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Novel insights into blood markers and cardiovascular disease: Results of the Netherlands Epidemiology of Obesity study

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REFERENCES

1. WHO, *Global status report on noncommunicable diseases 2014*. 2014, World Health Organization, Geneva, Switzerland.
2. CBS. *StatLine - Overledenen; doodsoorzaak (uitgebreide lijst), leeftijd, geslacht*. 2016 16-03-2018]; Available from: https://opendata.cbs.nl/statline/#/CBS/nl/dataset/7052_95/table?ts=1513242094737.
3. Libby, P. and G.K. Hansson, *Inflammation and immunity in diseases of the arterial tree: players and layers*. *Circ Res*, 2015. 116(2): p. 307-11.
4. Bennett, M.R., S. Sinha, and G.K. Owens, *Vascular Smooth Muscle Cells in Atherosclerosis*. *Circulation Research*, 2016. 118(4): p. 692-702.
5. Bot, I., et al., *Atorvastatin inhibits plaque development and adventitial neovascularization in ApoE deficient mice independent of plasma cholesterol levels*. *Atherosclerosis*, 2011. 214(2): p. 295-300.
6. Moulton, K.S., et al., *Inhibition of plaque neovascularization reduces macrophage accumulation and progression of advanced atherosclerosis*. *Proceedings of the National Academy of Sciences of the United States of America*, 2003. 100(8): p. 4736-4741.
7. Davignon, J. and P. Ganz, *Role of endothelial dysfunction in atherosclerosis*. *Circulation*, 2004. 109(23): p. 27-32.
8. White, S.J., A.C. Newby, and T.W. Johnson, *Endothelial erosion of plaques as a substrate for coronary thrombosis*. *Thrombosis and Haemostasis*, 2016. 115(3): p. 509-519.
9. Shaw, L.J., R. Bugiardini, and C.N.B. Merz, *Women and Ischemic Heart Disease Evolving Knowledge*. *Journal of the American College of Cardiology*, 2009. 54(17): p. 1561-1575.
10. Arnett, E.N. and W.C. Roberts, *Acute Myocardial-Infarction and Angiographically Normal Coronary-Arteries - Unproven Combination*. *Circulation*, 1976. 53(3): p. 395-400.
11. Li, C., et al., *Incidence of ischemic stroke in relation to asymptomatic carotid artery atherosclerosis in subjects with normal blood pressure. A prospective cohort study*. *Cerebrovasc Dis*, 2008. 26(3): p. 297-303.
12. Hamdy, O., S. Porramatikul, and E. Al-Ozairi, *Metabolic obesity: the paradox between visceral and subcutaneous fat*. *Curr Diabetes Rev*, 2006. 2(4): p. 367-73.
13. Kannel, W.B., et al., *Factors of Risk in Development of Coronary Heart Disease - 6-Year Follow-up Experience*. *Annals of Internal Medicine*, 1961. 55(1): p. 33-+.
14. Yusuf, S., et al., *Global burden of cardiovascular diseases - Part I: General considerations, the epidemiologic transition, risk factors, and impact of urbanization*. *Circulation*, 2001. 104(22): p. 2746-2753.
15. Hubert, H.B., et al., *Obesity as an Independent Risk Factor for Cardiovascular-Disease - a 26-Year Follow-up of Participants in the Framingham Heart-Study*. *Circulation*, 1983. 67(5): p. 968-977.
16. VWS, M.v., *Hoeveel mensen hebben overgewicht?* (Available at: <https://www.volksgezondheidenzorg.info/onderwerp/overgewicht/cijfers-context/huidige-situatie>. Accessed December 20, 2016), 2013.
17. Neeland, I.J., et al., *Body Fat Distribution and Incident Cardiovascular Disease in Obese Adults*. *Journal of the American College of Cardiology*, 2015. 65(19): p. 2150-2151.
18. Lu, Y., et al., *Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1.8 million participants*. *Lancet*, 2014. 383(9921): p. 970-83.

