cardiovascular disease. *Front Biosci.* 2010;15:35–45.

Willeit P, Willeit J, Brandstätter A, et al. Cellular aging reflected by leukocyte telomere length predicts advanced atherosclerosis and cardiovascular disease risk. *Arterioscler Thromb Vasc Biol.* 2010;30(8):1649–1656. <https://doi.org/10.1161/ATVBAHA.110.205492>.

Zhang W, Chen Y, Wang Y, et al. Short telomere length in blood leucocytes contributes to the presence of atherothrombotic stroke and haemorrhagic stroke and risk of post-stroke death. *Clin Sci.* 2013;125(1):27–43. <https://doi.org/10.1042/cs20120691>.

Salpea KD, Talmud PJ, Cooper JA, et al. Association of telomere length with type 2 diabetes, oxidative stress and UCP2 gene variation. *Atherosclerosis.* 2010;209(1):42–50. <https://doi.org/10.1016/j.atherosclerosis.2009.09.070>.

Sampson MJ, Winterbone MS, Hughes JC, Dozio N, Hughes DA. Monocyte telomere shortening and oxidative DNA damage in type 2 diabetes. *Diabetes Care.* 2006;29. <https://doi.org/10.2337/diacare.29.02.06.dc05-1715>.

Zee RYL, Cañonguay AJ, Barton NS, Germer S, Martin M. Mean leukocyte telomere length shortening and type 2 diabetes mellitus: a case-control study. *Transl Res.* 2010;155(4):166–169. <https://doi.org/10.1016/j.trsl.2009.09.012>.

Jenkins EC, Velinov MT, Ye L, et al. Telomere shortening in T lymphocytes of older individuals with Down syndrome and dementia. *Neurobiol Aging.* 2006;27(7):941–945. <https://doi.org/10.1016/j.neurobiolaging.2005.05.021>.

Rode L, Bojesen SE, Weischer M, Vestbo J, Nordestgaard BG. Short telomere length, lung function and chronic obstructive pulmonary disease in 46,396 individuals. *Thorax.* 2013;68(5):429–435. <https://doi.org/10.1136/thoraxjnl-2012-202544>.

Buckingham EM, Klingelutz AJ. The role of telomeres in the ageing of human skin. *Exp Dermatol.* 2011;20(4):297–302. <https://doi.org/10.1111/j.1600-0625.2010.01242.x>.

Samani NJ, Boulty R, Butler R, Thompson JR, Goodall AH. Telomere shortening in atherosclerosis. *Lancet*. 2001;358. [https://doi.org/10.1016/s0140-6736\(01\)05633-1](https://doi.org/10.1016/s0140-6736(01)05633-1).

Brouillette S, Singh RK, Thompson JR, Goodall AH, Samani NJ. White cell telomere length and risk of premature myocardial infarction. *Arterioscler Thromb Vasc Biol*. 2003;23(5):842–846. <https://doi.org/10.1161/01.ATV.0000067426.96344.32>.

Brouillette SW, Moore JS, McMahon AD, et al. Telomere length, risk of coronary heart disease, and statin treatment in the West of Scotland primary prevention study: a nested case-control study. *Lancet*. 2007;369(9556):107–114. [https://doi.org/10.1016/S0140-6736\(07\)60071-3](https://doi.org/10.1016/S0140-6736(07)60071-3).

Brouillette SW, Whittaker A, Stevens SE, van der Harst P, Goodall AH, Samani NJ. Telomere length is shorter in healthy offspring of subjects with coronary artery disease: support for the telomere hypothesis. *Heart*. 2008;94(4):422–425. <https://doi.org/10.1136/hrt.2007.139675>.

Carty CL, Kooperberg C, Liu J, et al. Leukocyte telomere length and risks of incident coronary heart disease and mortality in a racially diverse population of postmenopausal women. *Arterioscler Thromb Vasc Biol*. 2015;35(10):2225–2231. <https://doi.org/10.1161/atvbaha.115.305838>.

D'Mello MJJ, Ross SA, Briel M, Anand SS, Gerstein H, Paré G. Association between shortened leukocyte telomere length and cardiometabolic outcomes: systematic review and meta-analysis. *Circ Cardiovasc Genet*. 2015;8(1):82–90. <https://doi.org/10.1161/circgenetics.113.000485>.

Ellehoj H, Bendix L, Osler M. Leucocyte telomere length and risk of cardiovascular disease in a cohort of 1,397 Danish men and women. *Cardiology*. 2016;133(3):173–177. <https://doi.org/10.1159/000441819>.

Haycock PC, Heydon EE, Kaptoge S, Butterworth AS, Thompson A, Willeit P. Leucocyte telomere length and risk of cardiovascular disease: systematic review and meta-analysis. *BMJ*. 2014;349:g4227. <https://doi.org/10.1136/bmj.g4227>.

Matthews C, Gorenne I, Scott S, et al. Vascular smooth muscle cells undergo telomere-based senescence in human atherosclerosis: effects of telomerase and oxidative stress. *Circ Res*. 2006;99(2):156–164. <https://doi.org/10.1161/01.RES.0000233315.38086.bc>.

Willeit P, Willeit J, Mayr A, et al. Telomere length and risk of incident cancer and cancer mortality. *JAMA*. 2010;304(1):69–75. <https://doi.org/10.1001/jama.2010.897>.

Toupance S, Labat C, Temmar M, et al. Short telomeres, but not telomere attrition rates, are associated with carotid atherosclerosis. *Hypertension*. 2017;70(2):420–425. <https://doi.org/10.1161/hypertensionaha.117.09354>.

Bendix L, Gade MM, Staun PW, et al. Leukocyte telomere length and physical ability among Danish twins age 70+. *Mech Ageing Dev*. 2011;132(11–12):568–572. <https://doi.org/10.1016/j.mad.2011.10.003>.

Cherkas LF, Aviv A, Valdes AM, et al. The effects of social status on biological aging as measured by white-blood-cell telomere length. *Aging Cell*. 2006;5(5):361–365. <https://doi.org/10.1111/j.1474-9726.2006.00222.x>.

Denham J, Nelson CP, O'Brien BJ, et al. Longer leukocyte telomeres are associated with ultra-endurance exercise independent of cardiovascular risk factors. *PLoS One*. 2013;8. <https://doi.org/10.1371/journal.pone.0069377>.

Du M, Prescott J, Kraft P, et al. Physical activity, sedentary behavior, and leukocyte telomere length in women. *Am J Epidemiol*. 2012. <https://doi.org/10.1093/aje/kwr330>.

Garland SN, Johnson B, Palmer C, et al. Physical activity and telomere length in early stage breast cancer survivors. *Breast Cancer Res*. 2014;16(4):1–9. <https://doi.org/10.1186/s13058-014-0413-y>.

Kingma EM, de Jonge P, van der Harst P, Ormel J, Rosmalen JGM. The association between intelligence and telomere length: a longitudinal population based study. *PLoS One*. 2012;7(11):e49356. <https://doi.org/10.1371/journal.pone.0049356>.

Krauss J, Farzaneh-Far R, Puterman E, et al. Physical fitness and telomere length in patients with coronary heart disease: findings from the heart and soul study. *PLoS One*. 2011;6(11):e26983. <https://doi.org/10.1371/journal.pone.0026983>.

- LaRocca TJ, Seals DR, Pierce GL. Leukocyte telomere length is preserved with aging in endurance exercisetrained adults and related to maximal aerobic capacity. *Mech Ageing Dev.* 2010;131(2):165–167. <https://doi.org/10.1016/j.mad.2009.12.009>.
- Loprinzi PD. Cardiorespiratory capacity and leukocyte telomere length among adults in the United States. *Am J Epidemiol.* 2015;182(3):198–201. <https://doi.org/10.1093/aje/kwv056>.
- Ludlow AT, Zimmerman JOB, Witkowski S, Hearn JOEW, Hatfield BD, Roth SM. Relationship between physical activity level, telomere length, and telomerase activity. *Med Sci Sports Exerc.* 2008;40(10):1764–1771. <https://doi.org/10.1249/MSS.0b013e31817c92aa>.
- Østhus IBØ, Sgura A, Berardinelli F, et al. Telomere length and long-term endurance exercise: does exercise training affect biological age? A pilot study. *PLoS One.* 2012;7(12):e52769. <https://doi.org/10.1371/journal.pone.0052769>.
- Puterman E, Lin J, Krauss J, Blackburn EH, Epel ES. Determinants of telomere attrition over 1 year in healthy older women: stress and health behaviors matter. *Mol Psychiatry.* 2015;20(4):529–535. <https://doi.org/10.1038/mp.2014.70>.
- Savela S, Saijonmaa O, Strandberg TE, et al. Physical activity in midlife and telomere length measured in old age. *Exp Gerontol.* 2012;48(1):81–84. <https://doi.org/10.1016/j.exger.2012.02.003>.
- Silva LCR, de Araújo AL, Fernandes JR, et al. Moderate and intense exercise lifestyles attenuate the effects of aging on telomere length and the survival and composition of T cell subpopulations. *Age.* 2016;38(1):1–16. <https://doi.org/10.1007/s11357-016-9879-0>.
- Venturelli M, Morgan GR, Donato AJ, et al. Cellular aging of skeletal muscle: telomeric and free radical evidence that physical inactivity is responsible and not age. *Clin Sci.* 2014;127(6):415–421. <https://doi.org/10.1042/cs20140051>.
- Werner C, Furster T, Widmann T, et al. Physical exercise prevents cellular senescence in circulating leukocytes and in the vessel wall. *Circulation.* 2009;120(24):2438–2447. <https://doi.org/10.1161/CIRCULATIONAHA.109.861005>.
- Zhu H, Wang X, Gutin B, et al. Leukocyte telomere length in healthy Caucasian and African-American adolescents: relationships with race, sex, adiposity, adipokines, and physical activity. *J Pediatr.* 2011;158(2):215–220. <https://doi.org/10.1016/j.jpeds.2010.08.007>.
- Loprinzi PD, Sng E. Mode-specific physical activity and leukocyte telomere length among U.S. adults: implications of running on cellular aging. *Prev Med.* 2016;85:17–19. <https://doi.org/10.1016/j.ypmed.2016.01.002>.
- Borghini A, Giardini G, Tonacci A, et al. Chronic and acute effects of endurance training on telomere length. *Mutagenesis.* 2015;30(5):711–716. <https://doi.org/10.1093/mutage/gev038>.
- Latifovic L, Peacock SD, Massey TE, King WD. The influence of alcohol consumption, cigarette smoking, and physical activity on leukocyte telomere length. *Cancer Epidemiol Biomark Prev.* 2016;25(2):374–380. <https://doi.org/10.1158/1055-9965.epi-14-1364>.
- Saßenroth D, Meyer A, Salewsky B, et al. Sports and exercise at different ages and leukocyte telomere length in later life—data from the Berlin aging study II (BASE-II). *PLoS One.* 2015;10(12). <https://doi.org/10.1371/journal.pone.0142131>, e0142131.
- Shadyab AH, LaMonte MJ, Kooperberg C, et al. Leisure-time physical activity and leukocyte telomere length among older women. *Exp Gerontol.* 2017;95:141–147. <https://doi.org/10.1016/j.exger.2017.05.019>.
- Soares-Miranda L, Imamura F, Siscovick D, Jenny NS, Fitzpatrick AL, Mozaffarian D. Physical activity, physical fitness and leukocyte telomere length: the cardiovascular health study. *Med Sci Sports Exerc.* 2015;47(12):2525–2534. <https://doi.org/10.1249/MSS.0000000000000720>.
- Stenbäck V, Mutt SJ, Leppäluoto J, et al. Association of physical activity with telomere length among elderly adults—the Oulu cohort 1945. *Front Physiol.* 2019;10:444. <https://doi.org/10.3389/fphys.2019.00444>.
- Fretts AM, Mete M, Howard BV, et al. Physical activity and telomere length in American Indians: the strong heart study. *Eur J Epidemiol.* 2018;33(5):497–500. <https://doi.org/10.1007/s10654-018-0363-2>.

Ogawa EF, Leveille SG, Wright JA, Shi L, Camhi SM, You T. Physical activity domains/recommendations and leukocyte telomere length in U.S. adults. *Med Sci Sports Exerc.* 2017;49(7):1375–1382. <https://doi.org/10.1249/mss.0000000000001253>.

Magi F, Dimauro I, Margheritini F, et al. Telomere length is independently associated with age, oxidative biomarkers, and sport training in skeletal muscle of healthy adult males. *Free Radic Res.* 2018;52(6):639–647. <https://doi.org/10.1080/10715762.2018.1459043>.

Werner CM, Hecksteden A, Morsch A, et al. Differential effects of endurance, interval, and resistance training on telomerase activity and telomere length in a randomized, controlled study. *Eur Heart J.* 2019;40(1):34–46. <https://doi.org/10.1093/eurheartj/ehy585>.

Dankel SJ, Loenneke JP, Loprinzi PD. The impact of overweight/obesity duration and physical activity on telomere length: an application of the WATCH paradigm. *Obes Res Clin Pract.* 2017;11(2):247–252.

<https://doi.org/10.1016/j.orcp.2016.11.002>.

Muniesa CA, Verde Z, Diaz-Ureña G, et al. Telomere length in elite athletes. *Int J Sports Physiol Perform.* 2017;12(7):994–996. <https://doi.org/10.1123/ijspp.2016-0471>.

Puterman E, Weiss J, Lin J, et al. Aerobic exercise lengthens telomeres and reduces stress in family caregivers: a randomized controlled trial—Curt Richter award paper 2018. *Psychoneuroendocrinology.* 2018;98:245–252. <https://doi.org/10.1016/j.psyneuen.2018.08.002>.

Williams DM, Buxton JL, Kantomaa MT, Tammelin TH, Blakemore AIF, Järvelin M-R. Associations of leukocyte telomere length with aerobic and muscular fitness in young adults. *Am J Epidemiol.*

2017;185(7):529–537. <https://doi.org/10.1093/aje/kww123>.

Simoes HG, Sousa CV, Dos Santos Rosa T, et al. Longer telomere length in elite master sprinters: relationship to performance and body composition. *Int J Sports Med.* 2017;38(14):1111–1116. <https://doi.org/10.1055/s-0043-120345>.

Dimauro I, Sgura A, Pittaluga M, et al. Regular exercise participation improves genomic stability in diabetic patients: an exploratory study to analyse telomere length and DNA damage. *Sci Rep.* 2017;7(1):4137. <https://doi.org/10.1038/s41598-017-04448-4>.

Mason C, Risques R-A, Xiao L, et al. Independent and combined effects of dietary weight loss and exercise on leukocyte telomere length in postmenopausal women. *Obesity.* 2013;21(12):E549–E554. <https://doi.org/10.1002/oby.20509>.

Cassidy A, De Vivo I, Liu Y, et al. Associations between diet, lifestyle factors, and telomere length in women. *Am J Clin Nutr.* 2010. <https://doi.org/10.3945/ajcn.2009.28947>.

Denham J. Lack of association between PBMC telomere length and endurance exercise. *J Appl Biomed.* 2016. <https://doi.org/10.1016/j.jab.2016.09.004>.

Farzaneh-Far R, Lin J, Epel E, Lapham K, Blackburn E, Whooley MA. Telomere length trajectory and its determinants in persons with coronary artery disease: longitudinal findings from the heart and soul study. *PLoS One.* 2010;5(1):e8612. <https://doi.org/10.1371/journal.pone.0008612>.

Fujishiro K, Diez-Roux AV, Landsbergis PA, Jenny NS, Seeman T. Current employment status, occupational category, occupational hazard exposure and job stress in relation to telomere length: the multiethnic study of atherosclerosis (MESA). *Occup Environ Med.* 2013;70(8):552–560. <https://doi.org/10.1136/oemed-2012-101296>.

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

Hovatta I, Mello d, F D, et al. Leukocyte telomere length in the Finnish diabetes prevention study. *PLoS One.* 2012;7(4). <https://doi.org/10.1371/journal.pone.0034948>, e34948.

Kadi F, Ponsot E, Piehl-Aulin K, et al. The effects of regular strength training on telomere length in human skeletal

muscle. *Med Sci Sports Exerc.* 2008;40(1):82–87. <https://doi.org/10.1249/mss.0b013e3181596695>.

Laine MK, Eriksson JG, Kujala UM, et al. Effect of intensive exercise in early adult life on telomere length in later life in men. *J Sports Sci Med.* 2015;14(2):239–245.

Laye MJ, Solomon TPJ, Karstoft K, Pedersen KK, Nielsen SD, Pedersen BK. Increased shelterin mRNA expression in peripheral blood mononuclear cells and skeletal muscle following an ultra-long-distance running event. *J Appl Physiol.* 2012;112(5):773–781. <https://doi.org/10.1152/jappphysiol.00997.2011>.

Mathur S, Ardestani A, Parker B, Cappizzi J, Polk D, Thompson PD. Telomere length and cardiorespiratory fitness in marathon runners. *J Investig Med.* 2013;61(3):613–615. <https://doi.org/10.2310/JIM.0b013e3182814cc2>.

Ponsot E, Lexell J, Kadi F. Skeletal muscle telomere length is not impaired in healthy physically active old women and men. *Muscle Nerve.* 2008;37(4):467–472. <https://doi.org/10.1002/mus.20964>.

Rae DE, Vignaud A, Butler-Browne GS, et al. Skeletal muscle telomere length in healthy, experienced, endurance runners. *Eur J Appl Physiol.* 2010;109(2):323–330. <https://doi.org/10.1007/s00421-010-1353-6>.

Shin YA, Lee JH, Song W, Jun TW. Exercise training improves the antioxidant enzyme activity with no changes of telomere length. *Mech Ageing Dev.* 2008;129(5):254–260. <https://doi.org/10.1016/j.mad.2008.01.001>.

Song B, Ju J. Impact of miRNAs in gastrointestinal cancer diagnosis and prognosis. *Expert Rev Mol Med.* 2010;12. <https://doi.org/10.1017/s1462399410001663>.

Sun Q, Shi L, Prescott J, et al. Healthy lifestyle and leukocyte telomere length in U.S. women. *PLoS One.* 2012;7(5):e38374. <https://doi.org/10.1371/journal.pone.0038374>.

Svenson U, Nordfjäll K, Baird D, et al. Blood cell telomere length is a dynamic feature. *PLoS One.* 2011;6(6):e21485. <https://doi.org/10.1371/journal.pone.0021485>.

Tiainen AMK, Männistö S, Blomstedt PA, et al. Leukocyte telomere length and its relation to food and nutrient intake in an elderly population. *Eur J Clin Nutr.* 2012;66(12):1290–1294. <https://doi.org/10.1038/ejcn.2012.143>.

Woo J, Tang N, Leung J. No association between physical activity and telomere length in an elderly Chinese population 65 years and older. *Arch Intern Med.* 2008;168(19):2163–2164. <https://doi.org/10.1001/archinte.168.19.2163>.

Mundstock E, Zatti H, Louzada FM, et al. Effects of physical activity in telomere length: systematic review and meta-analysis. *Ageing Res Rev.* 2015;22:72–80. <https://doi.org/10.1016/j.arr.2015.02.004>.

Mirabello L, Huang WY, Wong JYY, et al. The association between leukocyte telomere length and cigarette smoking, dietary and physical variables, and risk of prostate cancer. *Aging Cell.* 2009;8(4):405–413. <https://doi.org/10.1111/j.1474-9726.2009.00485.x>.

von Kanel R, Bruwer EJ, Hamer M, de Ridder JH, Malan L. Association between objectively measured physical activity, chronic stress and leukocyte telomere length. *J Sports Med Phys Fitness.* 2017;57(10):1349–1358. <https://doi.org/10.23736/s0022-4707.16.06426-4>.

Wan ES, Goldstein RL, Fan VS, et al. Telomere length in COPD: relationships with physical activity, exercise capacity, and acute exacerbations. *PLoS One.* 2019;14(10). <https://doi.org/10.1371/journal.pone.0223891>, e0223891.

Ding LX, Zhang YH, Xu XZ, et al. Association between physical activity and telomere length in a north Chinese population: a China suboptimal health cohort study. *Biomed Environ Sci.* 2018;31(5):394–398. <https://doi.org/10.3967/bes2018.051>.

Denham J. The association between sperm telomere length, cardiorespiratory fitness and exercise training in humans. *Biomed J.* 2019;42(6):430–433. <https://doi.org/10.1016/j.bj.2019.07.003>.

Jantunen H, Wasenius NS, Guzzardi MA, et al. Physical activity and telomeres in old age: a longitudinal 10-year follow-up study. *Gerontology.* 2020;66(4):315–322. <https://doi.org/10.1159/000505603>.

Friedenreich CM, Wang Q, Ting NS, et al. Effect of a 12-month exercise intervention on leukocyte telomere length: results from the ALPHA trial. *Cancer Epidemiol.* 2018;56:67–74. <https://doi.org/10.1016/j.canep.2018.07.012>.

Campos RM, de Mello MT, Tock L, et al. Aerobic plus resistance training improves bone metabolism and inflammation in adolescents who are obese. *J Strength Cond Res.* 2014;28(3):758–766. <https://doi.org/10.1519/JSC.0b013e3182a996df>.

Gomes EC, Silva AN, de Oliveira MR. Oxidants, antioxidants, and the beneficial roles of exercise-induced production of reactive species. *Oxidative Med Cell Longev.* 2012;2012:756132. <https://doi.org/10.1155/2012/756132>.

Nimmo MA, Leggate M, Viana JL, King JA. The effect of physical activity on mediators of inflammation. *Diabetes Obes Metab.* 2013;15(s3):51–60. <https://doi.org/10.1111/dom.12156>.

Gomez-Cabrera M-C, Domenech E, Viña J. Moderate exercise is an antioxidant: upregulation of antioxidant genes by training. *Free Radic Biol Med.* 2008;44(2):126–131. <https://doi.org/10.1016/j.freeradbiomed.2007.02.001>.

Radák Z, Apor P, Pucsok J, et al. Marathon running alters the DNA base excision repair in human skeletal muscle. *Life Sci.* 2003;72(14):1627–1633. [https://doi.org/10.1016/S0024-3205\(02\)02476-1](https://doi.org/10.1016/S0024-3205(02)02476-1).

Bjork L, Jenkins NT, Witkowski S, Hagberg JM. Nitro-oxidative stress biomarkers in active and inactive men. *Int J Sports Med.* 2012;33(4):279–284. <https://doi.org/10.1055/s-0032-1301891>.

Ludlow AT, Roth SM. Physical activity and telomere biology: exploring the link with aging-related disease prevention. *J Aging Res.* 2011;2011:12. <https://doi.org/10.4061/2011/790378>.

Werner C, Hanhoun M, Widmann T, et al. Effects of physical exercise on myocardial telomere-regulating proteins, survival pathways, and apoptosis. *J Am Coll Cardiol.* 2008;52(6):470. <https://doi.org/10.1016/j.jacc.2008.04.034>.

Haigis MC, Yankner BA. The aging stress response. *Mol Cell.* 2010;40(2):333–344. <https://doi.org/10.1016/j.molcel.2010.10.002>.

Andersen JK. Oxidative stress in neurodegeneration: cause or consequence? *Nat Med.* 2004;10:S18–S25. <https://doi.org/10.1038/nrn1434>.

Shukla V, Mishra SK, Pant HC. Oxidative stress in neurodegeneration. *Adv Pharmacol Sci.* 2011;2011. <https://doi.org/10.1155/2011/572634>, 572634.

Paravicini TM, Touyz RM. Redox signaling in hypertension. *Cardiovasc Res.* 2006;71(2):247–258. <https://doi.org/10.1016/j.cardiores.2006.05.001>.

Trachootham D, Alexandre J, Huang P. Targeting cancer cells by ROS-mediated mechanisms: a radical therapeutic approach? *Nat Rev Drug Discov.* 2009;8(7):579–591. <https://doi.org/10.1038/nrd2803>.

Oikawa S, Kawanishi S. Site-specific DNA damage at GGG sequence by oxidative stress may accelerate telomere shortening. *FEBS Lett.* 1999;453. [https://doi.org/10.1016/s0014-5793\(99\)00748-6](https://doi.org/10.1016/s0014-5793(99)00748-6).

von Zglinicki T. Oxidative stress shortens telomeres. *Trends Biochem Sci.* 2002;27. [https://doi.org/10.1016/s0968-0004\(02\)02110-2](https://doi.org/10.1016/s0968-0004(02)02110-2).

von Zglinicki T, Pilger R, Sitte N. Accumulation of single-strand breaks is the major cause of telomere shortening in human fibroblasts. *Free Radic Biol Med.* 2000;28(1):64–74. [https://doi.org/10.1016/S0891-5849\(99\)00207-5](https://doi.org/10.1016/S0891-5849(99)00207-5).

Houben JM, Moonen HJ, van Schooten FJ, Hageman GJ. Telomere length assessment: biomarker of chronic oxidative stress? *Free Radic Biol Med.* 2008;44(3):235–246. <https://doi.org/10.1016/j.freeradbiomed.2007.10.001>.

Woo J, Suen E, Tang NLS. Telomeres and the ageing process. *Rev Clin Gerontol.* 2010;1–9. <https://doi.org/10.1017/S0959259809990451>.

Ji LL, Gomez-Cabrera MC, Vina J. Exercise and Hormesis: activation of cellular antioxidant signaling pathway. *Ann N Y Acad Sci.* 2006;1067(1):425–435. <https://doi.org/10.1196/annals.1354.061>.

McArdle A, Jackson MJ. Exercise, oxidative stress and ageing. *J Anat.* 2000;197(4):539–541. <https://doi.org/10.1046/j.1469-7580.2000.19740539.x>.

Mishra S, Kumar R, Malhotra N, Singh N, Dada R. Mild oxidative stress is beneficial for sperm telomere length

maintenance. *World J Methodol.* 2016;6(2):163–170. <https://doi.org/10.5662/wjm.v6.i2.163>.

Radak Z, Chung HY, Goto S. Exercise and hormesis: oxidative stress-related adaptation for successful aging. *BioGerontology.* 2005;6(1):71–75. <https://doi.org/10.1007/s10522-004-7386-7>.

Urso ML, Clarkson PM. Oxidative stress, exercise, and antioxidant supplementation. *Toxicology.* 2003;189(1–2):41–54. [https://doi.org/10.1016/S0300-483X\(03\)00151-3](https://doi.org/10.1016/S0300-483X(03)00151-3).

Richter T, von Zglinicki T. A continuous correlation between oxidative stress and telomere shortening in fibroblasts. *Exp Gerontol.* 2007;42(11):1039–1042. <https://doi.org/10.1016/j.exger.2007.08.005>.

Büchner N, Zschauer TC, Lukosz M, Altschmied J, Haendeler J. Downregulation of mitochondrial telomerase reverse transcriptase induced by H₂O₂ is Src kinase dependent. *Exp Gerontol.* 2010;45(7–8):558–562. Special Issue: Mitochondria in aging and age-related disease <https://doi.org/10.1016/j.exger.2010.03.003>.

Haendeler J, Dröse S, Büchner N, et al. Mitochondrial telomerase reverse transcriptase binds to and protects mitochondrial DNA and function from damage. *Arterioscler Thromb Vasc Biol.* 2009;29(6):929–935.

<https://doi.org/10.1161/ATVBAHA.109.185546>.

Khan S, Chaturgoon AA, Naidoo DP. Telomeres and atherosclerosis: review article. *Cardiovasc J Afr.* 2012;23(10):563–571.

O'Donovan A, Pantell MS, Puterman E, et al. Cumulative inflammatory load is associated with short leukocyte telomere length in the health, aging and body composition study. *PLoS One.* 2011;6(5):e19687. <https://doi.org/10.1371/journal.pone.0019687>.

Akiyama M, Yamada O, Hideshima T, et al. TNF α induces rapid activation and nuclear translocation of telomerase in human lymphocytes. *Biochem Biophys Res Commun.* 2004;316(2):528–532. <https://doi.org/10.1016/j.bbrc.2004.02.080>.

Aviv A. Telomeres and human aging: facts and fibs. *Sci Aging Knowl Environ.* 2004;2004(51):pe43. <https://doi.org/10.1126/sageke.2004.51.pe43>.

Jaiswal M, LaRusso NF, Burgart LJ, Gores GJ. Inflammatory cytokines induce DNA damage and inhibit DNA repair in cholangiocarcinoma cells by a nitric oxide-dependent mechanism. *Cancer Res.* 2000;60(1):184–190.

Parish ST, Wu JE, Effros RB. Modulation of T lymphocyte replicative senescence via TNF- α inhibition: role of caspase-3. *J Immunol.* 2009;182(7):4237–4243. <https://doi.org/10.4049/jimmunol.0803449>.

Xu D, Erickson M, Szeps A, et al. Interferon alpha downregulates telomerase reverse transcriptase and telomerase activity in human malignant and nonmalignant hematopoietic cells. *Blood.* 2000;96:4313–4318.

Coppé J-P, Patil C, Rodier F, et al. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. *PLoS Biol.* 2008;6. <https://doi.org/10.1371/journal.pbio.0060301>.

Rodier F, Coppe J-P, Patil CK, et al. Persistent DNA damage signalling triggers senescence-associated inflammatory cytokine secretion. *Nat Cell Biol.* 2009;11(8):973–979. <https://doi.org/10.1038/ncb1909>.

Beavers KM, Brinkley TE, Nicklas BJ. Effect of exercise training on chronic inflammation. *Clin Chim Acta.* 2010;411(11–12):785–793 [This Issue Includes Abstracts from the Asian Pacific Conference of Chromatography and Mass Spectrometry] <https://doi.org/10.1016/j.cca.2010.02.069>.

Woods JA, Keylock KT, Lowder T, et al. Cardiovascular exercise training extends influenza vaccine seroprotection in sedentary older adults: the immune function intervention trial. *J Am Geriatr Soc.* 2009;57(12):2183–2191. <https://doi.org/10.1111/j.1532-5415.2009.02563.x>.

Kendig EL, Le HH, Belcher SM. Defining hormesis: evaluation of a complex concentration response phenomenon. *Int J Toxicol.* 2010;29(3):235–246. <https://doi.org/10.1177/1091581810363012>.

Radak Z, Chung HY, Koltai E, Taylor AW, Goto S. Exercise, oxidative stress and hormesis. *Ageing Res Rev.* 2008;7(1):34–42. <https://doi.org/10.1016/j.arr.2007.04.004>.

Ludlow AT, Lima LCJ, Wang J, et al. Exercise alters mRNA expression of telomere-repeat binding factor 1 in skeletal muscle via p38 MAPK. *J Appl Physiol.* 2012;113(11):1737–1746. <https://doi.org/10.1152/japphysiol>.

ol.00200.2012.

Denham J, O'Brien BJ, Prestes PR, Brown NJ, Charchar FJ. Increased expression of telomere-regulating genes in endurance athletes with long leukocyte telomeres. *J Appl Physiol*. 2016;120(2):148–158. <https://doi.org/10.1152/japplphysiol.00587.2015>.

Chilton WL, Marques FZ, West J, et al. Acute exercise leads to regulation of telomere-associated genes and microRNA expression in immune cells. *PLoS One*. 2014;9(4):e92088. <https://doi.org/10.1371/journal.pone.0092088>.

Fraga MF, Ballestar E, Villar-Garea A, et al. Loss of acetylation at Lys16 and trimethylation at Lys20 of histone H4 is a common hallmark of human cancer. *Nat Genet*. 2005;37(4):391–400. <https://doi.org/10.1038/ng1531>.

Tommerup H, Dousmanis A, de Lange T. Unusual chromatin in human telomeres. *Mol Cell Biol*. 1994;14(9):5777–5785. <https://doi.org/10.1128/mcb.14.9.5777>.

van Overveld PGM, Lemmers RJFL, Sandkuijl LA, et al. Hypomethylation of D4Z4 in 4q-linked and non-4q-linked facioscapulohumeral muscular dystrophy. *Nat Genet*. 2003;35(4):315–317. <https://doi.org/10.1038/ng1262>.

García-Cao M, O'Sullivan R, Peters AH, Jenuwein T, Blasco MA. Epigenetic regulation of telomere length in mammalian cells by the Suv39h1 and Suv39h2 histone methyltransferases. *Nat Genet*. 2003;36(1):94–99. <https://doi.org/10.1038/ng1278>.

Peuscher MH, Jacobs JLL. Posttranslational control of telomere maintenance and the telomere damage response. *Cell Cycle*. 2012;11(8):1524–1534. <https://doi.org/10.4161/cc.19847>.

Walker JR, Zhu XD. Post-translational modifications of TRF1 and TRF2 and their roles in telomere maintenance. *Mech Ageing Dev*. 2012;133(6):421–434. <https://doi.org/10.1016/j.mad.2012.05.002>.

Castro-Vega LJ, Jouravleva K, Liu W-Y, et al. Telomere crisis in kidney epithelial cells promotes the acquisition of a microRNA signature retrieved in aggressive renal cell carcinomas. *Carcinogenesis*. 2013;34(5):1173–1180. <https://doi.org/10.1093/carcin/bgt029>.

Chan SY, Zhang YY, Hemann C, Mahoney CE, Zweier JL, Loscalzo J. MicroRNA-210 controls mitochondrial metabolism during hypoxia by repressing the iron-sulfur cluster assembly proteins ISCU1/2. *Cell Metab*. 2009;10(4):273–284. <https://doi.org/10.1016/j.cmet.2009.08.015>.

Williams AH, Liu N, Van Rooij E, Olson EN. MicroRNA control of muscle development and disease. *Curr Opin Cell Biol*. 2009;21(3):461–469. <https://doi.org/10.1016/j.ceb.2009.01.029>.

Zhang C. MicroRNAs in vascular biology and vascular disease. *J Cardiovasc Transl Res*. 2010;3(3):235–240. <https://doi.org/10.1007/s12265-010-9164-z>.

Neves VJd, Fernandes T, Roque FR, Soci UPR, Melo SFS, de Oliveira EM. Exercise training in hypertension: role of microRNAs. *World J Cardiol*. 2014;6(8):713–727. <https://doi.org/10.4330/wjcv.v6.i8.713>.

Kasiappan R, Shen Z, Tse AK-W, et al. 1,25-Dihydroxyvitamin D3 suppresses telomerase expression and human cancer growth through microRNA-498. *J Biol Chem*. 2012;287(49):41297–41309. <https://doi.org/10.1074/jbc.M112.407189>.

Buxton JL, Suderman M, Pappas JJ, et al. Human leukocyte telomere length is associated with DNA methylation levels in multiple subtelomeric and imprinted loci. *Sci Rep*. 2014;4:4954. <https://doi.org/10.1038/srep04954>.

Wong JYY, De Vivo I, Lin X, Grashow R, Cavallari J, Christiani DC. The association between global DNA methylation and telomere length in a longitudinal study of boilermakers. *Genet Epidemiol*. 2014;38(3):254–264. <https://doi.org/10.1002/gepi.21796>.

Gonzalo S, Jaco I, Fraga MF, et al. DNA methyltransferases control telomere length and telomere recombination in mammalian cells. *Nat Cell Biol*. 2006;8(4):416–424. <https://doi.org/10.1038/ncb1386>.

Ng LJ, Cropley JE, Pickett HA, Reddel RR, Suter CM. Telomerase activity is associated with an increase in DNA methylation at the proximal subtelomere and a reduction in telomeric transcription. *Nucleic Acids Res*. 2009;37(4):1152–1159. <https://doi.org/10.1093/nar/gkn1030>.

Cusanelli E, Chartrand P. Telomeric repeat-containing RNA TERRA: a noncoding RNA connecting telomere biol-

ogy to genome integrity. *Front Genet.* 2015;6:143. <https://doi.org/10.3389/fgene.2015.00143>.

Farnung BO, Brun CM, Arora R, Lorenzi LE, Azzalin CM. Telomerase efficiently elongates highly transcribing telomeres in human cancer cells. *PLoS One.* 2012;7(4):e35714. <https://doi.org/10.1371/journal.pone.0035714>.

Bettin N, Oss Pegorar C, Cusanelli E. The emerging roles of TERRA in telomere maintenance and genome stability. *Cell.* 2019;8(3):246. <https://doi.org/10.3390/cells8030246>.

Deng Z, Campbell AE, Lieberman PM. TERRA, CpG methylation and telomere heterochromatin: lessons from ICF syndrome cells. *Cell Cycle.* 2010;9(1):69–74. <https://doi.org/10.4161/cc.9.1.10358>.

Luke B, Panza A, Redon S, Iglesias N, Li Z, Lingner J. The Rat1p 5' to 3' exonuclease degrades telomeric repeat-containing RNA and promotes telomere elongation in *Saccharomyces cerevisiae*. *Mol Cell.* 2008;32(4):465–477. <https://doi.org/10.1016/j.molcel.2008.10.019>.

Nergadze SG, Farnung BO, Wischniewski H, et al. CpG-island promoters drive transcription of human telomeres. *RNA.* 2009;15(12):2186–2194. <https://doi.org/10.1261/rna.1748309>.

Schoeftner S, Blasco MA. Developmentally regulated transcription of mammalian telomeres by DNA-dependent RNA polymerase II. *Nat Cell Biol.* 2008;10(2):228–236. <https://doi.org/10.1038/ncb1685>.

Deng Z, Norseen J, Wiedmer A, Riethman H, Lieberman PM. TERRA RNA binding to TRF2 facilitates heterochromatin formation and ORC recruitment at telomeres. *Mol Cell.* 2009;35(4):403–413. <https://doi.org/10.1016/j.molcel.2009.06.025>.

Arora R, Lee Y, Wischniewski H, Brun CM, Schwarz T, Azzalin CM. RNaseH1 regulates TERRA-telomeric DNA hybrids and telomere maintenance in ALT tumour cells. *Nat Commun.* 2014;5:5220. <https://doi.org/10.1038/ncomms6220>.

Balk B, Maicher A, Dees M, et al. Telomeric RNA-DNA hybrids affect telomere-length dynamics and senescence. *Nat Struct Mol Biol.* 2013;20(10):1199–1205. <https://doi.org/10.1038/nsmb.2662>.

Pfeiffer V, Crittin J, Grolimund L, Lingner J. The THO complex component Thp2 counteracts telomeric R-loops and telomere shortening. *EMBO J.* 2013;32(21):2861–2871. <https://doi.org/10.1038/emboj.2013.217>.

Yu T-Y, Kao Y-W, Lin J-J. Telomeric transcripts stimulate telomere recombination to suppress senescence in cells lacking telomerase. *Proc Natl Acad Sci.* 2014;111(9):3377–3382. <https://doi.org/10.1073/pnas.1307415111>.

Ginno PA, Lott PL, Christensen HC, Korf I, Chédin F. R-loop formation is a distinctive characteristic of unmethylated human CpG island promoters. *Mol Cell.* 2012;45(6):814–825. <https://doi.org/10.1016/j.molcel.2012.01.017>.

Skourti-Stathaki K, Proudfoot NJ, Gromak N. Human senataxin resolves RNA/DNA hybrids formed at transcriptional pause sites to promote Xrn2-dependent termination. *Mol Cell.* 2011;42(6):794–805. <https://doi.org/10.1016/j.molcel.2011.04.026>.

Arnoult N, Van Beneden A, Decottignies A. Telomere length regulates TERRA levels through increased trimethylation of telomeric H3K9 and HP1 α . *Nat Struct Mol Biol.* 2012;19(9):948–956. <https://doi.org/10.1038/nsmb.2364>.

Cusanelli E, Romero CAP, Chartrand P. Telomeric noncoding RNA TERRA is induced by telomere shortening to nucleate telomerase molecules at short telomeres. *Mol Cell.* 2013;51(6):780–791. <https://doi.org/10.1016/j.molcel.2013.08.029>.

Porro A, Feuerhahn S, Delafontaine J, Riethman H, Rougemont J, Lingner J. Functional characterization of the TERRA transcriptome at damaged telomeres. *Nat Commun.* 2014;5:5379. <https://doi.org/10.1038/ncomms6379>.

Diman A, Boros J, Poulain F, et al. Nuclear respiratory factor 1 and endurance exercise promote human telomere transcription. *Sci Adv.* 2016;2(7). <https://doi.org/10.1126/sciadv.1600031>, e1600031.

Xavier MJ, Roman SD, Aitken RJ, Nixon B. Transgenerational inheritance: how impacts to the epigenetic and genetic information of parents affect offspring health. *Hum Reprod Update.* 2019;25(5):519–541.

Murashov AK, Pak ES, Koury M, et al. Paternal long-term exercise programs offspring for low energy expenditure and increased risk for obesity in mice. *FASEB J.* 2016;30(2):775–784.

Denham J, O'Brien BJ, Harvey JT, Charchar FJ. Genome-wide sperm DNA methylation changes after 3 months of

exercise training in humans. *Epigenomics*. 2015;7(5):717–731.

McCullough LE, Mendez MA, Miller EE, Murtha AP, Murphy SK, Hoyo C. Associations between prenatal physical activity, birth weight, and DNA methylation at genomically imprinted domains in a multiethnic newborn cohort. *Epigenetics*. 2015;10(7):597–606.

Laker RC, Lillard TS, Okutsu M, et al. Exercise prevents maternal high-fat diet–induced hypermethylation of the *Pgc-1 α* gene and age-dependent metabolic dysfunction in the offspring. *Diabetes*. 2014;63(5):1605–1611.

Short A, Yeshurun S, Powell R, et al. Exercise alters mouse sperm small noncoding RNAs and induces a transgenerational modification of male offspring conditioned fear and anxiety. *Transl Psychiatry*. 2017;7(5):e1114.

Spindler C, Segabinazi E, de Meireles ALF, et al. Paternal physical exercise modulates global DNA methylation status in the hippocampus of male rat offspring. *Neural Regen Res*. 2019;14(3):491.

Segabinazi E, Spindler C, de Meireles ALF, et al. Effects of maternal physical exercise on global DNA methylation and hippocampal plasticity of rat male offspring. *Neuroscience*. 2019;418:218–230.

Chapter 8

Horsthemke B. A critical view on transgenerational epigenetic inheritance in humans. *Nat Commun*. 2018;9:2973.

Soskic B, et al. Chromatin activity at GWAS loci identifies T cell states driving complex immune diseases. *Nat Genet*. 2019;51:1486–1493.

Deans C, Maggert KA. What do you mean, ‘epigenetic’? *Genetics*. 2015;199:887–896.

Denham J, O’Brien BJ, Marques FZ, Charchar FJ. Changes in the leukocyte methylome and its effect on cardiovascular-related genes after exercise. *J Appl Physiol*. 2015;118:475–488.

Zhang Q, Cao X. Epigenetic regulation of the innate immune response to infection. *Nat Rev Immunol*. 2019;19:417–432.

McGee SL, Hargreaves M. Epigenetics and exercise. *Trends Endocrinol Metab*. 2019;30:636–645.

Horsburgh S, Robson-Ansley P, Adams R, Smith C. Exercise and inflammation-related epigenetic modifications: focus on DNA methylation. *Exerc Immunol Rev*. 2015;21:26–41.

Pedersen BK, Febbraio MA. Muscle as an endocrine organ: focus on muscle-derived interleukin-6. *Physiol Rev*. 2008;88:1379–1406.

Brandt C, Pedersen BK. The role of exercise-induced myokines in muscle homeostasis and the defense against chronic diseases. *J Biomed Biotechnol*. 2010;2010:520258.

Lang Lehrslov L, et al. Interleukin-6 delays gastric emptying in humans with direct effects on glycemic control. *Cell Metab*. 2018;27:1201–1211. e3.

Wallenius V, et al. Interleukin-6-deficient mice develop mature-onset obesity. *Nat Med*. 2002;8:75–79.

Ellingsgaard H, et al. GLP-1 secretion is regulated by IL-6 signalling: a randomised, placebo-controlled study. *Diabetologia*. 2020;63:362–373.

Murphy TM, et al. Anxiety is associated with higher levels of global DNA methylation and altered expression of epigenetic and interleukin-6 genes. *Psychiatr Genet*. 2015;25:71–78.

Foran E, et al. Upregulation of DNA methyltransferase-mediated gene silencing, anchorage-independent growth, and migration of colon cancer cells by interleukin-6. *Mol Cancer Res*. 2010;8:471–481.

Cabral-Santos C, et al. Interleukin-10 responses from acute exercise in healthy subjects: a systematic review. *J Cell Physiol*. 2019;234:9956–9965.

Larsson L, Thorbert-Mros S, Rymo L, Berglundh T. Influence of epigenetic modifications of the interleukin-10 promoter on IL10 gene expression. *Eur J Oral Sci*. 2012;120:14–20.

Clifford T, et al. T-regulatory cells exhibit a biphasic response to prolonged endurance exercise in humans. *Eur J Appl Physiol*. 2017;117:1727–1737.

Lovinsky-Desir S, et al. Physical activity, black carbon exposure, and DNA methylation in the FOXP3 promoter.

Clin Epigenetics. 2017;9:65.

Hwang W, et al. Locus-specific reversible DNA methylation regulates transient IL-10 expression in Th1 cells. *J Immunol.* 2018;200:1865–1875.

Tonon S, et al. IL-10-producing B cells are characterized by a specific methylation signature. *Eur J Immunol.* 2019;49:1213–1225.

Warburton DER, Bredin SSD. Health benefits of physical activity: a systematic review of current systematic reviews. *Curr Opin Cardiol.* 2017;32:541–556.

Caspersen C, Powell K, Christenson G. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep.* 1985;100:126–131.

Soares FH, de Sousa MB. Different types of physical activity on inflammatory biomarkers in women with or without metabolic disorders: a systematic review. *Women Health.* 2013;53:298–316.

Zheng G, et al. Effect of aerobic exercise on inflammatory markers in healthy middle-aged and older adults: a systematic review and meta-analysis of randomized controlled trials. *Front Aging Neurosci.* 2019;11:98.

Hoffmann MJ, Schulz WA. Causes and consequences of DNA hypomethylation in human cancer. *Biochem Cell Biol.* 2005;83:296–321.

Zhang FF, et al. Physical activity and global genomic DNA methylation in a cancer-free population. *Epigenetics.* 2011;6:293–299.

Zhang FF, et al. White blood cell global methylation and IL-6 promoter methylation in association with diet and lifestyle risk factors in a cancer-free population. *Epigenetics.* 2012;7:606–614.

Shaw B, et al. A change in physical activity level affects leukocyte DNA methylation of genes implicated in cardiovascular disease in the elderly - The Physiological Society. *Proc Physiol Soc.* 2014;31:C46.

Sarzi-Puttini P, Atzeni F, Doria A, Iaccarino L, Turiel M. Tumor necrosis factor- α , biologic agents and cardiovascular risk. *Lupus.* 2005;14:780–784.

Braith RW, Stewart KJ. Resistance exercise training: its role in the prevention of cardiovascular disease. *Circulation.* 2006;113:2642–2650.

Phillips MD, et al. Resistance training reduces subclinical inflammation in obese, postmenopausal women. *Med Sci Sports Exerc.* 2012;44:2099–2110.

Strasser B, Arvandi M, Siebert U. Resistance training, visceral obesity and inflammatory response: a review of the evidence. *Obes Rev.* 2012;13:578–591.

Tidball JG, Villalta SA. Regulatory interactions between muscle and the immune system during muscle regeneration. *Am J Physiol Regul Integr Comp Physiol.* 2010;298:R1173–R1187.

Pillon NJ, Bilan PJ, Fink LN, Klip A. Cross-talk between skeletal muscle and immune cells: muscle-derived mediators and metabolic implications. *Am J Physiol Endocrinol Metab.* 2013;304:E453–E465.

Denham J, Marques FZ, Bruns EL, O'Brien BJ, Charchar FJ. Epigenetic changes in leukocytes after 8 weeks of resistance exercise training. *Eur J Appl Physiol.* 2016;116:1245–1253.

Consitt LA, Copeland JL, Tremblay MS. Endogenous anabolic hormone responses to endurance versus resistance exercise and training in women. *Sports Med.* 2002;32:1–22.

Häkkinen K, Pakarinen A, Newton RU, Kraemer WJ. Acute hormone responses to heavy resistance lower and upper extremity exercise in young versus old men. *Eur J Appl Physiol Occup Physiol.* 1998;77:312–319.

Kraemer WJ, Ratamess NA. Hormonal responses and adaptations to resistance exercise and training. *Sports Med.* 2005;35:339–361.

Sawada S, et al. Profiling of circulating microRNAs after a bout of acute resistance exercise in humans. *PLoS One.* 2013;8, e70823.

Engström G, et al. Incidence of obesity-associated cardiovascular disease is related to inflammation-sensitive plasma proteins: a population-based cohort study. *Arterioscler Thromb Vasc Biol.* 2004;24:1498–1502.

Mathieu P, Lemieux I, Després J-P. Obesity, inflammation, and cardiovascular risk. *Clin Pharmacol Ther.* 2010;87:407–416.

Dyck DJ. Adipokines as regulators of muscle metabolism and insulin sensitivity. This paper is one of a selection of papers published in this Special Issue, entitled 14th International Biochemistry of Exercise Conference – Muscles as Molecular and Metabolic Machines. *Appl Physiol Nutr Metab.* 2009;34:396–402.

Wang P, Mariman E, Renes J, Keijer J. The secretory function of adipocytes in the physiology of white adipose tissue. *J Cell Physiol.* 2008;216:3–13.

Jurca R, et al. Association of muscular strength with incidence of metabolic syndrome in men. *Med Sci Sports Exerc.* 2005;37:1849–1855.

Ruiz JR, et al. Muscular strength and adiposity as predictors of adulthood cancer mortality in men. *Cancer Epidemiol Biomark Prev.* 2009;18:1468–1476.

Pedersen BK. Anti-inflammatory effects of exercise: role in diabetes and cardiovascular disease. *Eur J Clin Investig.* 2017;47:600–611.

Robson-Ansley P, Barwood M, Eglin C, Ansley L. The effect of carbohydrate ingestion on the interleukin-6 response to a 90-minute run time trial. *Int J Sports Physiol Perform.* 2009;4:186–194.

Robson-Ansley PJ, et al. Dynamic changes in DNA methylation status in peripheral blood mononuclear cells following an acute bout of exercise: potential impact of exercise-induced elevations in interleukin-6 concentration. *J Biol Regul Homeost Agents.* 2014;28:407–417.

Malm C. Susceptibility to infections in elite athletes: the S-curve. *Scand J Med Sci Sport.* 2006;16:4–6.

Pedersen BK, Ullum H. NK cell response to physical activity: possible mechanisms of action. *Med Sci Sports Exerc.* 1994;26:140–146.

McHugh MP, et al. The role of passive muscle stiffness in symptoms of exercise-induced muscle damage. *Am J Sports Med.* 1999;27:594–599.

McHugh MP. Recent advances in the understanding of the repeated bout effect: the protective effect against muscle damage from a single bout of eccentric exercise. *Scand J Med Sci Sports.* 2003;13:88–97.

Nosaka K, Sakamoto K, Newton M, Sacco P. The repeated bout effect of reduced-load eccentric exercise on elbow flexor muscle damage. *Eur J Appl Physiol.* 2001;85:34–40.

Pizza FX, Koh TJ, McGregor SJ, Brooks SV. Muscle inflammatory cells after passive stretches, isometric contractions, and lengthening contractions. *J Appl Physiol.* 2002;92:1873–1878.

Deyhle MR, et al. Skeletal muscle inflammation following repeated bouts of lengthening contractions in humans. *Front Physiol.* 2016;6:1–11.

Jimenez-Jimenez R, et al. Eccentric training impairs NF- κ B activation and over-expression of inflammation-related genes induced by acute eccentric exercise in the elderly. *Mech Ageing Dev.* 2008;129:313–321.

Fernandez-Gonzalo R, De Paz JA, Rodriguez-Miguel P, Cuevas MJ, González-Gallego J. Effects of eccentric exercise on toll-like receptor 4 signaling pathway in peripheral blood mononuclear cells. *J Appl Physiol.* 2012;112:2011–2018.

Kong YW, Ferland-McCollough D, Jackson TJ, Bushell M. MicroRNAs in cancer management. *Lancet Oncol.* 2012;13:e249–e258.

Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell.* 2004;116:281–297.

Ntanasis-Stathopoulos J, Tzanninis JG, Philippou A, Koutsilieris M. Epigenetic regulation on gene expression induced by physical exercise. *Journal of Musculoskeletal and Neuronal Interactions.* 2013;13:133–146.

Handschin C, Spiegelman BM. The role of exercise and PGC1 α in inflammation and chronic disease. *Nature.* 2008;454:463–469.

Lancaster GI, Febbraio MA. The immunomodulating role of exercise in metabolic disease. *Trends Immunol.* 2014;35:262–269.

- Petersen AMW, Pedersen BK. The anti-inflammatory effect of exercise. *J Appl Physiol.* 2005;98:1154–1162.
- Jeukendrup AE, et al. Relationship between gastro-intestinal complaints and endotoxaemia, cytokine release and the acute-phase reaction during and after a long-distance triathlon in highly trained men. *Clin Sci.* 2000;98:47–55.
- Ostrowski K, Rohde T, Zacho M, Asp S, Pedersen BK. Evidence that interleukin-6 is produced in human skeletal muscle during prolonged running. *J Physiol.* 1998;508:949–953.
- de Gonzalo-Calvo D, et al. Circulating inflammatory miRNA signature in response to different doses of aerobic exercise. *J Appl Physiol.* 2015;119:124–134.
- O'Neill LA, Sheedy FJ, McCoy CE. MicroRNAs: the fine-tuners of Toll-like receptor signalling. *Nat Rev Immunol.* 2011;11:163–175.
- Baggish AL, et al. Dynamic regulation of circulating microRNA during acute exhaustive exercise and sustained aerobic exercise training. *J Physiol.* 2011;589:3983–3994.
- Baggish AL, et al. Rapid upregulation and clearance of distinct circulating microRNAs after prolonged aerobic exercise. *J Appl Physiol.* 2014;116:522–531.
- Mariathasan S, Monack DM. Inflammasome adaptors and sensors: intracellular regulators of infection and inflammation. *Nat Rev Immunol.* 2007;7:31–40.
- Yamamoto M, et al. ASC is essential for LPS-induced activation of procaspase-1 independently of TLR-associated signal adaptor molecules. *Genes Cells.* 2004;9:1055–1067.
- Nakajima K, et al. Exercise effects on methylation of ASC gene. *Int J Sports Med.* 2010;31:671–675.
- Itaya S, et al. No evidence of an association between the APOBEC3B deletion polymorphism and susceptibility to HIV infection and AIDS in Japanese and Indian populations. *J Infect Dis.* 2010;202:815–816. author reply 816–817.
- Dos Santos CMM, et al. Moderate physical exercise improves lymphocyte function in melanoma-bearing mice on a high-fat diet. *Nutr Metab (Lond).* 2019;16:63.
- Holick CN, et al. Physical activity and survival after diagnosis of invasive breast cancer. *Cancer Epidemiol Biomark Prev.* 2008;17:379–386.
- Holmes M, Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. *J Am Med Assoc.* 2005;293:2479–2486.
- Irwin ML, et al. Influence of pre- and postdiagnosis physical activity on mortality in breast cancer survivors: the health, eating, activity, and lifestyle study. *J Clin Oncol.* 2008;26:3958–3964.
- Goodwin PJ, et al. Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. *J Clin Oncol.* 2002;20:42–51.
- Ligibel JA, et al. Impact of a mixed strength and endurance exercise intervention on insulin levels in breast cancer survivors. *J Clin Oncol.* 2008;26:907–912.
- Fairey AS, et al. Effects of exercise training on fasting insulin, insulin resistance, insulin-like growth factors, and insulin-like growth factor binding proteins in postmenopausal breast cancer survivors: a randomized controlled trial. *Cancer Epidemiol Biomark Prev.* 2003;12:721–727.
- Zaidi SK, Van Wijnen AJ, Lian JB, Stein JL, Stein GS. Targeting deregulated epigenetic control in cancer. *J Cell Physiol.* 2013;228:2103–2108.
- Redd PS, et al. SETD1B activates iNOS expression in myeloid-derived suppressor cells. *Cancer Res.* 2017;77:2834–2843.
- Zeng H, et al. Physical activity and breast cancer survival: an epigenetic link through reduced methylation of a tumor suppressor gene L3MBTL1. *Breast Cancer Res Treat.* 2012;133:127–135.
- Bryan AD, Magnan RE, Hooper AEC, Harlaar N, Hutchison KE. Physical activity and differential methylation of breast cancer genes assayed from saliva: a preliminary investigation. *Ann Behav Med.* 2013;45:89–98.
- Caligiuri MA. Human natural killer cells. *Blood.* 2008;112:461–469.
- Cramp F, Daniel J. In: Cramp F, ed. *Cochrane Database of Systematic Reviews.* John Wiley & Sons, Ltd; 2008.

<https://doi.org/10.1002/14651858.CD006145.pub2>.

Schmitz KH, et al. Weight lifting in women with breast-cancer-related lymphedema. *N Engl J Med*. 2009;361:664–673.

Reinart N, et al. Delayed development of chronic lymphocytic leukemia in the absence of macrophage migration inhibitory factor. *Blood*. 2013;121:812–821.

Krockenberger M, et al. Macrophage migration-inhibitory factor levels in serum of patients with ovarian cancer correlates with poor prognosis. *Anticancer Res*. 2012;32:5233–5238.

Zimmer P, et al. Impact of exercise on pro inflammatory cytokine levels and epigenetic modulations of tumor-competitive lymphocytes in non-Hodgkin-lymphoma patients-randomized controlled trial. *Eur J Haematol*. 2014;93:527–532.

Zimmer P, et al. Exercise-induced natural killer cell activation is driven by epigenetic modifications. *Int J Sports Med*. 2015;36:510–515.

Fernández-Sánchez A, et al. DNA demethylation and histone H3K9 acetylation determine the active transcription of the NKG2D gene in human CD8+ T and NK cells. *Epigenetics*. 2013;8:66–78.

Schenk A, et al. Acute exercise increases the expression of KIR2DS4 by promoter demethylation in NK cells. *Int J Sports Med*. 2019;40:62–70.

Bezman NA, Chakraborty T, Bender T, Lanier LL. MiR-150 regulates the development of NK and iNKT cells. *J Exp Med*. 2011;208:2717–2731.

Cichocki F, et al. Cutting edge: microRNA-181 promotes human NK cell development by regulating Notch signaling. *J Immunol*. 2011;187:6171–6175.

96. Radom-Aizik S, Zaldivar F, Haddad F, Cooper DM. Impact of brief exercise on peripheral blood NK cell gene and microRNA expression in young adults. *J Appl Physiol*. 2013;114:628–636.

Chapter 9

Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimer's Dement*. 2013;9(1):63–75. Elsevier Inc. e2.

Mayeux R, Stern Y. Epidemiology of Alzheimer disease. *Cold Spring Harb Perspect Med*. 2012;2(8):a006239.

Graham WV, Bonito-Oliva A, Sakmar TP. Update on Alzheimer's disease therapy and prevention strategies. *Annu Rev Med*. 2017;68(1):413–430.

Lennon MJ, Makkar SR, Crawford JD, Sachdev PS. Midlife hypertension and Alzheimer's disease: a systematic review and meta-analysis. *J Alzheimers Dis*. 2019;71(1):307–316. IOS Press.

Sharma VK, Singh TG. Navigating Alzheimer's disease via chronic stress: the role of glucocorticoids. *Curr Drug Targets*. 2020;21(5):433–444.

Jash K, Gondaliya P, Kirave P, Kulkarni B, Sunkaria A, Kalia K. Cognitive dysfunction: a growing link between diabetes and Alzheimer's disease. *Drug Dev Res*. 2020;81(2):144–164.

Newcombe EA, Camats-Perna J, Silva ML, Valmas N, Huat TJ, Medeiros R. Inflammation: the link between comorbidities, genetics, and Alzheimer's disease. *J Neuroinflammation*. 2018;15(1):276. BioMed Central Ltd.

Giri M, Zhang M, Lü Y. Genes associated with Alzheimer's disease: an overview and current status. *Clin Interv Aging*. 2016;11:665–681. Dove Medical Press Ltd.

Nikolac Perkovic M, Pivac N. Genetic markers of Alzheimer's disease. *Adv Exp Med Biol*. 2019;1192:27–52. Springer New York LLC.

Strittmatter WJ, et al. Apolipoprotein E: high-avidity binding to β -amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proc Natl Acad Sci U S A*. 1993;90(5):1977–1981.

Moreno-Grau S, et al. Exploring APOE genotype effects on Alzheimer's disease risk and amyloid β burden in individuals with subjective cognitive decline: the FundacioACE Healthy Brain Initiative (FACEHBI) study baseline

results. *Alzheimers Dement*. 2018;14(5):634–643.

El Shamieh S, Coștănian C, Kassir R, Visvkiš-Sieřt S, Bissar-Tadmouri N. APOE genotypes in Lebanon: distribution and association with hypercholesterolemia and Alzheimer's disease. *Per Med*. 2019;16(1):15–23.

Farrer LA, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease: a meta-analysis. *J Am Med Assoc*. 1997;278(16):1349–1356.

Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein e and Alzheimer disease: risk, mechanisms and therapy. *Nat Rev Neurol*. 2013;9(2):106–118.

Hubacek JA, Pitha J, Skodová Z, Adámková V, Lánská V, Poledne R. A possible role of apolipoprotein E polymorphism in predisposition to higher education. *Neuropsychobiology*. 2001;43(3):200–203.

Evans S, et al. APOE E4 carriers show prospective memory enhancement under nicotine, and evidence for specialisation within medial BA10. *Neuropsychopharmacology*. 2013;38(4):655–663.

Feart C, et al. Associations of lower vitamin D concentrations with cognitive decline and long-term risk of dementia and Alzheimer's disease in older adults. *Alzheimers Dement*. 2017;13(11):1207–1216.

Harwood DG, et al. The effect of alcohol and tobacco consumption, and apolipoprotein E genotype, on the age of onset in Alzheimer's disease. *Int J Geriatr Psychiatry*. 2010;25(5):511–518.

Kulick ER, et al. Long-term exposure to ambient air pollution, APOE-ε4 status, and cognitive decline in a cohort of older adults in northern Manhattan. *Environ Int*. 2020;136:105440.

Jensen CS, et al. Patients with Alzheimer's disease who carry the APOE ε4 allele benefit more from physical exercise. *Alzheimers Dement (New York, NY)*. 2019;5:99–106.

Foraker J, et al. The APOE gene is differentially methylated in Alzheimer's disease. *J Alzheimers Dis*. 2015;48(3):745–755.

Deary IJ, et al. Age-associated cognitive decline. *Br Med Bull*. 2009;92(1):135–152.

Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol*. 2014;13(8):788–794.

Sun F, Norman IJ, While AE. Physical activity in older people: a systematic review. *BMC Public Health*. 2013;13(1):449.

Hamer M, Chida Y. Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. *Psychol Med*. 2009;39(1):3–11.

Erickson KI, et al. Aerobic fitness is associated with hippocampal volume in elderly humans. *Hippocampus*. 2009;19(10):1030–1039.

Park H, et al. Combined intervention of physical activity, aerobic exercise, and cognitive exercise intervention to prevent cognitive decline for patients with mild cognitive impairment: a randomized controlled clinical study. *J Clin Med*. 2019;8(7):940.

Snowden M, et al. Effect of exercise on cognitive performance in community-dwelling older adults: review of intervention trials and recommendations for public health practice and research. *J Am Geriatr Soc*. 2011;59(4):704–716.

Downey A, Stroud C, Landis S, Leshner A. Preventing Cognitive Decline and Dementia. Washington, DC: National Academies Press; 2017.

Cotman CW, Berchtold NC, Christie L-A. Exercise builds brain health: key roles of growth factor cascades and inflammation. *Trends Neurosci*. 2007;30(9):464–472.

Sleiman SF, Chao MV. Downstream consequences of exercise through the action of BDNF. *Brain Plast*. 2015;1(1):143–148.

Binder DK, Scharfman HE. Brain-derived neurotrophic factor. *Growth Factors*. 2004;22(3):123–131.

Mizuno M, Yamada K, Olariu A, Nawa H, Nabeshima T. Involvement of brain-derived neurotrophic factor in spatial memory formation and maintenance in a radial arm maze test in rats. *J Neurosci*. 2000;20(18):7116–7121.

Erickson KI, Miller DL, Roecklein KA. The aging hippocampus: interactions between exercise, depression, and

BDNF. *Neuroscientist*. 2012;18(1):82–97.

Peleg S, et al. Altered histone acetylation is associated with age-dependent memory impairment in mice. *Science (80-)*. 2010;328(5979):753–756.

Chouliaras L, et al. Consistent decrease in global DNA methylation and hydroxymethylation in the hippocampus of Alzheimer's disease patients. *Neurobiol Aging*. 2013;34(9):2091–2099.

Wen K, et al. The role of DNA methylation and histone modifications in neurodegenerative diseases: a systematic review. *PLoS One*. 2016;11(12):e0167201.

Soya H, et al. BDNF induction with mild exercise in the rat hippocampus. *Biochem Biophys Res Commun*. 2007;358(4):961–967.

Voss MW, Vivar C, Kramer AF, van Praag H. Bridging animal and human models of exercise-induced brain plasticity. *Trends Cogn Sci*. 2013;17(10):525–544.

Coelho FGdM, Gobbi S, Andreatto CAA, Corazza DI, Pedroso RV, Santos-Galduróz RF. Physical exercise modulates peripheral levels of brain-derived neurotrophic factor (BDNF): a systematic review of experimental studies in the elderly. *Arch Gerontol Geriatr*. 2013;56(1):10–15.

Vaynman S, Ying Z, Gomez-Pinilla F. Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. *Eur J Neurosci*. 2004;20(10):2580–2590.

Fernandes J, Arida RM, Gomez-Pinilla F. Physical exercise as an epigenetic modulator of brain plasticity and cognition. *Neurosci Biobehav Rev*. 2017;80:443–456.

Gomez-Pinilla F, Zhuang Y, Feng J, Ying Z, Fan G. Exercise impacts brain-derived neurotrophic factor plasticity by engaging mechanisms of epigenetic regulation. *Eur J Neurosci*. 2011;33(3):383–390.

Magill ST, et al. microRNA-132 regulates dendritic growth and arborization of newborn neurons in the adult hippocampus. *Proc Natl Acad Sci*. 2010;107(47):20382–20387.

Wang M, Qin L, Tang B. MicroRNAs in Alzheimer's disease. *Front Genet*. 2019;10:153.

Abel JL, Rissman EF. Running-induced epigenetic and gene expression changes in the adolescent brain. *Int J Dev Neurosci*. 2013;31(6):382–390.

McQuown SC, et al. HDAC3 is a critical negative regulator of long-term memory formation. *J Neurosci*. 2011;31(2):764–774.

Sleiman SF, et al. Exercise promotes the expression of brain derived neurotrophic factor (BDNF) through the action of the ketone body β -hydroxybutyrate. *Elife*. 2016;5, e15092.

Yao J, Chen S, Mao Z, Cadenas E, Brinton RD. 2-Deoxy-D-glucose treatment induces ketogenesis, sustains mitochondrial function, and reduces pathology in female mouse model of Alzheimer's disease. *PLoS One*. 2011;6(7):e21788.

Intlekofer KA, et al. Exercise and sodium butyrate transform a subthreshold learning event into longterm memory via a brain-derived neurotrophic factor-dependent mechanism. *Neuropsychopharmacology*. 2013;38(10):2027–2034.

Hansson AC, Sommer WH, Metsis M, Stromberg I, Agnati LF, Fuxe K. Corticosterone actions on the hippocampal brain-derived neurotrophic factor expression are mediated by exon IV promoter. *J Neuroendocrinol*. 2006;18(2):104–114.

Schaaf MJ, de Jong J, de Kloet ER, Vreugdenhil E. Downregulation of BDNF mRNA and protein in the rat hippocampus by corticosterone. *Brain Res*. 1998;813(1):112–120.

Tsankova NM, Berton O, Renthal W, Kumar A, Neve RL, Nestler EJ. Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. *Nat Neurosci*. 2006;9(4):519–525.

Makhathini KB, Abboussi O, Stein DJ, Mabandla MV, Daniels WMU. Repetitive stress leads to impaired cognitive function that is associated with DNA hypomethylation, reduced BDNF and a dysregulated HPA axis. *Int J Dev Neurosci*. 2017;60:63–69.

Laske C, et al. Exercise-induced normalization of decreased BDNF serum concentration in elderly women with remitted major depression. *Int J Neuropsychopharmacol*. 2010;13(05):595–602.

- Pan-Vazquez A, et al. Impact of voluntary exercise and housing conditions on hippocampal glucocorticoid receptor, miR-124 and anxiety. *Mol Brain*. 2015;8(1):40.
- Voisey J, et al. Differential BDNF methylation in combat exposed veterans and the association with exercise. *Gene*. 2019;698:107–112.
- Trejo JL, Carro E, Torres-Aleman I. Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. *J Neurosci*. 2001;21(5):1628–1634.
- Carro E, Nuñez A, Busiguina S, Torres-Aleman I. Circulating insulin-like growth factor I mediates effects of exercise on the brain. *J Neurosci*. 2000;20(8):2926–2933.
- Tang K, Xia FC, Wagner PD, Breen EC. Exercise-induced VEGF transcriptional activation in brain, lung and skeletal muscle. *Respir Physiol Neurobiol*. 2010;170(1):16–22.
- Fabel K, et al. VEGF is necessary for exercise-induced adult hippocampal neurogenesis. *Eur J Neurosci*. 2003;18(10):2803–2812.
- Iturria-Medina Y, Sotero RC, Toussaint PJ, Mateos-Pérez JM, Evans AC, Alzheimer's Disease Neuroimaging Initiative. Early role of vascular dysregulation on late-onset Alzheimer's disease based on multifactorial data-driven analysis. *Nat Commun*. 2016;7(1):11934.
- Ding Y-H, Li J, Zhou Y, Rafols JA, Clark JC, Ding Y. Cerebral angiogenesis and expression of angiogenic factors in aging rats after exercise. *Curr Neurovasc Res*. 2006;3(1):15–23.
- Delezie J, Handschin C. Endocrine crossstalk between skeletal muscle and the brain. *Front Neurol*. 2018;9:698.
- Morland C, et al. Exercise induces cerebral VEGF and angiogenesis via the lactate receptor HCAR1. *Nat Commun*. 2017;8(1):15557.
- Rich B, Scadeng M, Yamaguchi M, Wagner PD, Breen EC. Skeletal myofiber vascular endothelial growth factor is required for the exercise training-induced increase in dentate gyrus neuronal precursor cells. *J Physiol*. 2017;595(17):5931–5943.
- Kiuchi T, Lee H, Mikami T. Regular exercise cures depression-like behavior via VEGF-Flk-1 signaling in chronically stressed mice. *Neuroscience*. 2012;207:208–217.
- Sølvsten CAE, de Paoli F, Christensen JH, Nielsen AL. Voluntary physical exercise induces expression and epigenetic remodeling of VegfA in the rat hippocampus. *Mol Neurobiol*. 2018;55(1):567–582.
- Elsner VR, et al. Exercise induces age-dependent changes on epigenetic parameters in rat hippocampus: a preliminary study. *Exp Gerontol*. 2013;48(2):136–139.
- de Meireles LCF, Bertoldi K, Elsner VR, Moysés FdS, Siqueira IR. Treadmill exercise alters histone acetylation differently in rats exposed or not exposed to aversive learning context. *Neurobiol Learn Mem*. 2014;116:193–196.
- de Meireles LCF, et al. Treadmill exercise induces selective changes in hippocampal histone acetylation during the aging process in rats. *Neurosci Lett*. 2016;634:19–24.
- Cechinel LR, Basso CG, Bertoldi K, Schallenger B, de Meireles LCF, Siqueira IR. Treadmill exercise induces age and protocol-dependent epigenetic changes in prefrontal cortex of Wistar rats. *Behav Brain Res*. 2016;313:82–87.
- Smith PJ, et al. Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. *Psychosom Med*. 2010;72(3):239–252.
- Erickson KI, et al. Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A*. 2011;108(7):3017–3022.
- Sink KM, et al. Effect of a 24-month physical activity intervention vs health education on cognitive outcomes in sedentary older adults. *JAMA*. 2015;314(8):781.
- Maass A, et al. Relationships of peripheral IGF-1, VEGF and BDNF levels to exercise-related changes in memory, hippocampal perfusion and volumes in older adults. *NeuroImage*. 2016;131:142–154.
- Dinoff A, et al. The effect of exercise training on resting concentrations of peripheral brain-derived neurotrophic factor (BDNF): a meta-analysis. *PLoS One*. 2016;11(9):e0163037.

- Nielsen S, et al. The miRNA plasma signature in response to acute aerobic exercise and endurance training. *PLoS One*. 2014;9(2):e87308.
- Szuhany KL, Bugatti M, Otto MW. A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor. *J Psychiatr Res*. 2015;60:56–64.
- Vital TM, Stein AM, de Melo Coelho FG, Arantes FJ, Teodorov E, Santos-Galduróz RF. Physical exercise and vascular endothelial growth factor (VEGF) in elderly: a systematic review. *Arch Gerontol Geriatr*. 2014;59(2):234–239.
- Leckie RL, et al. BDNF mediates improvements in executive function following a 1-year exercise intervention. *Front Hum Neurosci*. 2014;8:985.
- Gomes WF, et al. Effect of exercise on the plasma BDNF levels in elderly women with knee osteoarthritis. *Rheumatol Int*. 2014;34(6):841–846.
- Jabbour G, Majed L. Ratings of perceived exertion misclassify intensities for sedentary older adults during graded cycling test: effect of supramaximal high-intensity interval training. *Front Physiol*. 2018;9:1505.
- Knaepen K, Goekint M, Heyman EM, Meeusen R. Neuroplasticity – exercise-induced response of peripheral brain-derived neurotrophic factor. *Sport Med*. 2010;40(9):765–801.
- Inoue K, et al. Long-term mild, rather than intense, exercise enhances adult hippocampal neurogenesis and greatly changes the transcriptomic profile of the hippocampus. *PLoS One*. 2015;10(6):e0128720.
- Cho S-Y, Roh H-T. Taekwondo enhances cognitive function as a result of increased neurotrophic growth factors in elderly women. *Int J Environ Res Public Health*. 2019;16(6):962.
- Acevedo EO, Kraemer RR, Kamimori GH, Durand RJ, Johnson LG, Castracane VD. Stress hormones, effort sense, and perceptions of stress during incremental exercise: an exploratory investigation. *J Strength Cond Res*. 2007;21(1):283–288.
- Baggish AL, et al. Dynamic regulation of circulating microRNA during acute exhaustive exercise and sustained aerobic exercise training. *J Physiol*. 2011;58916(58916):3983–3994.
- Ramos AE, et al. Specific circulating microRNAs display dose-dependent responses to variable intensity and duration of endurance exercise. *Am J Physiol Heart Circ Physiol*. 2018;315(2):H273–H283.
- Jekauc D. Enjoyment during exercise mediates the effects of an intervention on exercise adherence. *Psychology*. 2015;6(1):48–54.
- Egan MF, et al. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell*. 2003;112(2):257–269.
- Lim YY, et al. Effect of BDNF Val66Met on memory decline and hippocampal atrophy in prodromal Alzheimer's disease: a preliminary study. *PLoS One*. 2014;9(1):e86498.
- Lim YY, et al. BDNF Val66Met in preclinical Alzheimer's disease is associated with short-term changes in episodic memory and hippocampal volume but not serum mBDNF. *Int Psychogeriatrics*. 2017;29(11):1825–1834.
- Ieraci A, Madaio AI, Mallei A, Lee FS, Popoli M. Brain-derived neurotrophic factor Val66Met human polymorphism impairs the beneficial exercise-induced neurobiological changes in mice. *Neuropsychopharmacology*. 2016;41(13):3070–3079.
- Canivet A, et al. Effects of BDNF polymorphism and physical activity on episodic memory in the elderly: a cross sectional study. *Eur Rev Aging Phys Act*. 2015;12(1):15.
- Herring A, et al. Exercise during pregnancy mitigates Alzheimer-like pathology in mouse offspring. *FASEB J*. 2012;26(1):117–128.
- Gomes da Silva S, et al. Maternal exercise during pregnancy increases BDNF levels and cell numbers in the hippocampal formation but not in the cerebral cortex of adult rat offspring. *PLoS One*. 2016;11(1):e0147200.
- Rahimi R, Akhavan MM, Kamyab K, Ebrahimi SA. Maternal voluntary exercise ameliorates learning deficit in rat pups exposed, in utero, to valproic acid; role of BDNF and VEGF and their receptors. *Neuropeptides*. 2018;71:43–53.
- Yin MM, et al. Paternal treadmill exercise enhances spatial learning and memory related to hippocampus among

male offspring. *Behav Brain Res.* 2013;253:297–304.

Mega F, et al. Paternal physical exercise demethylates the hippocampal DNA of male pups without modifying the cognitive and physical development. *Behav Brain Res.* 2018;348:1–8.

Spindler C, et al. Paternal physical exercise modulates global DNA methylation status in the hippocampus of male rat offspring. *Neural Regen Res.* 2019;14(3):491.

Benito E, et al. RNA-dependent intergenerational inheritance of enhanced synaptic plasticity after environmental enrichment. *Cell Rep.* 2018;23(2):546–554.

Denham J, O'Brien BJ, Harvey JT, Charchar FJ. Genome-wide sperm DNA methylation changes after 3 months of exercise training in humans. *Epigenomics.* 2015;7(5):717–731.

Bakulski KM, et al. Genome-wide DNA methylation differences between late-onset Alzheimer's disease and cognitively normal controls in human frontal cortex. *J Alzheimers Dis.* 2012;29(3):571–588.

Chapter 10

1. Bouchard C, Malina RM, Perusse L. *Genetics of Fitness and Physical Performance.* Champaign, IL: Human Kinetics; 1997.

2. Lightfoot JT, Hubal M, Roth SM. *Routledge Handbook of Sport and Exercise Systems Genetics.* New York: Routledge; 2019.

3. Rico-Sanz J, Rankinen T, Rice T, et al. Quantitative trait loci for maximal exercise capacity phenotypes and their responses to training in the HERITAGE family study. *Physiol Genomics.* 2004;16(2):256–260.

4. de Garay AL, Levine L, Carter JEL. *Genetic and Anthropological Studies of Olympic Athletes.* New York: Academic Press; 1974.

5. Miyamoto-Mikami E, Zempo H, Fuku N, Kikuchi N, Miyachi M, Murakami H. Heritability estimates of endurance-related phenotypes: a systematic review and meta-analysis.

6. Zempo H, Miyamoto-Mikami E, Kikuchi N, Fuku N, Miyachi M, Murakami H. Heritability estimates of muscle strength-related phenotypes: a systematic review and meta-analysis. *Scand J Med Sci Sports.* 2017;27(12):1537–1546.

7. Rankinen T, Perusse L, Rauramaa R, Rivera MA, Wolfarth B, Bouchard C. The human gene map for performance and health-related fitness phenotypes. *Med Sci Sports Exerc.* 2001;33(6):855–867

8. Sarzynski MA, Loos RJ, Lucia A, et al. Advances in exercise, fitness, and performance genomics in 2015. *Med Sci Sports Exerc.* 2016;48(10):1906–1916.

9. McPherron AC, Lee SJ. Double muscling in cattle due to mutations in the myostatin gene. *Proc Natl Acad Sci U S A.* 1997;94(23):12457–12461.

10. Grobet L, Martin LJ, Poncelet D, et al. A deletion in the bovine myostatin gene causes the double-muscling phenotype in cattle. *Nat Genet.* 1997;17(1):71–74.

11. Ferrell RE, Conte V, Lawrence EC, Roth SM, Hagberg JM, Hurley BF. Frequent sequence variation in the human myostatin (GDF8) gene as a marker for analysis of muscle-related phenotypes. *Genomics.* 1999;62:203–207.

12. Ivey FM, Roth SM, Ferrell RE, et al. Effects of age, gender, and myostatin genotype on the hypertrophic response to heavy resistance strength training. *J Gerontol A Biol Sci Med Sci.* 2000;55(11):M641–M648.

13. Thomis MA, Huygens W, Heuninckx S, et al. Exploration of myostatin polymorphisms and the angiotensin-converting enzyme insertion/deletion genotype in responses of human muscle to strength training. *Eur J Appl Physiol.* 2004;92:267–274.

14. Venezia AC, Roth SM. Recent research in the genetics of exercise training adaptation. *Med Sport*

Sci. 2016;61:29–40. 15. Sarzynski MA, Ghosh S, Bouchard C. Genomic and transcriptomic predictors of response levels to endurance exercise training. *J Physiol.* 2017;595(9):2931–2939. 16. Moir HJ, Kemp R, Folkerts D, Spendiff

- O, Pavlidis C, Opara E. Genes and elite Marathon running performance: a systematic review. *J Sports Sci Med*. 2019;18(3):559–568.
17. Ahmetov II, Egorova ES, Gabdrakhmanova LJ, Fedotovskaya ON. Genes and athletic performance: an update. *Med Sport Sci*. 2016;61:41–54.
18. Guo MH, Hirschhorn JN, Dauber A. Insights and implications of genome-wide association studies of height. *J Clin Endocrinol Metab*. 2018;103(9):3155–3168.
19. Lightfoot JT, Hubal M, Roth SM. Afterword—closing the loop: observations and conclusions. In: Lightfoot JT, Hubal M, Roth SM, eds. *Routledge Handbook of Sport and Exercise Systems Genetics*. New York: Routledge; 2019:494–502.
20. Tierney RT, McDevitt JK. Sport concussion genetics. In: Lightfoot JT, Hubal M, Roth SM, eds. *Routledge Handbook of Sport and Exercise Systems Genetics*. New York: Routledge; 2019:388–401.
21. Vaughn NH, Stepanyan H, Gallo RA, Dhawan A. Genetic factors in tendon injury: a systematic review of the literature. *Orthop J Sports Med*. 2017;5(8):1–11.
22. Rahim M, September AV, Collins M. Systems genetic factors underlying soft tissue injury. In: Lightfoot JT, Hubal M, Roth SM, eds. *Routledge Handbook of Sport and Exercise Systems Genetics*. New York: Routledge; 2019:402–415.
23. Montgomery HE, Marshall R, Hemingway H, et al. Human gene for physical performance. *Nature*. 1998;393:221–222.
24. Gayagay G, Yu B, Hambly B, et al. Elite endurance athletes and the ACE I allele—the role of genes in athletic performance. *Hum Genet*. 1998;103:48–50.
25. Hagberg JM, Ferrell RE, McCole SD, Wilund KR, Moore GE. VO₂max is associated with ACE genotype in postmenopausal women. *J Appl Physiol*. 1998;85(5):1842–1846.
26. Williams AG, Rayson MP, Jubb M, et al. The ACE gene and muscle performance. *Nature*. 2000;403:614.
27. Myerson S, Hemingway H, Budget R, Martin J, Humphries S, Montgomery H. Human angiotensin I-converting enzyme gene and endurance performance. *J Appl Physiol*. 1999;87:1313–1316.
28. Danser AH, Schalekamp MA, Bax WA, et al. Angiotensin-converting enzyme in the human heart. Effect of the deletion/insertion polymorphism. *Circulation*. 1995;92(6):1387–1388.
29. Rigat B, Hubert C, Alhenc-Gelas F, Cambien F, Corvol P, Soubrier F. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. *J Clin Invest*. 1990;86(4):1343–1346.
30. Rankinen T, Wolfarth B, Simoneau JA, et al. No association between the angiotensin-converting enzyme ID polymorphism and elite endurance athlete status. *J Appl Physiol*. 2000;88:1571–1575.
31. Rankinen T, Perusse L, Gagnon J, et al. Angiotensin-converting enzyme ID polymorphism and fitness phenotype in the HERITAGE family study. *J Appl Physiol*. 2000;88:1029–1035.
32. Bouchard C, Rankinen T, Chagnon YC, et al. Genomic scan for maximal oxygen uptake and its response to training in the HERITAGE family study. *J Appl Physiol*. 2000;88:551–559.
33. Pescatello L, Corso LML, Santos LP, Livingston J, Taylor BA. Angiotensin-converting enzyme and the genomics of endurance performance. In: Lightfoot JT, Hubal M, Roth SM, eds. *Routledge Handbook of Sport and Exercise Systems Genetics*. New York: Routledge; 2019:216–249.
34. Valdivieso P, Vaughan D, Laczko E, et al. The metabolic response of skeletal muscle to endurance exercise is modified by the ACE-I/D gene polymorphism and training state. *Front Physiol*. 2017;8:993.
35. Vaughan D, Brogioli M, Maier T, et al. The angiotensin converting enzyme insertion/deletion polymorphism modifies exercise-induced muscle metabolism. *PLoS One*. 2016;11(3), e0149046.
36. Vaughan D, Huber-Abel FA, Graber F, Hoppeler H, Fluck M. The angiotensin converting enzyme insertion/deletion polymorphism alters the response of muscle energy supply lines to exercise. *Eur J Appl Physiol*. 2013;113(7):1719–1729.

37. van Ginkel S, Ruoss S, Valdivieso P, et al. ACE inhibition modifies exercise-induced pro-angiogenic and mitochondrial gene transcript expression. *Scand J Med Sci Sports*. 2016;26(10):1180–1187.
38. Webborn N, Williams A, McNamee M, et al. Direct-to-consumer genetic testing for predicting sports performance and talent identification: consensus statement. *Br J Sports Med*. 2015;49(23):1486–1491.
39. Vlahovich N, Fricker PA, Brown MA, Hughes D. Ethics of genetic testing and research in sport: a position statement from the Australian Institute of Sport. *Br J Sports Med*. 2017;51(1):5–11.
40. Williams AG, Wackerhage H, Day SH. Genetic testing for sports performance, responses to training and injury risk: practical and ethical considerations. *Med Sport Sci*. 2016;61:105–119.
41. North KN, Yang N, Wattanasirichaigoon D, Mills M, Eastal S, Beggs AH. A common nonsense mutation results in alpha-actinin-3 deficiency in the general population. *Nat Genet*. 1999;21(4):353–354.
42. Mac Arthur DG, Seto JT, Raftery JM, et al. Loss of ACTN3 gene function alters mouse muscle metabolism and shows evidence of positive selection in humans. *Nat Genet*. 2007;39(10):1261–1265.
43. North KN, Beggs AH. Deficiency of a skeletal muscle isoform of alpha-actinin (alpha-actinin-3) in merosin-positive congenital muscular dystrophy. *Neuromuscul Disord*. 1996;6(4):229–235.
44. Yang N, Mac Arthur DG, Gulbin JP, et al. ACTN3 genotype is associated with human elite athletic performance. *Am J Hum Genet*. 2003;73:627–631.
45. Mikami E, Fuku N, Murakami H, et al. ACTN3 R577X genotype is associated with sprinting in elite Japanese athletes. *Int J Sports Med*. 2014;35(2):172–177.
46. Niemi AK, Majamaa K. Mitochondrial DNA and ACTN3 genotypes in Finnish elite endurance and sprint athletes. *Eur J Hum Genet*. 2005;13(8):965–969.
47. Druzhevskaya AM, Ahmetov II, Astratekova IV, Rogozkin VA. Association of the ACTN3 R577X polymorphism with power athlete status in Russians. *Eur J Appl Physiol*. 2008;103(6):631–634.
48. Yang R, Shen X, Wang Y, et al. ACTN3 R577X gene variant is associated with muscle-related phenotypes in elite Chinese Sprint/power athletes. *J Strength Cond Res*. 2017;31(4):1107–1115.
49. Yang N, Mac Arthur DG, Wolde B, et al. The ACTN3 R577X polymorphism in east and west African athletes. *Med Sci Sports Exerc*. 2007;39:1985–1988.
50. Scott RA, Irving R, Irwin L, et al. ACTN3 and ACE genotypes in elite Jamaican and US sprinters. *Med Sci Sports Exerc*. 2010;42(1):107–112.
51. Hanson ED, Ludlow AT, Sheaff AK, Park J, Roth SM. ACTN3 genotype does not influence muscle power. *Int J Sports Med*. 2010;31(11):834–838.
52. Magi A, Unt E, Prans E, et al. The association analysis between ACE and ACTN3 genes polymorphisms and endurance capacity in young cross-country skiers: longitudinal study. *J Sports Sci Med*. 2016;15(2):287–294.
53. Silva MS, Bolani W, Alves CR, et al. Elimination of influences of the ACTN3 R577X variant on oxygen uptake by endurance training in healthy individuals. *Int J Sports Physiol Perform*. 2015;10(5):636–641.
54. Papadimitriou ID, Lockey SJ, Voisin S, et al. No association between ACTN3 R577X and ACE I/D polymorphisms and endurance running times in 698 Caucasian athletes. *BMC Genomics*. 2018;19(1):13.
55. Clarkson PM, Devaney JM, Gordish-Dressman H, et al. ACTN3 genotype is associated with increases in muscle strength in response to resistance training in women. *J Appl Physiol*. 2005;99:154–163.
56. Delmonico MJ, Kostek MC, Doldo NA, et al. Alpha-actinin-3 (ACTN3) R577X polymorphism influences knee extensor peak power response to strength training in older men and women. *J Gerontol A Biol Sci Med Sci*. 2007;62(2):206–212.
57. Lima RM, Leite TK, Pereira RW, Rabelo HT, Roth SM, Oliveira RJ. ACE and ACTN3 genotypes in older women: muscular phenotypes. *Int J Sports Med*. 2011;32(1):66–72.
58. Mac Arthur DG, Seto JT, Chan S, et al. An Actn 3 knockout mouse provides mechanistic insights into the association between alpha-actinin-3 deficiency and human athletic performance. *Hum Mol Genet*. 2008;17(8):1076–1086.
59. Lee FX, Houweling PJ, North KN, Quinlan KG. How does alpha-actinin-3 deficiency alter muscle function?

Mechanistic insights into ACTN3, the 'gene for speed'. *Biochim Biophys Acta*. 2016;1863(4):686–693.

60. Mac Arthur DG, North KN. A gene for speed? The evolution and function of alpha-actinin-3. *Bioessays*. 2004;26(7):786–795.

61. Del Coso J, Hiam D, Houweling P, Perez LM, Eynon N, Lucia A. More than a 'speed gene': ACTN3 R577X genotype, trainability, muscle damage, and the risk for injuries. *Eur J Appl Physiol*. 2019;119(1):49–60.

62. Ruiz JR, Fernandez del Valle M, Verde Z, et al. ACTN3 R577X polymorphism does not influence explosive leg muscle power in elite volleyball players. *Scand J Med Sci Sports*. 2011;21(6):e34–e41.

63. Wang G, Mikami E, Chiu LL, et al. Association analysis of ACE and ACTN3 in elite Caucasian and east Asian swimmers. *Med Sci Sports Exerc*. 2013;45(5):892–900.

64. Norman B, Esbjornsson M, Rundqvist H, Osterlund T, von Walden F, Tesch PA. Strength, power, fiber types, and mRNA expression in trained men and women with different ACTN3 R577X genotypes. *J Appl Physiol*. 2009;106(3):959–965.

65. Erskine RM, Williams AG, Jones DA, Stewart CE, Degens H. The individual and combined influence of ACE and ACTN3 genotypes on muscle phenotypes before and after strength training. *Scand J Med Sci Sports*. 2014;24(4):642–648.

66. Kim H, Song KH, Kim CH. The ACTN3 R577X variant in sprint and strength performance. *J Exerc Nutr Biochem*. 2014;18(4):347–353.

67. Ben-Zaken S, Eliakim A, Nemet D, Meckel Y. Genetic variability among power athletes: the stronger vs. the faster. *J Strength Cond Res*. 2019;33(6):1505–1511.

68. Papadimitriou ID, Eynon N, Yan X, et al. A "human knockout" model to investigate the influence of the alpha-actinin-3 protein on exercise-induced mitochondrial adaptations. *Sci Rep*. 2019;9(1):12688.

69. Papadimitriou ID, Lucia A, Pitsiladis YP, et al. ACTN3 R577X and ACE I/D gene variants influence performance in elite sprinters: a multi-cohort study. *BMC Genomics*. 2016;17:285.

70. Lucia A, Oliván J, Gomez-Gallego F, Santiago C, Montil M, Foster C. Citius and longius (faster and longer) with no alpha-actinin-3 in skeletal muscles? *Br J Sports Med*. 2007;41:616–617.

71. Encode Project Consortium. An integrated encyclopedia of DNA elements in the human genome. *Nature*. 2012;489(7414):57–74.

72. Bouchard C, Sarzynski MA, Rice TK, et al. Genomic predictors of the maximal O uptake response to standardized exercise training programs. *J Appl Physiol*. 2011;110(5):1160–1170.

73. Rankinen T, Sung YJ, Sarzynski MA, Rice TK, Rao DC, Bouchard C. Heritability of submaximal exercise heart rate response to exercise training is accounted for by nine SNPs. *J Appl Physiol* (1985). 2012;112(5):892–897.

74. Zillikens MC, Demissie S, Hsu YH, et al. Large meta-analysis of genome-wide association studies identifies five loci for lean body mass. *Nat Commun*. 2017;8(1):80.

75. Willems SM, Wright DJ, Day FR, et al. Large-scale GWAS identifies multiple loci for hand grip strength providing biological insights into muscular fitness. *Nat Commun*. 2017;8:16015.

76. Ahmetov I, Kulemin N, Popov D, et al. Genome-wide association study identifies three novel genetic markers associated with elite endurance performance. *Biol Sport*. 2015;32(1):3–9.

77. Pickering C, Suraci B, Semenova EA, et al. A genome-wide association study of Sprint performance in elite youth football players. *J Strength Cond Res*. 2019;33(9):2344–2351.

78. Rankinen T, Fuku N, Wolfarth B, et al. No evidence of a common DNA variant profile specific to World class endurance athletes. *PLoS One*. 2016;11(1), e0147330.

79. Midha MK, Wu M, Chiu KP. Long-read sequencing in deciphering human genetics to a greater depth. *Hum Genet*. 2019;138:1201–1215.

80. Tachmazidou I, Suveges D, Min JL, et al. Whole-genome sequencing coupled to imputation discovers genetic signals for anthropometric traits. *Am J Hum Genet*. 2017;100(6):865–884.

81. Pescatello LS, Schifano ED, Ash GI, et al. Deep-targeted sequencing of endothelial nitric oxide synthase gene exons uncovers exercise intensity and ethnicity-dependent associations with post-exercise hypotension. *Physiol Rep*. 2017;5(22).
82. Deane CS, Ames RM, Phillips BE, et al. The acute transcriptional response to resistance exercise: impact of age and contraction mode. *Aging (Albany NY)*. 2019;11(7):2111–2126.
83. Wolfarth B, Rankinen T, Muhlbauer S, et al. Endothelial nitric oxide synthase gene polymorphism and elite endurance athlete status: the Genathlete study. *Scand J Med Sci Sports*. 2008;18(4):485–490.
84. Moran CN, Williams AG, Wang G. Using elite athletes as a model for genetic research. In: Lightfoot JT, Hubal M, Roth SM, eds. *Routledge Handbook of Sport and Exercise Systems Genetics*. New York: Routledge; 2019:357–371.
85. Bouchard C, Leon AS, Rao DC, Skinner JS, Wilmore JH, Gagnon J. The HERITAGE family study. Aims, design, and measurement protocol. *Med Sci Sports Exerc*. 1995;27(5):721–729.
86. Bouchard C, An P, Rice T, et al. Familial aggregation of VO₂max response to exercise training: results from the HERITAGE family study. *J Appl Physiol*. 1999;87(3):1003–1008.
87. Bouchard C, Daw EW, Rice T, et al. Familial resemblance for VO₂max in the sedentary state: the HERITAGE family study. *Med Sci Sports Exerc*. 1998;30(2):252–258.
88. Feitosa MF, Rice T, Rankinen T, et al. Evidence of QTLs on chromosomes 13q and 14q for triglycerides before and after 20 weeks of exercise training: the HERITAGE family study. *Atherosclerosis*. 2005;182(2):349–360.
89. Chagnon YC, Rice T, Perusse L, et al. Genomic scan for genes affecting body composition before and after training in Caucasians from HERITAGE. *J Appl Physiol (1985)*. 2001;90(5):1777–1787.
90. Rankinen T, Rice T, Leon AS, et al. G protein beta 3 polymorphism and hemodynamic and body composition phenotypes in the HERITAGE family study. *Physiol Genomics*. 2002;8(2):151–157.
91. Ghosh S, Vivar JC, Sarzynski MA, et al. Integrative pathway analysis of a genome-wide association study of (V) O₂max response to exercise training. *J Appl Physiol (1985)*. 2013;115(9):1343–1359.
92. Ghosh S, Hota M, Chai X, et al. Exploring the underlying biology of intrinsic cardiorespiratory fitness through integrative analysis of genomic variants and muscle gene expression profiling. *J Appl Physiol (1985)*. 2019;126(5):1292–1314.
93. Thompson PD, Moyna NM, Seip RL, et al. Functional polymorphisms associated with human muscle size and strength. *Med Sci Sports Exerc*. 2004;36:1132–1139.
94. Hubal MJ, Gordish-Dressman H, Thompson PD, et al. Variability in muscle size and strength gain after unilateral resistance training. *Med Sci Sports Exerc*. 2005;37(6):964–972.
95. Pescatello LS, Kostek MA, Gordish-Dressman H, et al. ACE ID genotype and the muscle strength and size response to unilateral resistance training. *Med Sci Sports Exerc*. 2006;38(6):1074–1081.
96. Pescatello LS, Devaney JM, Hubal MJ, Thompson PD, Hoffman EP. Highlights from the functional single nucleotide polymorphisms associated with human muscle size and strength or FAMuSS study. *Bio Med Res Int*. 2013;2013:643575.
97. Pitsiladis YP, Tanaka M, Eynon N, et al. Athlome project consortium: a concerted effort to discover genomic and other “omic” markers of athletic performance. *Physiol Genomics*. 2016;48(3):183–190.
98. Tanaka M, Wang G, Pitsiladis YP. Advancing sports and exercise genomics: moving from hypothesis-driven single study approaches to large multi-omics collaborative science. *Physiol Genomics*. 2016;48(3):173–174.
99. Marouli E, Graff M, Medina-Gomez C, et al. Rare and low-frequency coding variants alter human adult height. *Nature*. 2017;542(7640):186–190.
100. Juvonen E, Ikkala E, Fyhrquist F, Ruutu T. Autosomal dominant erythrocytosis caused by increased sensitivity to erythropoietin. *Blood*. 1991;78(11):3066–3069.
101. de la Chapelle A, Traskelin AL, Juvonen E. Truncated erythropoietin receptor causes dominantly inherited

benign human erythrocytosis. *Proc Natl Acad Sci U S A*. 1993;90(10):4495–4499.

102. Lundby C, Montero D, Joyner M. Biology of VO₂ max: looking under the physiology lamp. *Acta Physiol (Oxf)*. 2017;220(2):218–228.

103. Miyamoto-Mikami E, Murakami H, Tsuchie H, et al. Lack of association between genotype score and sprint/power performance in the Japanese population. *J Sci Med Sport*. 2017;20(1):98–103.

104. Eynon N, Ruiz JR, Meckel Y, Moran M, Lucia A. Mitochondrial biogenesis related endurance genotype score and sports performance in athletes. *Mitochondrion*. 2011;11(1):64–69.

105. Bouchard C. Exercise genomics, epigenomics, and transcriptomics: a reality check! In: Lightfoot JT, Hubal M, Roth SM, eds. *Routledge Handbook of Sport and Exercise Systems Genetics*. New York: Routledge; 2019:487–493.

106. Scheiman J, Lubner JM, Chavkin TA, et al. Meta-omics analysis of elite athletes identifies a performance-enhancing microbe that functions via lactate metabolism. *Nat Med*. 2019;25(7):1104–1109.

107. Timmons JA, Knudsen S, Rankinen T, et al. Using molecular classification to predict gains in maximal aerobic capacity following endurance exercise training in humans. *J Appl Physiol*. 2010;108(6):1487–1496.

108. Yan X, Eynon N, Papadimitriou ID, et al. The gene SMART study: method, study design, and preliminary findings. *BMC Genomics*. 2017;18(Suppl 8):821.

109. Molecular Transducers of Physical Activity in Humans Consortium. <https://commonfund.nih.gov/molecular-transducers>. Accessed 22 October 2019.

110. Bouchard C. DNA sequence variations contribute to variability in fitness and trainability. *Med Sci Sports Exerc*. 2019;51(8):1781–1785.

111. Joyner MJ. Limits to the evidence that DNA sequence differences contribute to variability in fitness and trainability. *Med Sci Sports Exerc*. 2019;51(8):1786–1789.

Chapter 11

Blyth FM, Briggs AM, Schneider CH, Hoy DG, March LM. The global burden of musculoskeletal pain where to from here? *Am J Public Health*. 2019;109(1):35–40.

Hopkins C, Fu SC, Chua E, et al. Critical review on the socio-economic impact of tendinopathy. *Asia Pac J Sports Med Arthrosc Rehabil Technol*. 2016;4:9–20.

Mather 3rd RC, Koenig L, Kocher MS, et al. Societal and economic impact of anterior cruciate ligament tears. *J Bone Joint Surg Am*. 2013;95(19):1751–1759.

Rahim M, Gibbon A, Collins M, September AV. Chapter fifteen—Genetics of musculoskeletal soft tissue injuries: current status, challenges, and future directions. In: Barh D, Ahmetov II, eds. *Sports, Exercise, and Nutritional Genomics*. Academic Press; 2019:317–339.

Rahim M, September AV, Collins M. Systems genetic factors underlying soft tissue injury. In: *Routledge Handbook of Sport and Exercise Systems Genetics*. Routledge; 2019:402–415.

El Khoury L, Posthumus M, Collins M, Handley CJ, Cook J, Raleigh SM. Polymorphic variation within the ADAMTS2, ADAMTS14, ADAMTS5, ADAM12 and TIMP2 genes and the risk of Achilles tendon pathology: a genetic association study. *J Sci Med Sport*. 2013;16(6):493–498.

El Khoury L, Ribbans WJ, Raleigh SM. MMP3 and TIMP2 gene variants as predisposing factors for Achilles tendon pathologies: attempted replication study in a British case-control cohort. *Meta Gene*. 2016;9:52–55.

Lulinska-Kuklik E, Rahim M, Moska W, et al. Are MMP3, MMP8 and TIMP2 gene variants associated with anterior cruciate ligament rupture susceptibility? *J Sci Med Sport*. 2019;22(7):753–757.

Shen J, Wang C, Li D, et al. DNA methyltransferase 3b regulates articular cartilage homeostasis by altering metabolism. *JCI Insight*. 2017;2(12).

Magnusson K, Turkiewicz A, Englund M. High genetic contribution to anterior cruciate ligament injury in 88 000 Swedish twins. *Osteoarthr Cartil*. 2019;27:S258–S259.

Collins M, Raleigh SM. Genetic risk factors for musculoskeletal soft tissue injuries. *Med Sport Sci.* 2009;54:136–149.

El Khoury LY, Rickaby R, Samiric T, Raleigh SM. Promoter methylation status of the TIMP2 and ADAMTS4 genes and patellar tendinopathy. *J Sci Med Sport.* 2018;21(4):378–382.

Leal MF, Caires Dos Santos L, Martins de Oliveira A, et al. Epigenetic regulation of metalloproteinases and their inhibitors in rotator cuff tears. *PLoS ONE.* 2017;12(9), e0184141.

Rickaby R, El Khoury LY, Samiric T, Raleigh SM. Epigenetic status of the human MMP11 gene promoter is altered in patellar tendinopathy. *J Sports Sci Med.* 2019;18(1):155–159.

Abrahams Y, Laguette MJ, Prince S, et al. Polymorphisms within the COL5A1 3'UTR that alters mRNA structure and the MIR608 gene are associated with Achilles tendinopathy. *Ann Hum Genet.* 2013;77(3):204–214.

Pasternak B, Aspenberg P. Metalloproteinases and their inhibitors—diagnostic and therapeutic opportunities in orthopedics. *Acta Orthop.* 2009;80(6):693–703.

Cui N, Hu M, Khalil RA. Biochemical and biological attributes of matrix metalloproteinases. *Prog Mol Biol Transl Sci.* 2017;147:1–73.

Parkinson J, Samiric T, Ilic MZ, Cook J, Feller JA, Handley CJ. Change in proteoglycan metabolism is a characteristic of human patellar tendinopathy. *Arthritis Rheum.* 2010;62(10):3028–3035.

Attia M, Scott A, Carpentier G, et al. Greater glycosaminoglycan content in human patellar tendon biopsies is associated with more pain and a lower VISA score. *Br J Sports Med.* 2014;48(6):469–475.

Suijkerbuijk MAM, Reijman M, Oei EHG, van Meer BL, van Arkel ERA, Meuffels DE. Predictive factors of hamstring tendon regeneration and functional recovery after harvesting: a prospective follow-up study. *Am J Sports Med.* 2018;46(5):1166–1174.

Gibbon A, Hobbs H, van der Merwe W, et al. The MMP3 gene in musculoskeletal soft tissue injury risk profiling: a study in two independent sample groups. *J Sports Sci.* 2017;35(7):655–662.

Posthumus M, Collins M, van der Merwe L, et al. Matrix metalloproteinase genes on chromosome 11q22 and the risk of anterior cruciate ligament (ACL) rupture. *Scand J Med Sci Sports.* 2012;22(4):523–533.

September AV, Cook J, Handley CJ, van der Merwe L, Schwellnus MP, Collins M. Variants within the COL5A1 gene are associated with Achilles tendinopathy in two populations. *Br J Sports Med.* 2009;43(5):357–365.

Laguette MJ, Abrahams Y, Prince S, Collins M. Sequence variants within the 3'-UTR of the COL5A1 gene alters mRNA stability: implications for musculoskeletal soft tissue injuries. *Matrix Biol.* 2011;30(5–6):338–345.

Sun M, Chen S, Adams SM, et al. Collagen V is a dominant regulator of collagen fibrillogenesis: dysfunctional regulation of structure and function in a corneal-stroma-specific Col5a1-null mouse model. *J Cell Sci.* 2011;124(Pt 23):4096–4105.

Wenstrup RJ, Florer JB, Brunskill EW, Bell SM, Chervoneva I, Birk DE. Type V collagen controls the initiation of collagen fibril assembly. *J Biol Chem.* 2004;279(51):53331–53337.

Mayr C. What are 3' UTRs doing? *Cold Spring Harb Perspect Biol.* 2019;11(10).

Rahim M, Collins M, September A. Genes and musculoskeletal soft-tissue injuries. *Med Sport Sci.* 2016;61:68–91.

Collins M, Posthumus M. Type V collagen genotype and exercise-related phenotype relationships: a novel hypothesis. *Exerc Sport Sci Rev.* 2011;39(4):191–198.

Kim SK, Roos TR, Roos AK, et al. Genome-wide association screens for Achilles tendon and ACL tears and tendinopathy. *PLoS ONE.* 2017;12(3), e0170422.

Slusarz A, Pulakat L. The two faces of miR-29. *J Cardiovasc Med (Hagerstown).* 2015;16(7):480–490.

Willard K, Laguette MN, Alves de Souza Rios L, et al. Altered expression of proteoglycan, collagen and growth factor genes in a TGF-beta1 stimulated genetic risk model for musculoskeletal soft tissue injuries. *J Sci Med Sport.* 2020;23(8):695–700.

Willard K, Mannion S, Saunders CJ, Collins M, September AV. The interaction of polymorphisms in extracellular

matrix genes and underlying miRNA motifs that modulate susceptibility to anterior cruciate ligament rupture. *J Sci Med Sport*. 2018;21(1):22–28.

Iozzo RV. The family of the small leucine-rich proteoglycans: key regulators of matrix assembly and cellular growth. *Crit Rev Biochem Mol Biol*. 1997;32(2):141–174.

Holmes DI, Zachary I. The vascular endothelial growth factor (VEGF) family: angiogenic factors in health and disease. *Genome Biol*. 2005;6(2):209.

Thankam FG, Boosani CS, Dilisio MF, Agrawal DK. MicroRNAs associated with inflammation in shoulder tendinopathy and glenohumeral arthritis. *Mol Cell Biochem*. 2018;437(1–2):81–97.

Thankam FG, Boosani CS, Dilisio MF, Dietz NE, Agrawal DK. MicroRNAs associated with shoulder tendon matrix disorganization in glenohumeral arthritis. *PLoS ONE*. 2016;11(12), e0168077.

Zhang S, Chen N. Regulatory role of microRNAs in muscle atrophy during exercise intervention. *Int J Mol Sci*. 2018;19(2).

Chen JF, Callis TE, Wang DZ. microRNAs and muscle disorders. *J Cell Sci*. 2009;122(Pt 1):13–20.

Carrio E, Suelves M. DNA methylation dynamics in muscle development and disease. *Front Aging Neurosci*. 2015;7:19.

van Wijnen AJ, Westendorf JJ. Epigenetics as a new frontier in orthopedic regenerative medicine and oncology. *J Orthop Res*. 2019;37(7):1465–1474.

Sadoghi P, von Keudell A, Vavken P. Effectiveness of anterior cruciate ligament injury prevention training programs. *J Bone Joint Surg Am*. 2012;94(9):769–776.

Voskarian N. ACL injury prevention in female athletes: review of the literature and practical considerations in implementing an ACL prevention program. *Curr Rev Musculoskelet Med*. 2013;6(2):158–163.

Suijkerbuijk MAM, Ponzetti M, Rahim M, et al. Functional polymorphisms within the inflammatory pathway regulate expression of extracellular matrix components in a genetic risk dependent model for anterior cruciate ligament injuries. *J Sci Med Sport*. 2019;22(11).

Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med*. 2015;372(9):793–795.

Janssens ACJW, van Duijn CM. Genome-based prediction of common diseases: advances and prospects. *Hum Mol Genet*. 2008;17(R2):R166–R173.

Wray NR, Goddard ME, Visscher PM. Prediction of individual genetic risk of complex disease. *Curr Opin Genet Dev*. 2008;18(3):257–263.

Small AM, O'Donnell CJ, Damrauer SM. Large-scale genomic biobanks and cardiovascular disease. *Curr Cardiol Rep*. 2018;20(4):22.

Erlich Y, Shor T, Pe'er I, Carmi S. Identity inference of genomic data using long-range familial searches. *Science* (New York, NY). 2018;362(6415):690–694.

Green RC, Berg JS, Grody WW, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med*. 2013;15(7):565–574.

Webborn N, Williams A, McNamee M, et al. Direct-to-consumer genetic testing for predicting sports performance and talent identification: consensus statement. *Br J Sports Med*. 2015;49(23):1486–1491.

Phillips AM. Only a click away—DTC genetics for ancestry, health, love...and more: a view of the business and regulatory landscape. *Appl Transl Genom*. 2016;8:16–22.

Kutz G. Direct-to-Consumer Genetic Tests. Misleading Test Results Are Further Complicated by Deceptive Marketing and Other Questionable Practices. United States Government Accountability Office; 2010:3.

Thakore PI, Black JB, Hilton IB, Gersbach CA. Editing the epigenome: technologies for programmable transcription and epigenetic modulation. *Nat Methods*. 2016;13(2):127–137.

Liu J-J, Orlova N, Oakes BL, et al. CasX enzymes comprise a distinct family of RNA-guided genome editors. *Nature*. 2019;566(7743):218–223.

Cox DBT, Gootenberg JS, Abudayyeh OO, et al. RNA editing with CRISPR-Cas13. *Science* (New York, NY). 2017;358(6366):1019–1027.

Mali P, Yang L, Esvelt KM, et al. RNA-guided human genome engineering via Cas9. *Science* (New York, NY). 2013;339(6121):823–826.

Shin JW, Kim K-H, Chao MJ, et al. Permanent inactivation of Huntington's disease mutation by personalized allele-specific CRISPR/Cas9. *Hum Mol Genet.* 2016;25(20):4566–4576.

Firth AL, Menon T, Parker GS, et al. Functional gene correction for cystic fibrosis in lung epithelial cells generated from patient iPSCs. *Cell Rep.* 2015;12(9):1385–1390.

Ousterout DG, Kabadi AM, Thakore PI, Majoros WH, Reddy TE, Gersbach CA. Multiplex CRISPR/Cas9-based genome editing for correction of dystrophin mutations that cause Duchenne muscular dystrophy. *Nat Commun.* 2015;6:6244.

Callaway E. Gene-Editing Research in Human Embryos Gains Momentum; 2016:289–290.

Zhai X, Ng V, Lie R. No ethical divide between China and the west in human embryo research. *Dev World Bioeth.* 2016;16(2):116–120.

Ahmetov II, Egorova ES, Gabdrakhmanova LJ, Fedotovskaya ON. Genes and athletic performance: an update. *Med Sport Sci.* 2016;61:41–54.

Moir HJ, Kemp R, Folkerts D, Spendiff O, Pavlidis C, Opara E. Genes and elite marathon running performance: a systematic review. *J Sports Sci Med.* 2019;18(3):559–568.

Miyamoto-Mikami E, Zempo H, Fuku N, Kikuchi N, Miyachi M, Murakami H. Heritability estimates of endurance-related phenotypes: a systematic review and meta-analysis. *Scand J Med Sci Sports.* 2018;28(3):834–845.

Flynn RK, Pedersen CL, Birmingham TB, Kirkley A, Jackowski D, Fowler PJ. The familial predisposition toward tearing the anterior cruciate ligament: a case control study. *Am J Sports Med.* 2005;33(1):23–28.

Caso E, Maestro A, Sabiers CC, et al. Whole-exome sequencing analysis in twin sibling males with an anterior cruciate ligament rupture. *Injury.* 2016;47(Suppl 3):S41–S50.

Tashjian RZ, Granger EK, Farnham JM, Cannon-Albright LA, Teerlink CC. Genome-wide association study for rotator cuff tears identifies two significant single-nucleotide polymorphisms. *J Shoulder Elbow Surg.* 2016;25(2):174–179.

Schroder C, Steimer W. gDNA extraction yield and methylation status of blood samples are affected by longterm storage conditions. *PLoS ONE.* 2018;13(2), e0192414.

Redshaw N, Huggett JF, Taylor MS, Foy CA, Devonshire AS. Quantification of epigenetic biomarkers: an evaluation of established and emerging methods for DNA methylation analysis. *BMC Genomics.* 2014;15:1174.

Chapter 12

Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: a brief overview. *J Head Trauma Rehabil.* 2006;21(5):375–378. <https://doi.org/10.1097/00001199-200609000-00001>.

Prien A, Grafe A, Rössler R, Junge A, Verhagen E. Epidemiology of head injuries focusing on concussions in team contact sports: a systematic review. *Sports Med.* 2018;48(4):953–969. <https://doi.org/10.1007/s40279-017-0854-4>.

Pfister T, Pfister K, Hagel B, Ghali WA, Ronksley PE. The incidence of concussion in youth sports: a systematic review and meta-analysis. *Br J Sports Med.* 2015. <https://doi.org/10.1136/bjsports-2015-094978>.

Gardner A, Shores EA, Batchelor J. Reduced processing speed in rugby union players reporting three or more previous concussions. *Arch Clin Neuropsychol.* 2010;25:174–181. <https://doi.org/10.1093/arclin/acq007>.

Dupuis F, Johnston KM, Lavoie M, Lepore F, Lassonde M. Concussions in athletes produce brain dysfunction as revealed by event-related potentials. *Clin Neurosci Neuropathol.* 2000;11(18):4087–4092. <https://doi.org/10.1097/00001756-200012180-00035>.

De Beaumont L, Brisson B, Lassonde M, Jolicoeur P. Long-term electrophysiological changes in athletes with a history of multiple concussions. *Brain Inj.* 2007;21(6):631–644. <https://doi.org/10.1080/02699050701426931>.

Omalu BI, DeKosky ST, Minster RL, Kamboh MI, Hamilton RL, Wecht CH. Chronic traumatic encephalopathy in a National Football League player. *Neurosurgery.* 2005;57(1):128–134.

Mez J, Daneshvar DH, Kiernan PT, et al. Clinicopathological evaluation of chronic traumatic encephalopathy in players of American football. *J Am Med Assoc.* 2017;318(4):360–370. <https://doi.org/10.1001/jama.2017.8334>.

Chiampas GT, Kirkendall DT. Point-counterpoint: should heading be restricted in youth football? Yes, heading should be restricted in youth football. *Sci Med Footb.* 2018;2(1):80–82.

Pollock AM, White AJ, Kirkwood G. Evidence in support of the call to ban the tackle and harmful contact in school rugby: a response to World Rugby. *Br J Sports Med.* 2017;51(15):1113–1117. <https://doi.org/10.1136/bjsports-2016-096996>.

Bulkley A. For the love of the game: the case for state bans on youth tackle football. *U Mich JL Reform Caveat.* 2014;48:1.

Rougraff BT. Letter to the editor: editorial: orthopaedic surgeons should recommend that children and young adults not play tackle football. *Clin Orthop Relat Res.* 2016;474(11):2541–2542. <https://doi.org/10.1007/s11999-016-5005-y>.

Tucker R, Raftery M, Verhagen E. Injury risk and a tackle ban in youth Rugby Union: reviewing the evidence and searching for targeted, effective interventions. A critical review. *Br J Sports Med.* 2016;50(15):921–925. <https://doi.org/10.1136/bjsports-2016-096322>.

Kuhn AW, Yengo-Kahn AM, Kerr ZY, Zuckerman SL. Sports concussion research, chronic traumatic encephalopathy and the media: repairing the disconnect. *Br J Sports Med.* 2017;51(24):1732–1733. <https://doi.org/10.1136/bjsports-2016-096508>.

Rutherford A, Stewart W, Bruno D. Heading for trouble: is dementia a game changer for football? *Br J Sports Med.* 2019;53(6):321–322. <https://doi.org/10.1136/bjsports-2017-097627>.

Mc Fic S, September AV. Genetics of sport-related concussion. In: *Sports, Exercise, and Nutritional Genomics.* Elsevier; 2019:341–374.

Panenka W, Gardner A, Dretsch M, Crynen G, Crawford FC, Iverson GL. Systematic review of genetic risk factors for sustaining a mild traumatic brain injury. *J Neurotrauma.* 2017;33. <https://doi.org/10.1089/neu.2016.4833>.

Mccrea M, Meier T, Huber D, et al. Role of advanced neuroimaging, fluid biomarkers and genetic testing in the assessment of sport-related concussion: a systematic review. *Br J Sports Med.* 2017;51(12):919–929. <https://doi.org/10.1136/bjsports-2016-097447>.

McCrory P, Meeuwisse W, Dvorak J, et al. Consensus statement on concussion in sport—the 5th international conference on concussion in sport held in Berlin, October 2016. *Br J Sports Med.* 2017. <https://doi.org/10.1136/bjsports-2017-097699>.

Voss JD, Connolly J, Schwab KA, Scher AI. Update on the epidemiology of concussion/mild traumatic brain injury. *Curr Pain Headache Rep.* 2015;19(7):506. <https://doi.org/10.1007/s11916-015-0506-z>.

McCrory P, Meeuwisse WH, Aubry M, et al. Consensus statement on concussion in sport: the 4th international conference on concussion in sport held in Zurich, November 2012. *Br J Sports Med.* 2013;47(2):250–258. <https://doi.org/10.1136/bjsports-2013-092313>.

Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. *Lancet.* 1974;304(7872):81–84. [https://doi.org/10.1016/S0140-6736\(74\)91639-0](https://doi.org/10.1016/S0140-6736(74)91639-0).

Shackford SR, Wald SL, Ross SE, et al. The clinical utility of computed tomographic scanning and neurologic examination in the management of patients with minor head injuries. *J Trauma.* 1992;33(3):385–394.

Giza CC, Hovda DA. The new neurometabolic cascade of concussion. *Neurosurgery.* 2014;75(3):S24–S33. <https://doi.org/10.1227/NEU.0000000000000505>.

Barth FJT, Broshek JR, Varney DK, Robert N. Acceleration-deceleration sport-related concussion: the gravity of

it all. *J Athl Train.* 2001;36(3):253–256.

McCroly PR, Berkovic SF. Concussion: the history of clinical and pathophysiological concepts and misconceptions. *Neurology.* 2001;57:2283–2289. <https://doi.org/10.1212/WNL.57.12.2283>.

Pošt A, Hoshizaki TB. Rotational acceleration, brain tissue strain, and the relationship to concussion. *J Biomech Eng.* 2015;137(3). https://doi.org/10.1115/1.4028983_030801.

Bazarian JJ, Blyth B, Cimpello L. Bench to bedside: evidence for brain injury after concussion—looking beyond the computed tomography scan. *Acad Emerg Med.* 2006;13(2):199–214. <https://doi.org/10.1197/j.aem.2005.07.031>.

Katayama Y, Becker D, Tamura T, Hovda DA. Massive increases in extracellular potassium and the indiscriminate release of glutamate following concussive brain injury. *J Neurosurg.* 1990;73:889–900.

Giza CC, Difiori JP. Pathophysiology of sports-related concussion: an update on basic science and translational research. *Sports Health.* 2011;3(1):46–51. <https://doi.org/10.1177/1941738110391732>.

Kawamata T, Katayama Y, Hovda DA, Yoshino A, Becker DP. Lactate accumulation following concussive brain injury: the role of ionic fluxes induced by excitatory amino acids. *Brain Res.* 1995;674(2):196–204.

[https://doi.org/10.1016/0006-8993\(94\)01444-M](https://doi.org/10.1016/0006-8993(94)01444-M).

Giza CC, Hovda DA. The new neurometabolic cascade of concussion. *Neurosurgery.* 2014;75(4):S24–S33.

<https://doi.org/10.1227/NEU.0000000000000505>.

Momeni HR. Role of calpain in apoptosis. *Cell J.* 2011;13(2):65–72.

Vagnozzi R, Tavazzi B, Signoretti S, et al. Temporal window of metabolic brain vulnerability to concussions: mitochondrial-related impairment—part I. *Neurosurgery.* 2007;61(2):379–388. <https://doi.org/10.1227/01.NEU.0000280002.41696.D8>.

Arundine M, Tymianski M. Molecular mechanisms of glutamate-dependent neurodegeneration in ischemia and traumatic brain injury. *Cell Mol Life Sci.* 2004;61(6):657–668. <https://doi.org/10.1007/s00018-003-3319-x>.

Apel K, Hirt H. Reactive oxygen species: metabolism, oxidative stress, and signal transduction. *Annu Rev Plant Biol.* 2004;55:373–399. <https://doi.org/10.1146/annurev.arplant.55.031903.141701>.

Butterfield DA, Koppal T, Howard B, Yatin S, Allen K, Aksenov M. Structural and functional changes in proteins induced by free radical-mediated oxidative antioxidants N-tert-Butyl-a-phenylnitron and vitamin E. *Ann N Y Acad Sci.* 1998;845:448–462.

Raghupathi R, Conti AC, Graham DI, et al. Mild traumatic brain injury induces apoptotic cell death in the cortex that is preceded by decreases in cellular bcl-2 immunoreactivity. *Science (80-).* 2002;110(4):605–616.

Rink A, Fung KM, Trojanowski JQ, Lee VM, Neugebauer E, McIntosh TK. Evidence of apoptotic cell death after experimental traumatic brain injury in the rat. *Am J Pathol.* 1995;147(6):1575–1583. <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1869937&tool=pmcentrez&rendertype=abstract>.

Conti AC, Raghupathi R, Trojanowski JQ, McIntosh TK. Experimental brain injury induces regionally distinct apoptosis during the acute and delayed post-traumatic period. *J Neurosci.* 1998;18(15):5663–5672.

Morganti-Kossmann MC, Rancan M, Stahel PF, Kossmann T. Inflammatory response in acute traumatic brain injury: a double-edged sword. *Curr Opin Crit Care.* 2002;8(2):101–105. <https://doi.org/10.1097/00075198-200204000-00002>.

Patterson ZR, Holahan MR. Understanding the neuroinflammatory response following concussion to develop treatment strategies. *Front Cell Neurosci.* 2012;6:58. <https://doi.org/10.3389/fncel.2012.00058>.

Smith C, Gentleman SM, Leclercq PD, et al. The neuroinflammatory response in humans after traumatic brain injury. *Neuropathol Appl Neurobiol.* 2013;39(6):654–666. <https://doi.org/10.1111/nan.12008>.

Holm L, Cassidy JD, Carroll LJ, Borg J. Summary of the WHO collaborating centre for neurotrauma task force on mild traumatic brain injury. *J Rehabil Med.* 2005;37(3):137–141.

Mckee AC, Cantu RC, Nowinski CJ, et al. Chronic traumatic encephalopathy in athletes: progressive tauopathy following repetitive head injury. *J Neuropathol Exp Neurol.* 2009;68(7):709–735. <https://doi.org/10.1097/>

NEN.0b013e3181a9d503.Chronic.

Baugh CM, Stamm JM, Riley DO, et al. Chronic traumatic encephalopathy: neurodegeneration following repetitive concussive and subconcussive brain trauma. *Brain Imaging Behav.* 2012;6(2):244–254. <https://doi.org/10.1007/s11682-012-9164-5>.

Guskiewicz KM, Mihalik JP. Biomechanics of sport concussion. *Exerc Sport Sci Rev.* 2011;39(1):4–11. <https://doi.org/10.1097/JES.0b013e318201f53e>.

McCrea M, Hammeke T, Olsen G, Leo P, Guskiewicz K. Unreported concussion in high school football players. *Clin J Sport Med.* 2004;14(1):13–17. <https://doi.org/10.1097/00042752-200401000-00003>.

Kerr ZY, Register-Mihalik JK, Kay MC, DeFreese JD, Marshall SW, Guskiewicz KM. Concussion nondisclosure during professional career among a cohort of former national football league athletes. *Am J Sports Med.* 2018;46(1):22–29. <https://doi.org/10.1177/0363546517728264>.

Kroshus E, Garnett B, Hawrilenko M, Baugh CM, Calzo JP. Concussion under-reporting and pressure from coaches, teammates, fans, and parents. *Soc Sci Med.* 2015;134:66–75. <https://doi.org/10.1016/j.socscimed.2015.04.011>.

Wallace J, Covassin T, Nogle S, Gould D, Kovan J. Knowledge of concussion and reporting behaviors in high school athletes with or without access to an athletic trainer. *J Athl Train.* 2017;52(3):228–235. <https://doi.org/10.4085/1062-6050-52.1.07>.

Patricios J, Fuller GW, Ellenbogen R, et al. What are the critical elements of sideline screening that can be used to establish the diagnosis of concussion? A systematic review. *Br J Sports Med.* 2017;51(11):888–894.

<https://doi.org/10.1136/bjsports-2016-097441>.

Zetterberg H, Morris HR, Hardy J, Blennow K. Update on fluid biomarkers for concussion. *Concussion.* 2016;1(3):CNC12. <https://doi.org/10.2217/cnc-2015-0002>.

Rogatzki MJ, Baker JS. Traumatic brain injury in sport with special focus on biomarkers of concussion injury. *J Neurol Neurophysiol.* 2016;7(3):3–6. <https://doi.org/10.4172/2155-9562.1000383>.

Papa L, Ramia MM, Edwards D, Johnson BD, Slobounov SM. Systematic review of clinical studies examining biomarkers of brain injury in athletes after sports-related concussion. *J Neurotrauma.* 2015;32(10):661–673. <https://doi.org/10.1089/neu.2014.3655>.

Barth JT, Alves WM, Ryan TV, et al. Mild head injury in sports: neuropsychological sequelae and recovery of function. *Mild Head Inj.* 1989;257–275.

McCrea M, Guskiewicz KM, Marshall SW, et al. Acute effects and recovery time following concussion in collegiate football players. *JAMA.* 2014;290(19):2556–2563.

Cancelliere C, Hincapié CA, Keightley M, et al. Systematic review of prognosis and return to play after sport concussion: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Arch Phys Med Rehabil.* 2014;95(3 Suppl):S210–S229. <https://doi.org/10.1016/j.apmr.2013.06.035>.

Ellis MJ, McDonald PJ, Cordingley D, Mansouri B, Essig M, Ritchie L. Retirement-from-sport considerations following pediatric sports-related concussion: case illustrations and institutional approach. *Neurosurg Focus.* 2016;40(4):E8. 1–13 <https://doi.org/10.3171/2016.1.FOCUS15600>.

Covassin T, Crutcher B, Bleecker A, Heiden O, Dailey A, Yang J. Postinjury anxiety and social support among collegiate athletes: a comparison between orthopaedic injuries and concussions. *J Athl Train.* 2014;49(4):462–468. <https://doi.org/10.4085/1062-6059-49.2.03>.

Ransom DM, Vaughan CG, Pratson L, Sady MD. Academic effects of concussion in children and adolescents. *Pediatrics.* 2015;135(6):1043–1050. <https://doi.org/10.1542/peds.2014-3434>.

Iverson GL, Gardner AJ, Terry DP, et al. Predictors of clinical recovery from concussion: a systematic review. *Br J Sports Med.* 2017;51(12):941–948. <https://doi.org/10.1136/bjsports-2017-097729>.

Schneider KJ, Iverson GL, Emery CA, McCrory P, Herring SA, Meeuwisse WH. The effects of rest and treatment following sport-related concussion: a systematic review of the literature. *Br J Sports Med.* 2013;47:304–307. <https://doi.org/10.1136/bjsports-2012-097729>.

doi.org/10.1136/bjsports-2013-092190.

Silverberg ND, Iverson GL, McCrea M, Apps JN, Hammeke TA, Thomas DG. Activity-related symptom exacerbations after pediatric concussion. *JAMA Pediatr.* 2016;53226(10):1–8. <https://doi.org/10.1001/jamapediatrics.2016.1187>.

Ackery A, Provvienza C, Tator CH. Concussion in hockey: compliance with return to play advice and follow-up status. *Can J Neurol Sci.* 2009;36(2):207–212. <https://doi.org/10.1017/S0317167100120281>.

Guskiewicz KM, Weaver NL, Padua DA, Garrett WE. Epidemiology of concussion in collegiate and high school football players. *Am J Sports Med.* 2000;28:643–650.

McCrary P, Davis G, Makdissi M. Second impact syndrome or cerebral swelling after sporting head injury. *Curr Sports Med Rep.* 2012;11(1):21–23. <https://doi.org/10.1249/JSR.0b013e3182423bfd>.

Wetjen NM, Pichelmann MA, Atkinson JLD. Second impact syndrome: concussion and second injury brain complications. *J Am Coll Surg.* 2010;211(4):553–557. <https://doi.org/10.1016/j.jamcollsurg.2010.05.020>.

Delahunty SE, Delahunty E, Condon B, Toomey D, Blake C. Prevalence of and attitudes about concussion in Irish schools' rugby union players. *J Sch Health.* 2015;85(1):17–26. <https://doi.org/10.1111/josh.12219>.

Walker SP. Concussion knowledge and return-to-play attitudes among subelite rugby union players. *South African J Sport Med.* 2015;27(2):50–54. <https://doi.org/10.7196/SAJSM.536>.

Snow CL, Chatterjee A, Libfeld P, Mackenzie HM, Thornton JS. Premature return to play and return to learn after a sport-related concussion. *Can Fam Physician.* 2014;60:310–315.

Bailes JE, Turner RC, Lucke-Wold BP, Patel V, Lee JM. Chronic traumatic encephalopathy: is it real? The relationship between neurotrauma and neurodegeneration. *Neurosurgery.* 2015;62(1):15–24. <https://doi.org/10.1227/NEU.0000000000000811>.

Mckee AC, Stein TD, Nowinski CJ, et al. The spectrum of disease in chronic traumatic encephalopathy. *Brain.* 2013;136(2012):43–64. <https://doi.org/10.1093/brain/aws307>.

Lee EB, Kinch K, Johnson VE, Trojanowski JQ, Smith DH, Stewart W. Chronic traumatic encephalopathy is a common co-morbidity, but less frequent primary dementia in former soccer and rugby players. *Acta Neuropathol.* 2019;0123456789. <https://doi.org/10.1007/s00401-019-02030-y>.

McKee AC, Cairns NJ, Dickson DW, et al. The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. *Acta Neuropathol.* 2016;131(1):75–86. <https://doi.org/10.1007/s00401-015-1515-z>.

Smith DH, Johnson VE, Trojanowski JQ, Stewart W. Chronic traumatic encephalopathy—confusion and controversies. *Nat Rev Neurol.* 2019;15(3):179–183. <https://doi.org/10.1038/s41582-018-0114-8>.

Brandenburg W, Hallervorden J. Dementia pugilistica with anatomical findings. *Virchows Arch Pathol Anat Physiol Klin Med.* 1954;325(6):680.

Montenigro PH, Corp DT, Stein TD, Cantu RC, Stern RA. Chronic traumatic encephalopathy: historical origins and current perspective. *Annu Rev Clin Psychol.* 2015;11:309–330. <https://doi.org/10.1146/annurev-clinpsy-032814-112814>.

Manley G, Gardner AJ, Schneider KJ, et al. A systematic review of potential long-term effects of sport-related concussion. *Br J Sports Med.* 2017;51(12):969–977. <https://doi.org/10.1136/bjsports-2017-097791>.

Finkbeiner NWB, Max JE, Longman S, Debert C. Knowing what we don't know: long-term psychiatric outcomes following adult concussion in sports. *Can J Psychiatr.* 2016;61(5):270–276.

Martini DN, Broglio SP. Long-term effects of sport concussion on cognitive and motor performance: a review. *Int J Psychophysiol.* 2018;132:25–30.

Brush CJ, Ehmann PJ, Olson RL, Bixby WR, Alderman BL. Do sport-related concussions result in long-term cognitive impairment? A review of event-related potential research. *Int J Psychophysiol.* 2018;132:124–134.

Kutcher JS, Eckner JT. At-risk populations in sports-related concussion. *Curr Sports Med Rep.* 2010;9(1):16–

20. <https://doi.org/10.1249/JSR.0b013e3181caa89d>.

Schneider DK, Grandhi RK, Bansal P, et al. Current state of concussion prevention strategies: a systematic review and meta-analysis of prospective, controlled studies. *Br J Sports Med*. 2016. <https://doi.org/10.1136/bjsports-2015-095645>.

Nathoo N, Chetty R, van Dellen JR, Barnett GH. Genetic vulnerability following traumatic brain injury: the role of apolipoprotein E. *Mol Pathol*. 2003;56(3):132–136. <https://doi.org/10.1136/mp.56.3.132>.

Heise V, Filippini N, Ebmeier KP, Mackay CE. The APOE ϵ 4 allele modulates brain white matter integrity in healthy adults. *Mol Psychiatry*. 2011;16(9):908–916. <https://doi.org/10.1038/mp.2010.90>.

Persson J, Lind J, Larsson A, et al. Altered brain white matter integrity in healthy carriers of the APOE epsilon 4 allele: a risk for AD? *Neurology*. 2006;66(7):1029–1033. <https://doi.org/10.1212/01.wnl.0000204180.25361.48>.

Crawford F, Wood M, Ferguson S, et al. Apolipoprotein E-genotype dependent hippocampal and cortical responses to traumatic brain injury. *Neuroscience*. 2009;159(4):1349–1362. <https://doi.org/10.1016/j.neuroscience.2009.01.033>.

Vitek MP, Brown CM, Colton CA. APOE genotype-specific differences in the innate immune response. *Neurobiol Aging*. 2009;30(9):1350–1360. <https://doi.org/10.1016/j.neurobiolaging.2007.11.014>.

Terrell TR, Abramson R, Barth JT, et al. Genetic polymorphisms associated with the risk of concussion in 1056 college athletes: a multicentre prospective cohort study. *Br J Sports Med*. 2018;52(3):192–198. <https://doi.org/10.1136/bjsports-2016-097419>.

Merritt VC, Arnett PA. Apolipoprotein e (APOE) ϵ 4 allele is associated with increased symptom reporting following sports concussion. *J Int Neuropsychol Soc*. 2016;22:89–94. <https://doi.org/10.1017/S1355617715001022>.

Merritt V, Ukueberuwa D, Arnett P. Relationship between the apolipoprotein E gene and headache following sports-related concussion. *J Clin Exp Neuropsychol*. 2016;38(9):941–949. <https://doi.org/10.1080/13803395.2016.1177491>.

Merritt VC, Rabinowitz AR, Arnett PA. The influence of the apolipoprotein e (APOE) gene on subacute post-concussion neurocognitive performance in college athletes. *Arch Clin Neuropsychol*. 2018;33(1):36–46. <https://doi.org/10.1093/arclin/acx051>.

Abrahams S, Mc Fie S, Patricios J, Suter J, Posthumus M, September AV. An association between polymorphisms within the APOE gene and concussion aetiology in rugby union players. *J Sci Med Sport*. 2018;21(2):117–122. <https://doi.org/10.1016/j.jsams.2017.06.004>.

Mietelska-Porowska A, Wasik U, Goras M, Filipek A, Niewiadomska G. Tau protein modifications and interactions: their role in function and dysfunction. *Int J Mol Sci*. 2014;15(3):4671–4713. <https://doi.org/10.3390/ijms15034671>.

Frośt B, Feany MB. Connecting the dots between tau dysfunction and neurodegeneration. *Trends Cell Biol*. 2015;25(1):46–53. <https://doi.org/10.1016/j.tcb.2014.07.005>.

Abrahams S, Mc Fie S, Patricios J, Suter J, September AV, Posthumus M. Toxic tau: the TAU gene polymorphisms associate with concussion history in rugby union players. *J Sci Med Sport*. 2018. <https://doi.org/10.1016/j.jsams.2018.06.012>.

Terrell TR, Bostick RM, Abramson R, et al. APOE, APOE promoter, and Tau genotypes and risk for concussion in college athletes. *Clin J Sport Med*. 2008;18(1):10–17. <https://doi.org/10.1097/JSM.0b013e31815c1d4c>.

Balestri M, Calati R, Serretti A, De Ronchi D. Genetic modulation of personality traits: a systematic review of the literature. *Int Clin Psychopharmacol*. 2014;29:1–15. <https://doi.org/10.1097/YIC.0b013e328364590b>.

Dalley JW, Roiser JP. Dopamine, serotonin and impulsivity. *Neuroscience*. 2012;215:42–58. <https://doi.org/10.1016/j.neuroscience.2012.03.065>.

Amst adter AB, MacPherson L, Wang F, et al. The relationship between risk-taking propensity and the COMT Val 158Met polymorphism among early adolescents as a function of sex. *J Psychiatr Res*. 2012;46(7):940–945. <https://doi.org/10.1016/j.jpsychires.2012.04.010>.

Mc Fie S, Abrahams S, Patricios J, Suter J, Posthumus M, September AV. The association between COMT rs4680

and 5-HTTLPR genotypes and concussion history in South African rugby union players. *J Sports Sci.* 2018;36(8):920–933. <https://doi.org/10.1080/02640414.2017.1346274>.

Cochrane GD, Sundman MH, Hall EE, et al. Genetics influence neurocognitive performance at baseline but not concussion history in collegiate student-athletes. *Clin J Sport Med.* 2018;28(2):125–129. <https://doi.org/10.1097/JSM.0000000000000443>.

McDevitt JK, Tierney RT, Mansell JL, et al. Neuronal structural protein polymorphism and concussion in college athletes. *Brain Inj.* 2011;25(11):1108–1113. <https://doi.org/10.3109/02699052.2011.607790>.

Hisanaga S, Hirokawa N. Structure of the peripheral domains of neurofilaments revealed by low angle rotary shadowing. *J Mol Biol.* 1988;202(2):297–305. [https://doi.org/10.1016/0022-2836\(88\)90459-7](https://doi.org/10.1016/0022-2836(88)90459-7).

McDevitt JK, Tierney RT, Phillips J, Gaughan JP, Torg JS, Krynetskiy E. Association between GRIN2A promoter polymorphism and recovery from concussion. *Brain Inj.* 2015;29(13-14):1674–1681. <https://doi.org/10.3109/02699052.2015.1075252>.

Madura SA, McDevitt JK, Tierney RT, et al. Genetic variation in SLC17A7 promoter associated with response to sport-related concussions. *Brain Inj.* 2016;30(7):908–913. <https://doi.org/10.3109/02699052.2016.1146958>.

Mc Fie S, Abrahams S, Patricios J, Suter J, Pothumus M, September AV. Inflammatory and apoptotic signalling pathways and concussion severity: a genetic association study. *J Sports Sci.* 2018;00(00):1–9. <https://doi.org/10.1080/02640414.2018.1448570>.

Chanock S, Manolio T, Boehnke M, et al. Replicating genotype–phenotype associations. *Nature.* 2007;447(June):655–660. <https://doi.org/10.1038/447655a>.

Merchant-Borna K, Lee H, Wang D, et al. Genome-wide changes in peripheral gene expression following sports-related concussion. *J Neurotrauma.* 2016;33(17):1576–1585. <https://doi.org/10.1089/neu.2015.4191>.

Giza CC, Prins ML, Hovda DA, Herschman HR, Feldman JD. Genes preferentially induced by depolarization after concussive brain injury: effects of age and injury severity. *J Neurotrauma.* 2002;19(4):387–402. <https://doi.org/10.1089/08977150252932352>.

McGinn MJ, Povlishock JT. Pathophysiology of traumatic brain injury. *Neurosurg Clin.* 2016;27(4):397–407.

Heard E, Martienssen RA. Transgenerational epigenetic inheritance: myths and mechanisms. *Cell.* 2014;157(1):95–109. <https://doi.org/10.1016/j.cell.2014.02.045>.

Wong VS, Langley B. Epigenetic changes following traumatic brain injury and their implications for outcome, recovery and therapy. *Neurosci Lett.* 2016;625:26–33. <https://doi.org/10.1016/j.neulet.2016.04.009>.

Holliday R, Pugh JE. DNA modification mechanisms and gene activity during development. *Science (80-).* 1975;187(4173):226–232.

Zhang Z-Y, Zhang Z, Fauser U, Schluesener HJ. Global hypomethylation defines a sub-population of reactive microglia/macrophages in experimental traumatic brain injury. *Neurosci Lett.* 2007;429(1):1–6.

Haghighi F, Ge Y, Chen S, et al. Neuronal DNA methylation profiling of blast-related traumatic brain injury. *J Neurotrauma.* 2015;32(16):1200–1209.

Schober ME, Ke X, Xing B, et al. Traumatic brain injury increased IGF-1B mRNA and altered IGF-1 exon 5 and promoter region epigenetic characteristics in the rat pup hippocampus. *J Neurotrauma.* 2012;29(11):2075–2085.

Isgaard J, Aberg D, Nilsson M. Protective and regenerative effects of the GH/IGF-I axis on the brain. *Minerva Endocrinol.* 2007;32(2):103–113.

Brywe KG, Mallard C, Gustavsson M, et al. IGF-I neuroprotection in the immature brain after hypoxiaischemia, involvement of Akt and GSK3 β ? *Eur J Neurosci.* 2005;21(6):1489–1502.

Gao W-M, Chadha MS, Kline AE, et al. Immunohistochemical analysis of histone H3 acetylation and methylation—evidence for altered epigenetic signaling following traumatic brain injury in immature rats. *Brain Res.* 2006;1070(1):31–34.

Shein NA, Grigoriadis N, Alexandrovich AG, et al. Histone deacetylase inhibitor ITF2357 is neuroprotective,

improves functional recovery, and induces glial apoptosis following experimental traumatic brain injury. *FASEB J*. 2009;23(12):4266–4275.

Yu F, Wang Z, Tanaka M, et al. Posttrauma cotreatment with lithium and valproate: reduction of lesion volume, attenuation of blood-brain barrier disruption, and improvement in motor coordination in mice with traumatic brain injury. *J Neurosurg*. 2013;119(3):766–773.

Tai Y-T, Lee W-Y, Lee F-P, et al. Low dose of valproate improves motor function after traumatic brain injury. *Biomed Res Int*. 2014;2014.

Gibson CL, Murphy SP. Benefits of histone deacetylase inhibitors for acute brain injury: a systematic review of animal studies. *J Neurochem*. 2010;115(4):806–813.

Na'ama AS, Shohami E. Histone deacetylase inhibitors as therapeutic agents for acute central nervous system injuries. *Mol Med*. 2011;17(5-6):448–456.

Wang G, Shi Y, Jiang X, et al. HDAC inhibition prevents white matter injury by modulating microglia/macrophage polarization through the GSK3 β /PTEN/Akt axis. *Proc Natl Acad Sci U S A*. 2015;112(9):2853–2858.

Berdasco M, Esteller M. Clinical epigenetics: seizing opportunities for translation. *Nat Rev Genet*. 2019;20(2):109–127. <https://doi.org/10.1038/s41576-018-0074-2>.

Lardenoije R, Iatrou A, Kenis G, et al. The epigenetics of aging and neurodegeneration. *Prog Neurobiol*. 2015;131:21–64.

Mitra B, Rau TF, Surendran N, et al. Plasma micro-RNA biomarkers for diagnosis and prognosis after traumatic brain injury: a pilot study. *J Clin Neurosci*. 2017;38:37–42.

Zhang Y, Liao Y, Wang D, et al. Altered expression levels of miRNAs in serum as sensitive biomarkers for early diagnosis of traumatic injury. *J Cell Biochem*. 2011;112(9):2435–2442.

Redell JB, Liu Y, Dash PK. Traumatic brain injury alters expression of hippocampal microRNAs: potential regulators of multiple pathophysiological processes. *J Neurosci Res*. 2009;87(6):1435–1448.

Balakathiresan N, Bhomia M, Chandran R, Chavko M, McCarron RM, Maheshwari RK. MicroRNA let-7i is a promising serum biomarker for blast-induced traumatic brain injury. *J Neurotrauma*. 2012;29(7):1379–1387.

Taheri S, Tanriverdi F, Zararsiz G, et al. Circulating microRNAs as potential biomarkers for traumatic brain injury-induced hypopituitarism. *J Neurotrauma*. 2016;33(20):1818–1825.

Di Pietro V, Ragusa M, Davies D, et al. MicroRNAs as novel biomarkers for the diagnosis and prognosis of mild and severe traumatic brain injury. *J Neurotrauma*. 2017;34(11):1948–1956.

Di Pietro V, Yakoub KM, Scarpa U, Di Pietro C, Belli A. MicroRNA signature of traumatic brain injury: from the biomarker discovery to the point-of-care. *Front Neurol*. 2018;9.

Toffolo K, Osei J, Kelly W, et al. Circulating microRNAs as biomarkers in traumatic brain injury. *Neuropharmacology*. 2019;145:199–208.

Di Pietro V, Porto E, Ragusa M, et al. Salivary microRNAs: diagnostic markers of mild traumatic brain injury in contact-sport. *Front Mol Neurosci*. 2018;11(August):1–13. <https://doi.org/10.3389/fnmol.2018.00290>.

Davies D, Yakoub KM, Scarpa U, et al. Serum miR-502: a potential biomarker in the diagnosis of concussion in a pilot study of patients with normal structural brain imaging. *J Concussion*. 2019. <https://doi.org/10.1177/2059700219886190>.

Svingos AM, Asken BM, Bauer RM, et al. Exploratory study of sport-related concussion effects on peripheral micro-RNA expression. *Brain Inj Bl*. 2019;33(4):1–7. <https://doi.org/10.1080/02699052.2019.1573379>.

LaRocca D, Barns S, Hicks SD, et al. Comparison of serum and saliva miRNAs for identification and characterization of mTBI in adult mixed martial arts fighters. *PLoS One*. 2019;14(1):1–38. <https://doi.org/10.1371/journal.pone.0207785>.

Johnson JJ, Loeffert AC, Stokes J, Olympia RP, Bramley H, Hicks SD. Association of salivary microRNA changes with prolonged concussion symptoms. *JAMA Pediatr*. 2018;172(1):65–73. <https://doi.org/10.1001/jamapediatrics.2017.3884>.

- Bhomia M, Balakathiresan NS, Wang KK, Papa L, Maheshwari RK. A panel of serum miRNA biomarkers for the diagnosis of severe to mild traumatic brain injury in humans. *Sci Rep*. 2016;6(June):1–12. <https://doi.org/10.1038/srep28148>.
- Echemendia RJ, Meeuwisse W, McCrory P, et al. The sport concussion assessment tool 5th edition (SCAT5): background and rationale. *Br J Sports Med*. 2017;51(11):848–850.
- Hutchison MG, Lawrence DW, Cusimano MD, Schweizer TA. Head trauma in mixed martial arts. *Am J Sports Med*. 2014;42(6):1352–1358.
- Kroshus E, Baugh CM, Daneshvar DH, Stamm JM, Laursen RM, Austin SB. Pressure on sports medicine clinicians to prematurely return collegiate athletes to play after concussion. *J Athl Train*. 2015;50(9):944–951. <https://doi.org/10.4085/1062-6050-50.6.03>.
- Kontos AP, Sufirinko A, Womble M, Kegel N. Neuropsychological assessment following concussion: an evidence-based review of the role of neuropsychological assessment pre-and post-concussion. *Curr Pain Headache Rep*. 2016;20(6):38.
- Yengo-Kahn AM, Hale AT, Zalneraitis BH, Zuckerman SL, Sills AK, Solomon GS. The sport concussion assessment tool: a systematic review. *Neurosurg Focus*. 2016;40(4), E6.
- Dessy AM, Yuk FJ, Maniya AY, et al. Review of assessment scales for diagnosing and monitoring sportsrelated concussion. *Cureus*. 2017;9(12).
- Hicks SD, Johnson J, Carney MC, et al. Overlapping microRNA expression in saliva and cerebrospinal fluid accurately identifies pediatric traumatic brain injury. *J Neurotrauma*. 2018;35(1):64–72.
- Casson IR, Sethi NK. Early symptom burden predicts recovery after sport-related concussion. *Neurology*. 2015;85(1):110–111. <https://doi.org/10.1212/WNL.0000000000001700>.
- Berson A, Nativio R, Berger SL, Bonini NM. Epigenetic regulation in neurodegenerative diseases. *Trends Neurosci*. 2018;41(9):587–598.
- Coppede F. The potential of epigenetic therapies in neurodegenerative diseases. *Front Genet*. 2014;5:220. <https://doi.org/10.3389/fgene.2014.00220>.
- Landgrave-Gomez J, Mercado-Gomez O, Guevara-Guzman R. Epigenetic mechanisms in neurological and neurodegenerative diseases. *Front Cell Neurosci*. 2015;9:58. <https://doi.org/10.3389/fncel.2015.00058>.

Chapter 13

García-Giménez JL. *Epigenetic Biomarkers and Diagnostics*. 1st ed. Cambridge, MA, USA: Academic Press Books – Elsevier; 2015.

Pagiatakis C, Musolino E, Gornati R, Bernardini G, Papait R. Epigenetics of aging and disease: a brief overview. *Aging Clin Exp Res*. 2019. <https://doi.org/10.1007/s40520-019-01430-0>.

Berson A, Nativio R, Berger SL, Bonini NM. Epigenetic regulation in neurodegenerative diseases. *Trends Neurosci*. 2018;41(9):587–598.

Hulshoff MS, Xu X, Krenning G, Zeisberg EM. Epigenetic regulation of endothelial-to-mesenchymal transition in chronic heart disease. *Arterioscler Thromb Vasc Biol*. 2018;38(9):1986–1996.

Dawson MA, Kouzarides T. Cancer epigenetics: from mechanism to therapy. *Cell*. 2012;150(1):12–27.

Kim M, Costello J. DNA methylation: an epigenetic mark of cellular memory. *Exp Mol Med*. 2017;49(4), e322.

Zhao Z, Shilatifard A. Epigenetic modifications of histones in cancer. *Genome Biol*. 2019;20(1):245.

Fedoriw A, Mugford J, Magnuson T. Genomic imprinting and epigenetic control of development. *Cold Spring Harb Perspect Biol*. 2012;4(7):a008136.

Chuang JC, Jones PA. Epigenetics and microRNAs. *Pediatr Res*. 2007;61(5):24R–29R.

Yao Q, Chen Y, Zhou X. The roles of microRNAs in epigenetic regulation. *Curr Opin Chem Biol*. 2019;51:11–17.

Croce CM, Fisher PB. MicroRNAs and epigenetics. In: *Advances in Cancer Research*. vol. 135. Cambridge, MA, USA: Academic Press Books – Elsevier; 2017:1–220.

Liu X, Chen X, Yu X, et al. Regulation of microRNAs by epigenetics and their interplay involved in cancer. *J Exp Clin Cancer Res*. 2013;32(1):96.

Baer C, Claus R, Plass C. Genome-wide epigenetic regulation of miRNAs in cancer. *Cancer Res*. 2013;73(2):473–477.

He L, Hannon GJ. MicroRNAs: small RNAs with a big role in gene regulation. *Nat Rev Genet*. 2004;5(7):522–531.

Sontheimer EJ, Carthew RW. Silence from within: endogenous siRNAs and miRNAs. *Cell*. 2005;122(1):9–12.

Filipowicz W, Jaskiewicz L, Kolb FA, Pillai RS. Post-transcriptional gene silencing by siRNAs and miRNAs. *Curr Opin Struct Biol*. 2005;15(3):331–341.

Alvarez-Garcia I, Miska EA. MicroRNA functions in animal development and human disease. *Development*. 2005;132(21):4653–4662.

Griffiths-Jones S. The microRNA Registry. *Nucleic Acids Res*. 2004;32:D109–D111.

Lim LP, Lau NC, Garrett-Engele P, et al. Microarray analysis shows that some microRNAs downregulate large numbers of target mRNAs. *Nature*. 2005;433(7027):769–773.

Sohel MH. Extracellular/circulating microRNAs: release mechanisms, functions and challenges. *Achiev Life Sci*. 2016;10(2):175–186.

Landthaler M, Yalcin A, Tuschl T. The human DiGeorge syndrome critical region gene 8 and its D. melanogaster homolog are required for miRNA biogenesis. *Curr Biol*. 2004;14(23):2162–2167.

Lee Y, Ahn C, Han J, et al. The nuclear RNase III Drosha initiates microRNA processing. *Nature*. 2003;425:415–419.

Yi R, Qin Y, Macara IG, Cullen BR. Exportin-5 mediates the nuclear export of pre-microRNAs and short hairpin RNAs. *Genes Dev*. 2003;17(24):3011–3016.

Chendrimada TP, Gregory RI, Kumaraswamy E, et al. TRBP recruits the Dicer complex to Ago2 for microRNA processing and gene silencing. *Nature*. 2005;436(7051):740–744.

Zhang H, Kolb FA, Brondani V, Billy E, Filipowicz W. Human Dicer preferentially cleaves dsRNAs at their termini without a requirement for ATP. *EMBO J*. 2002;21(21):5875–5885.

Ender C, Meister G. Argonaute proteins at a glance. *J Cell Sci*. 2010;123(11):1819–1823.

Okamura K, Ishizuka A, Siomi H, Siomi MC. Distinct roles for argonaute proteins in small RNA-directed RNA cleavage pathways. *Genes Dev.* 2004;18(14):1655–1666.

O'Brien J, Hayder H, Zayed Y, Peng C. Overview of microRNA biogenesis, mechanisms of actions, and circulation. *Front Endocrinol (Lausanne).* 2018;9:402.

Cai Y, Yu X, Hu S, Yu J. A brief review on the mechanisms of miRNA regulation. *Genomics Proteomics Bioinformatics.* 2009;7(4):147–154.

Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell.* 2004;116(2):281–297.

Salamin O, De Angelis S, Tissot JD, Saugy M, Leuenberger N. Autologous blood transfusion in sports: emerging biomarkers. *Transfus Med Rev.* 2016;30(3):109–115.

Leuenberger N, Robinson N, Saugy M. Circulating miRNAs: a new generation of anti-doping biomarkers. *Anal Bioanal Chem.* 2013;405(30):9617–9623.

Leuenberger N, Saugy M. Circulating microRNAs: the future of biomarkers in anti-doping field. *Adv Exp Med Biol.* 2015;888:401–408.

Haberberger A, Kirchner B, Riedmaier I, et al. Changes in the microRNA expression profile during blood storage. *BMJ Open Sport Exerc Med.* 2018;4(1), e000354.

Ponzetto F, Giraud S, Leuenberger N, et al. Methods for doping detection. *Front Horm Res.* 2016;47:153–167.

Kaid C, Assoni A, Marçola M, et al. Proteome and miRNome profiling of microvesicles derived from medulloblastoma cell lines with stem-like properties reveals biomarkers of poor prognosis. *Brain Res.* 1730;2020:146646.

Baraniskin A, Kuhnhenh J, Schlegel U, et al. Identification of microRNAs in the cerebrospinal fluid as biomarker for the diagnosis of glioma. *Neuro-Oncology.* 2012;14(1):29–33.

Teplyuk NM, Mollenhauer B, Gabriely G, et al. MicroRNAs in cerebrospinal fluid identify glioblastoma and metastatic brain cancers and reflect disease activity. *Neuro-Oncology.* 2012;14(6):689–700.

Sheinerman KS, Umansky SR. Circulating cell-free microRNA as biomarkers for screening, diagnosis and monitoring of neurodegenerative diseases and other neurologic pathologies. *Front Cell Neurosci.* 2013;7:150.

Zhao Y, Zhang Y, Zhang L, Dong Y, Ji H, Shen L. The potential markers of circulating microRNAs and long non-coding RNAs in Alzheimer's disease. *Aging Dis.* 2019;10(6):1293–1301.

Gupta P, Bhattacharjee S, Sharma AR, Sharma G, Lee SS, Chakraborty C. miRNAs in Alzheimer disease – a therapeutic perspective. *Curr Alzheimer Res.* 2017;14(11):1198–1206.

Muñoz-San Martín M, Reverter G, Robles-Cedeño R, et al. Analysis of miRNA signatures in CSF identifies up-regulation of miR-21 and miR-146a/b in patients with multiple sclerosis and active lesions. *J Neuroinflammation.* 2019;16(1):220.

Mendes FC, Paciência I, Ferreira AC, et al. Development and validation of exhaled breath condensate microRNAs to identify and endotype asthma in children. *PLoS One.* 2019;14(11), e0224983.

Sinha A, Yadav AK, Chakraborty S, et al. Exosome-enclosed microRNAs in exhaled breath hold potential for biomarker discovery in patients with pulmonary diseases. *J Allergy Clin Immunol.* 2013;132(1):219–222.

Pinkerton M, Chinchilli V, Banta E, et al. Differential expression of microRNAs in exhaled breath condensates of patients with asthma, patients with chronic obstructive pulmonary disease, and healthy adults. *J Allergy Clin Immunol.* 2013;132(1):217–219.

Mozzoni P, Banda I, Goldoni M, et al. Plasma and EBC microRNAs as early biomarkers of non-small-cell lung cancer. *Biomarkers.* 2013;18(8):679–686.

Gallo A, Alevizos I. Isolation of circulating microRNA in saliva. *Methods Mol Biol.* 2013;1024:183–190.

Patil S, Arakeri G, Alamir AWH, et al. Role of salivary transcriptomics as potential biomarkers in oral cancer: a systematic review. *J Oral Pathol Med.* 2019;48(10):871–879.

Nowicka Z, Stawiski K, Tomasik B, Fendler W. Extracellular miRNAs as biomarkers of head and neck cancer progression and metastasis. *Int J Mol Sci.* 2019;20(19), E4799.

- Hoseok I, Cho JY. Lung cancer biomarkers. *Adv Clin Chem.* 2015;72:107–170.
- Nisha KJ, Janam P, Harshakumar K. Identification of a novel salivary biomarker miR-143-3p for periodontal diagnosis: a proof of concept study. *J Periodontol.* 2019;90(10):1149–1159.
- Bagheri A, Khorram Khorshid HR, Mowla SJ, et al. Altered miR-223 expression in sputum for diagnosis of non-small cell lung cancer. *Avicenna J Med Biotechnol.* 2017;9(4):189–195.
- Sriram KB, Relan V, Clarke BE, et al. Diagnostic molecular biomarkers for malignant pleural effusions. *Future Oncol.* 2011;7(6):737–752.
- Qian Q, Sun W, Zhu W, et al. The role of microRNA-93 regulating angiopoietin2 in the formation of malignant pleural effusion. *Cancer Med.* 2017;6(5):1036–1048.
- Ohzawa H, Kumagai Y, Yamaguchi H, et al. Exosomal microRNA in peritoneal fluid as a biomarker of peritoneal metastases from gastric cancer. *Ann Gastroenterol Surg.* 2019;4(1):84–93.
- Mari-Alexandre J, Barceló-Molina M, Belmonte-López E, et al. Micro-RNA profile and proteins in peritoneal fluid from women with endometriosis: their relationship with sterility. *Fertil Steril.* 2018;109(4):675–684.
- Ferracin M, Lupini L, Salamon I, et al. Absolute quantification of cell-free microRNAs in cancer patients. *Oncotarget.* 2015;6(16):14545–14555.
- Finotti A, Allegretti M, Gasparello J, et al. Liquid biopsy and PCR-free ultrasensitive detection systems in oncology (Review). *Int J Oncol.* 2018;53(4):1395–1434.
- Zhao Y, Song Y, Yao L, Song G, Teng C. Circulating microRNAs: promising biomarkers involved in several cancers and other diseases. *DNA Cell Biol.* 2017;36(2):77–94.
- Desmond BJ, Dennett ER, Danielson KM. Circulating extracellular vesicle microRNA as diagnostic biomarkers in early colorectal cancer—a review. *Cancers (Basel).* 2019;12(1), E52.
- Galardi A, Colletti M, Di Paolo V, et al. Exosomal MiRNAs in pediatric cancers. *Int J Mol Sci.* 2019;20(18), E4600.
- Blondal T, Jensby Nielsen S, Baker A, et al. Assessing sample and miRNA profile quality in serum and plasma or other biofluids. *Methods.* 2013;59(1):S1–S6.
- Zhu L, Liu F, Xie H, Feng J. Diagnostic performance of microRNA-133a in acute myocardial infarction: a meta-analysis. *Cardiol J.* 2018;25(2):260–267.
- Guarino E, Delli Poggi C, Grieco GE, et al. Circulating microRNAs as biomarkers of gestational diabetes mellitus: updates and perspectives. *Int J Endocrinol.* 2018;2018:6380463.
- Salloum-Asfar S, Satheesh NJ, Abdulla SA. Circulating miRNAs, small but promising biomarkers for autism spectrum disorder. *Front Mol Neurosci.* 2019;12:253.
- Sun IO, Lerman LO. Urinary microRNA in kidney disease: utility and roles. *Am J Physiol Renal Physiol.* 2019;316(5):F785–F793.
- Kutwin P, Konecki T, Borkowska EM, Traczyk-Borszyńska M, Jabłonowski Z. Urine miRNA as a potential biomarker for bladder cancer detection – a meta-analysis. *Cent European J Urol.* 2018;71(2):177–185.
- Hosseini M, Khatamianfar S, Hassanian SM, et al. Exosome-encapsulated microRNAs as potential circulating biomarkers in colon cancer. *Curr Pharm Des.* 2017;23(11):1705–1709.
- Yau TO, Wu CW, Dong Y, et al. microRNA-221 and microRNA-18a identification in stool as potential biomarkers for the non-invasive diagnosis of colorectal carcinoma. *Br J Cancer.* 2014;111(9):1765–1771.
- Liu T, Cheng W, Gao Y, Wang H, Liu Z. Microarray analysis of microRNA expression patterns in the semen of infertile men with semen abnormalities. *Mol Med Rep.* 2012;6(3):535–542.
- Barceló M, Mata A, Bassas L, Larriba S. Exosomal microRNAs in seminal plasma are markers of the origin of azoospermia and can predict the presence of sperm in testicular tissue. *Hum Reprod.* 2018;33(6):1087–1098.
- Li YH, Tavallae G, Tokar T, et al. Identification of synovial fluid microRNA signature in knee osteoarthritis: differentiating early- and late-stage knee osteoarthritis. *Osteoarthr Cartil.* 2016;24(9):1577–1586.
- Yin CM, Suen WC, Lin S, Wu XM, Li G, Pan XH. Dysregulation of both miR-140-3p and miR-140-5p in synovial

fluid correlate with osteoarthritis severity. *Bone Joint Res.* 2017;6(11):612–618.

Leuenberger N, Jan N, Pradervand S, Robinson N, Saugy M. Circulating microRNAs as long-term biomarkers for the detection of erythropoiesis-stimulating agent abuse. *Drug Test Anal.* 2011;3(11–12):771–776.

Salamin O, Jaggi L, Baume N, Robinson N, Saugy M, Leuenberger N. Circulating microRNA-122 as potential biomarker for detection of testosterone abuse. *PLoS One.* 2016;11(5), e0155248.

Kelly BN, Haverstick DM, Lee JK, et al. Circulating microRNA as a biomarker of human growth hormone administration to patients. *Drug Test Anal.* 2014;6(3):234–238.

Marchand A, Roulland I, Semence F, Schröder K, Domergue V, Audran M. Detection of hypoxia-regulated microRNAs in blood as potential biomarkers of HIF Stabilizer Molidustat. *MicroRNA.* 2019;8(3):189–197.

Leuenberger N, Schumacher YO, Pradervand S, Sander T, Saugy M, Pottgiesser T. Circulating microRNAs as biomarkers for detection of autologous blood transfusion. *PLoS One.* 2013;8(6), e66309.

Donati F, Boccia F, de la Torre X, Stampella A, Botrè F. *MicroRNA Analysis for the Detection of Autologous Blood Transfusion in Doping Control.* Agilent Technologies; 2015.

Gasparello J, Lamberti N, Papi C, et al. Altered erythroid-related miRNA levels as a possible novel biomarker for detection of autologous blood transfusion misuse in sport. *Transfusion.* 2019;59(8):2709–2721.

Kenny A, Jiménez-Mateos EM, Zea-Sevilla MA, et al. Proteins and microRNAs are differentially expressed in tear fluid from patients with Alzheimer's disease. *Sci Rep.* 2019;9(1):15437.

Segura MF, Belitskaya-Lévy I, Rose AE, et al. Melanoma microRNA signature predicts post-recurrence survival. *Clin Cancer Res.* 2010;16(5):1577–1586.

Lecellier CH, Dunoyer P, Arar K, et al. A cellular microRNA mediates antiviral defense in human cells. *Science.* 2005;308(5721):557–560.

van Rooij E, Sutherland LB, Liu N, et al. A signature pattern of stress-responsive microRNAs that can evoke cardiac hypertrophy and heart failure. *Proc Natl Acad Sci U S A.* 2006;103(48):18255–18260.

Eisenberg I, Eran A, Nishino I, et al. Distinctive patterns of microRNA expression in primary muscular disorders. *Proc Natl Acad Sci U S A.* 2007;104(43):17016–17021.

Gasparello J, Fabbri E, Bianchi N, et al. BCL11A mRNA targeting by miR-210: a possible network regulating γ -globin gene expression. *Int J Mol Sci.* 2017;18(12):2530.

Wang J, Chen J, Sen S. MicroRNA as biomarkers and diagnostics. *J Cell Physiol.* 2016;231(1):25–30.

Correia CN, Nalpas NC, McLoughlin KE, Browne JA, Gordon SV, MacHugh DE. Circulating microRNAs as potential biomarkers of infectious disease. *Front Immunol.* 2017;8:118.

Watier T, Mj Sanchez A. Micro-RNAs, exercise and cellular plasticity in humans: the impact of dietary factors and hypoxia. *MicroRNA.* 2017;6(2):110–124.

Alquraini H, Auchus RJ. Strategies that athletes use to avoid detection of androgenic-anabolic steroid doping and sanctions. *Mol Cell Endocrinol.* 2018;464:28–33.

Sessa F, Salerno M, Di Mizio G, et al. Anabolic androgenic steroids: searching new molecular biomarkers. *Front Pharmacol.* 2018;9:1321.

Holt RIG, Ho KKY. The use and abuse of growth hormone in sports. *Endocr Rev.* 2019;40(4):1163–1185.

Sonksen PH, Cowan D, Holt RI. Use and misuse of hormones in sport. *Lancet Diabetes Endocrinol.* 2016;4(11):882–883.

Nallamshetty S, Chan SY, Loscalzo J. Hypoxia: a master regulator of microRNA biogenesis and activity. *Free Radic Biol Med.* 2013;64:20–30.

Greco S, Martelli F. MicroRNAs in hypoxia response. *Antioxid Redox Signal.* 2014;21(8):1164–1166.

Bertero T, Rezzonico R, Pottier N, Mari B. Impact of microRNAs in the cellular response to hypoxia. *Int Rev Cell Mol Biol.* 2017;333:91–158.

Turunen TA, Roberts TC, Laitinen P, et al. Changes in nuclear and cytoplasmic microRNA distribution in response

to hypoxic stress. *Sci Rep.* 2019;9(1):10332.

Lamon S, Giraud S, Egli L, et al. A high-throughput test to detect C.E.R.A. doping in blood. *J Pharm Biomed Anal.* 2009;50(5):954–958.

Leuenberger N, Lamon S, Robinson N, Giraud S, Saugy M. How to confirm C.E.R.A. doping in athletes' blood? *Forensic Sci Int.* 2011;213(1–3):101–103.

World Anti-Doping Agency. 2018 List of Prohibited Substances and Methods. <https://www.wada-ama.org/en/content/what-is-prohibited>. Accessed 14 February 2017.

Jelkmann W, Lundby C. Blood doping and its detection. *Blood.* 2011;118(9):2395–2404.

Mørkeberg J. Detection of autologous blood transfusions in athletes: a historical perspective. *Transfus Med Rev.* 2012;26(3):199–208.

Segura J, Lundby C. Blood doping: potential of blood and urine sampling to detect autologous transfusion. *Br J Sports Med.* 2014;48(10):837–841.

Segura J, Monfort N, Ventura R. Detection methods for autologous blood doping. *Drug Test Anal.* 2012;4(11):876–881.

Gore CJ, Parisotto R, Ashenden MJ, et al. Second-generation blood tests to detect erythropoietin abuse by athletes. *Haematologica.* 2003;88(3):333–344.

Pottgiesser T, Sottas PE, Echter T, Robinson N, Umhau M, Schumacher YO. Detection of autologous blood doping with adaptively evaluated biomarkers of doping: a longitudinal blinded study. *Transfusion.* 2011;51(8):1707–1715.

Schumacher YO, Saugy M, Pottgiesser T, Robinson N. Detection of EPO doping and blood doping: the haematological module of the Athlete Biological Passport. *Drug Test Anal.* 2012;4(11):846–853.

Malm CB, Khoo NS, Granlund I, Lindstedt E, Hult A. Autologous doping with cryopreserved red blood cells – effects on physical performance and detection by multivariate statistics. *PLoS One.* 2016;11, e0156157.

Damsgaard R, Munch T, Mørkeberg J, Mortensen SP, González-Alonso J. Effects of blood withdrawal and reinfusion on biomarkers of erythropoiesis in humans: implications for antidoping strategies. *Haematologica.* 2006;91(7):1006–1008.

Leuenberger N, Barras L, Nicoli R, et al. Hcpicidin as a new biomarker for detecting autologous blood transfusion. *Am J Hematol.* 2016;91(5):467–472.

Leuenberger N, Barras L, Nicoli R, et al. Urinary di-(2-ethylhexyl) phthalate metabolites for detecting transfusion of autologous blood stored in plasticizer-free bags. *Transfusion.* 2016;56(3):571–578.

Lamberti N, Finotti A, Gasparello J, et al. Changes in hemoglobin profile reflect autologous blood transfusion misuse in sports. *Intern Emerg Med.* 2018;13(4):517–526.

Noren Hooten N, Fitzpatrick M, Wood 3rd WH, et al. Age-related changes in microRNA levels in serum. *Aging (Albany, NY).* 2013;5(10):725–740.

Faraldi M, Sansoni V, Perego S, et al. Study of the preanalytical variables affecting the measurement of clinically relevant free-circulating microRNAs: focus on sample matrix, platelet depletion, and storage conditions. *Biochem Med (Zagreb).* 2020;30(1), 010703.

Feng X, Liu Y, Wan N. Plasma microRNA detection standardization test. *J Clin Lab Anal.* 2020;34(2), e23058.

Glinge C, Clauss S, Boddum K, et al. Stability of circulating blood-based microRNAs – pre-analytical methodological considerations. *PLoS One.* 2017;12(2), e0167969.

Aiso T, Takigami S, Yamaki A, Ohnishi H. Degradation of serum microRNAs during transient storage of serum samples at 4°C. *Ann Clin Biochem.* 2018;55(1):178–180.

Lombardi G, Perego S, Sansoni V, Banfi G. Circulating miRNA as fine regulators of the physiological responses to physical activity: pre-analytical warnings for a novel class of biomarkers. *Clin Biochem.* 2016;49(18):1331–1339.

Chen X, Xie X, Xing Y, Yang X, Yuan Z, Wei Y. MicroRNA dysregulation associated with red blood cell storage. *Transfus Med Hemother.* 2018;45(6):397–402.

Silva FCD, Iop RDR, Andrade A, Cořta VP, Gutierrez Filho PJB, Silva RD. Effects of physical exercise on the expression of microRNAs: a systematic review. *J Strength Cond Res.* 2020;34(1):270–280.

Bao F, Slusher AL, Whitehurst M, Huang CJ. Circulating microRNAs are upregulated following acute aerobic exercise in obese individuals. *Physiol Behav.* 2018;197:15–21.

Zhao J, Qiao CR, Ding Z, et al. A novel pathway in NSCLC cells: miR 191, targeting NFIA, is induced by chronic hypoxia, and promotes cell proliferation and migration. *Mol Med Rep.* 2017;15(3):1319–1325.

Nagpal N, Ahmad HM, Chameettachal S, Sundar D, Ghosh S, Kulshreshtha R. HIF-inducible miR191 promotes migration in breast cancer through complex regulation of TGF β -signaling in hypoxic microenvironment. *Sci Rep.* 2015;5:9650.

Song Z, Ren H, Gao S, Zhao X, Zhang H, Hao J. The clinical significance and regulation mechanism of hypoxia-inducible factor-1 and miR-191 expression in pancreatic cancer. *Tumour Biol.* 2014;35(11):11319–11328.

Liu N, Hargreaves VV, Zhu Q, et al. Direct promoter repression by BCL11A controls the fetal to adult hemoglobin switch. *Cell.* 2018;173(2):430–442. e17.

Finotti A, Gasparello J, Breveglieri G, et al. Development and characterization of K562 cell clones expressing BCL11A-XL: decreased hemoglobin production with fetal hemoglobin inducers and its rescue with mithramycin. *Exp Hematol.* 2015;43(12):1062–1071. e3.

Sankaran VG, Menne TF, Xu J, et al. Human fetal hemoglobin expression is regulated by the developmental stage-specific repressor BCL11A. *Science.* 2008;322(5909):1839–1842.

Lulli V, Romania P, Morsilli O, et al. MicroRNA-486-3p regulates γ -globin expression in human erythroid cells by directly modulating BCL11A. *PLoS One.* 2013;8(4), e60436.

Chapter 14

Montgomery HE, Marshall R, Hemingway H, et al. Human gene for physical performance. *Nature.* 1998;393(6682):221–222. <https://doi.org/10.1038/30374>.

Cieszczyk P, Krupecki K, Maciejewska A, Sawczuk M. The angiotensin converting enzyme gene I/D polymorphism in Polish rowers. *Int J Sports Med.* 2009;30(8):624–627. <https://doi.org/10.1055/s-0029-1202825>.

Puthuchery Z, Skipworth JR, Rawal J, Loosemore M, Van Someren K, Montgomery HE. The ACE gene and human performance: 12 years on. *Sports Med.* 2011;41(6):433–448. <https://doi.org/10.2165/11588720-000000000-00000>.

Papadimitriou ID, Lockey SJ, Voisin S, et al. No association between ACTN3 R577X and ACE I/D polymorphisms and endurance running times in 698 Caucasian athletes. *BMC Genomics.* 2018;19(1):13. <https://doi.org/10.1186/s12864-017-4412-0>.

Grealy R, Herruer J, Smith CL, Hiller D, Haseler LJ, Griffiths LR. Evaluation of a 7-gene genetic profile for athletic endurance phenotype in Ironman Championship triathletes. *PLoS One.* 2015;10(12):e0145171. <https://doi.org/10.1371/journal.pone.0145171>.

Ash GI, Scott RA, Deason M, et al. No association between ACE gene variation and endurance athlete status in Ethiopians. *Med Sci Sports Exerc.* 2011;43(4):590–597. <https://doi.org/10.1249/MSS.0b013e3181f70bd6>.

Raleigh SM. Epigenetic regulation of the ACE gene might be more relevant to endurance physiology than the I/D polymorphism. *J Appl Physiol (1985).* 2012;112(6):1082–1083. <https://doi.org/10.1152/jappphysiol.00828.2011>.

Riviere G, Lienhard D, Andrieu T, Vieau D, Frey BM, Frey FJ. Epigenetic regulation of somatic angiotensin-converting enzyme by DNA methylation and histone acetylation. *Epigenetics.* 2011;6(4):478–489. doi:14961.

Rotroff DM. A bioinformatics crash course for interpreting genomics data. *Chest.* 2020;158(1S):S113–S123. doi:S0012-3692(20)30449-9 [pii].

Rankinen T, Fuku N, Wolfarth B, et al. No evidence of a common DNA variant profile specific to world class endurance athletes. *PLoS One.* 2016;11(1):e0147330 [Published 2016 Jan 29] <https://doi.org/10.1371/journal.pone.0147330>.

Schranner D, Kaštenmüller G, Schönfelder M, Romisch-Margl W, Wackerhage H. Metabolite concentration changes in humans after a bout of exercise: a systematic review of exercise metabolomics studies. *Sports Med Open*. 2020;6(1):11–14. <https://doi.org/10.1186/s40798-020-0238-4>.

Fabre O, Ingerslev LR, Garde C, Donkin I, Simar D, Barres R. Exercise training alters the genomic response to acute exercise in human adipose tissue. *Epigenomics*. 2018;10(8):1033–1050. <https://doi.org/10.2217/epi-2018-0039>.

Butts B, Butler J, Dunbar SB, Corwin E, Gary RA. Effects of exercise on ASC methylation and IL-1 cytokines in heart failure. *Med Sci Sports Exerc*. 2018;50(9):1757–1766. <https://doi.org/10.1249/MSS.0000000000001641>.

Atif H, Hicks SD. A review of MicroRNA biomarkers in traumatic brain injury. *J Exp Neurosci*. 2019;13. <https://doi.org/10.1177/1179069519832286>. 1179069519832286.

Brennan GP, Henshall DC. MicroRNAs as regulators of brain function and targets for treatment of epilepsy. *Nat Rev Neurol*. 2020. <https://doi.org/10.1038/s41582-020-0369-8>.

Alibegovic AC, Sonne MP, Hojbjerg L, et al. Insulin resistance induced by physical inactivity is associated with multiple transcriptional changes in skeletal muscle in young men. *Am J Physiol Endocrinol Metab*. 2010;299(5):752. <https://doi.org/10.1152/ajpendo.00590.2009>.

Denham J, Marques FZ, Bruns EL, O'Brien BJ, Charchar FJ. Epigenetic changes in leukocytes after 8 weeks of resistance exercise training. *Eur J Appl Physiol*. 2016;116(6):1245–1253. <https://doi.org/10.1007/s00421-016-3382-2>.

Nocon M, Hiemann T, Müller-Riemenschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. *Eur J Cardiovasc Prev Rehabil*. 2008;15(3):239–246. <https://doi.org/10.1097/HJR.0b013e3282f55e09>.

Axson JE, Libonati JR. Impact of parental exercise on epigenetic modifications inherited by offspring: a systematic review. *Physiol Rep*. 2019;7(22):e14287. <https://doi.org/10.14814/phy2.14287>.

Lightfoot AP, McCormick R, Nye GA, McArdle A. Mechanisms of skeletal muscle ageing; avenues for therapeutic intervention. *Curr Opin Pharmacol*. 2014;16:116–121. <https://doi.org/10.1016/j.coph.2014.05.005>.

Faienza MF, Lassandro G, Chiarito M, Valente F, Ciaccia L, Giordano P. How physical activity across the lifespan can reduce the impact of bone ageing: a literature review. *Int J Environ Res Public Health*. 2020;17(6). <https://doi.org/10.3390/ijerph17061862>. doi:E1862 [pii].

Thomas ET, Guppy M, Straus SE, Bell KJL, Glasziou P. Rate of normal lung function decline in ageing adults: a systematic review of prospective cohort studies. *BMJ Open*. 2019;9(6):e028150. <https://doi.org/10.1136/bmjopen-2018-028150>.

Hurley M, Dickson K, Hallett R, et al. Exercise interventions and patient beliefs for people with hip, knee or hip and knee osteoarthritis: a mixed methods review. *Cochrane Database Syst Rev*. 2018;4:CD010842. <https://doi.org/10.1002/14651858.CD010842.pub2>.

Sunny SK, Zhang H, Rezwani FI, et al. Changes of DNA methylation are associated with changes in lung function during adolescence. *Respir Res*. 2020;21(1):80. <https://doi.org/10.1186/s12931-020-01342-y>.

Mukherjee N, Lockett GA, Merid SK, et al. DNA methylation and genetic polymorphisms of the leptin gene interact to influence lung function outcomes and asthma at 18 years of age. *Int J Mol Epidemiol Genet*. 2016;7(1):1–17.

Ryan J, Wrigglesworth J, Loong J, Fransquet PD, Woods RL. A systematic review and meta-analysis of environmental, lifestyle, and health factors associated with DNA methylation age. *J Gerontol A Biol Sci Med Sci*. 2020;75(3):481–494. <https://doi.org/10.1093/gerona/glz099>.

Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol*. 2020;5(4):536–544. <https://doi.org/10.1038/s41564-020-0695-z>.

Vabret N, Britton GJ, Gruber C, et al. Immunology of COVID-19: current state of the science. *Immunity*. 2020;52(6):910–941. <https://doi.org/10.1016/j.immuni.2020.05.002>.

Horowitz RI, Freeman PR. Three novel prevention, diagnostic, and treatment options for COVID-19 urgently ne-

cessitating controlled randomized trials. *Med Hypotheses*. 2020;143:109851. doi:S0306-9877(20)30827-6 [pii].

Raoult D, Zumla A, Locatelli F, Ippolito G, Kroemer G. Coronavirus infections: epidemiological, clinical and immunological features and hypotheses. *Cell Stress*. 2020;4(4):66–75 [Published 2020 Mar 2] 10.15698/cst2020.04.216.

Prete M, Favoino E, Catacchio G, Racanelli V, Perosa F. SARS-CoV-2 inflammatory syndrome. clinical features and rationale for immunological treatment. *Int J Mol Sci*. 2020;21(9). <https://doi.org/10.3390/ijms21093377>. doi:E3377 [pii].

Lu L, Zhong W, Bian Z, et al. A comparison of mortality-related risk factors of COVID-19, SARS, and MERS: a systematic review and meta-analysis. *J Infect*. 2020. doi:S0163-4453(20)30460-6 [pii].

Vepa A, Bae JP, Ahmed F, Pareek M, Khunti K. COVID-19 and ethnicity: A novel pathophysiological role for inflammation. *Diabetes Metab Syndr*. 2020;14(5):1043–1051. doi:S1871-4021(20)30225-3 [pii].

Lighter J, Phillips M, Hochman S, et al. Obesity in patients younger than 60 years is a risk factor for covid-19 hospital admission. *Clin Infect Dis*. 2020. doi:ciaa415 [pii].

Pedersen BK, Toft AD. Effects of exercise on lymphocytes and cytokines. *Br J Sports Med*. 2000;34(4):246–251. <https://doi.org/10.1136/bjism.34.4.246>.

Cao Dinh H, Beyer I, Mets T, et al. Effects of physical exercise on markers of cellular immunosenescence: a systematic review. *Calcif Tissue Int*. 2017;100(2):193–215. <https://doi.org/10.1007/s00223-016-0212-9>.

Sellami M, Gasmii M, Denham J, et al. Effects of acute and chronic exercise on immunological parameters in the elderly aged: can physical activity counteract the effects of aging? *Front Immunol*. 2018;9:2187. <https://doi.org/10.3389/fimmu.2018.02187>.

Zbinden-Foncea H, Francaux M, Deldicque L, Hawley JA. Does high cardiorespiratory fitness confer some protection against pro-inflammatory responses after infection by SARS-CoV-2? *Obesity (Silver Spring)*. 2020. <https://doi.org/10.1002/oby.22849>.

Fan R, Mao SQ, Gu TL, et al. Preliminary analysis of the association between methylation of the ACE2 promoter and essential hypertension. *Mol Med Rep*. 2017;15(6):3905–3911. <https://doi.org/10.3892/mmr.2017.6460>.

Pinto BGG, Oliveira AER, Singh Y, et al. ACE2 expression is increased in the lungs of patients with comorbidities associated with severe COVID-19. *J Infect Dis*. 2020. doi:jjaa332 [pii].

Echeverria-Rodriguez O, Gallardo-Ortiz IA, Del Valle-Mondragon L, Villalobos-Molina R. Angiotensin-(1-7) participates in enhanced skeletal muscle insulin sensitivity after a bout of exercise. *J Endocr Soc*. 2020;4(2):bvaa007. <https://doi.org/10.1210/jendso/bvaa007>.

Biemont C. From genotype to phenotype. What do epigenetics and epigenomics tell us? *Heredity (Edinb)*. 2010;105(1):1–3. <https://doi.org/10.1038/hdy.2010.66>.

Perry MM, Moschos SA, Williams AE, Shepherd NJ, Larner-Svensson HM, Lindsay MA. Rapid changes in microRNA-146a expression negatively regulate the IL-1beta-induced inflammatory response in human lung alveolar epithelial cells. *J Immunol*. 2008;180(8):5689–5698. doi:180/8/5689 [pii].

Kim HJ, Seo EH, Bae DH, et al. Methylation of the CDX2 promoter in H. pylori-infected gastric mucosa increases with age and its rapid demethylation in gastric tumors is associated with upregulated gene expression. *Carcinogenesis*. 2020;41:1341–1352. doi:bgaa083 [pii].

Barter MJ, Cheung K, Falk J, et al. Dynamic chromatin accessibility landscape changes following interleukin-1 stimulation. *Epigenetics*. 2020;1–14. <https://doi.org/10.1080/15592294.2020.1789266>.

Jorgensen RA. Epigenetics: biology's quantum mechanics. *Front Plant Sci*. 2011;2:10. <https://doi.org/10.3389/fpls.2011.00010>.