19. Ridker, P.M., LDL cholesterol: controversies and future therapeutic directions. *Lancet*, 2014. 384(9943): p. 607-17.
20. Kuivenhoven, J.A., et al, The role of a common variant of the cholesteryl ester transfer protein gene in the progression of coronary atherosclerosis. The Regression Growth Evaluation Statin Study Group. *N Engl J Med*, 1998. 338(2): p. 86-93.
21. Lim, S., M.J. Quon, and K.K. Koh, Modulation of adiponectin as a potential therapeutic strategy. *Atherosclerosis*, 2014. 233(2): p. 721-728.
22. Libby, P., *Inflammation in Atherosclerosis. Arteriosclerosis Thrombosis and Vascular Biology*, 2012. 32(9): p. 2045-2051.
23. Van Harmelen, V., et al, Leptin secretion from subcutaneous and visceral adipose tissue in women. *Diabetes*, 1998. 47(6): p. 913-7.
24. Kern, P.A., et al, Adiponectin expression from human adipose tissue - Relation to obesity, insulin resistance, and tumor necrosis factor-alpha expression. *Diabetes*, 2003. 52(7): p. 1779-1785.
25. Samaras, K., et al, Subcutaneous and Visceral Adipose Tissue Gene Expression of Serum Adipokines That Predict Type 2 Diabetes. *Obesity*, 2010. 18(5): p. 884-889.
26. Guenther, M., et al, Adiposity distribution influences circulating adiponectin levels. *Translational Research*, 2014. 164(4): p. 270-277.
27. Zhu, N., et al, High-Molecular-Weight Adiponectin and the Risk of Type 2 Diabetes in the ARIC Study. *The Journal of Clinical Endocrinology & Metabolism*, 2010. 95(11): p. 5097-5104.
28. Zhao, L., et al, Globular adiponectin ameliorates metabolic insulin resistance via AMPK-mediated restoration of microvascular insulin responses. *J Physiol*, 2015. 593(17): p. 4067-79.
29. Cowley, M.A., et al, Leptin activates anorexigenic POMC neurons through a neural network in the arcuate nucleus. *Nature*, 2001. 411(6836): p. 480-4.
30. Csongradi, E., et al, Adipokines as atherothrombotic risk factors in obese subjects: Associations with haemostatic markers and common carotid wall thickness. *Nutrition Metabolism and Cardiovascular Diseases*, 2017. 27(6): p. 571-580.
31. Eikelis, N., et al, Interactions between leptin and the human sympathetic nervous system. *Hypertension*, 2003. 41(5): p. 1072-1079.
32. Kohara, K., et al, Clinical characteristics of high plasma adiponectin and high plasma leptin as risk factors for arterial stiffness and related end-organ damage. *Atherosclerosis*, 2014. 235(2): p. 424-9.
33. Lambert, G., et al, Early Regression of Carotid Intima-Media Thickness after Bariatric Surgery and Its Relation to Serum Leptin Reduction. *Obes Surg*, 2017.
34. Pandey, A., et al, Arterial Stiffness and Risk of Overall Heart Failure, Heart Failure With Preserved Ejection Fraction, and Heart Failure With Reduced Ejection Fraction The Health ABC Study (Health, Aging, and Body Composition). *Hypertension*, 2017. 69(2): p. 267-+.
35. Tyrrell, P.N., et al, Rheumatic Disease and Carotid Intima-Media Thickness A Systematic Review and Meta-Analysis. *Arteriosclerosis Thrombosis and Vascular Biology*, 2010. 30(5): p. 1014-1026.
36. Svenungsson, E., et al, Risk factors for cardiovascular disease in systemic lupus erythematosus. *Circulation*, 2001. 104(16): p. 1887-1893.
37. Moore, K.J., F.J. Sheedy, and E.A. Fisher, Macrophages in atherosclerosis: a dynamic balance. *Nature Reviews Immunology*, 2013. 13(10): p. 709-721.

38. Tabas, I. and K.E. Bornfeldt, *Macrophage Phenotype and Function in Different Stages of Atherosclerosis*. *Circulation Research*, 2016. 118(4): p. 653-667.
39. Ridker, P.M., et al, *Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease*. *New England Journal of Medicine*, 2017. 377(12): p. 1119-1131.
40. Yudkin, J.S., et al, *C-reactive protein in wealthy subjects: Associations with obesity, insulin resistance, and endothelial dysfunction - A potential role for cytokines originating from adipose tissue? Arteriosclerosis Thrombosis and Vascular Biology*, 1999. 19(4): p. 972-978.
41. Cleeman, J.I., et al, *Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III)*. *Jama-Journal of the American Medical Association*, 2001. 285(19): p. 2486-2497.
42. Collaborators, C., *Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins (vol 366, pg 1267, 2005)*. *Lancet*, 2005. 366(9494): p. 1358-1358.
43. Schmidt, A.F., et al, *PCSK9 genetic variants and risk of type 2 diabetes: a mendelian randomisation study*. *Lancet Diabetes & Endocrinology*, 2017. 5(2): p. 97-105.
44. Sattar, N., et al, *Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials*. *Lancet*, 2010. 375(9716): p. 735-742.
45. Voight, B.F., et al, *Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study*. *Lancet*, 2012. 380(9841): p. 572-580.
46. Schwartz, G.G., et al, *Effects of Dalcetrapib in Patients with a Recent Acute Coronary Syndrome*. *New England Journal of Medicine*, 2012. 367(22): p. 2089-2099.
47. Nicholls, S.J., et al, *Assessment of the clinical effects of cholesteryl ester transfer protein inhibition with evacetrapib in patients at high-risk for vascular outcomes: Rationale and design of the ACCELERATE trial*. *American Heart Journal*, 2015. 170(6): p. 1061-1069.
48. Group, H.T.R.C., *Effects of Anacetrapib in Patients with Atherosclerotic Vascular Disease*. *N Engl J Med*, 2017.
49. Yu, Q., et al, *Association between TaqIB polymorphism of cholesteryl ester transfer protein and coronary artery disease in the Chinese population*. *J Zhejiang Univ Sci B*, 2012. 13(5): p. 342-7.
50. Kakko, S., et al, *Cholesteryl ester transfer protein gene polymorphisms are associated with carotid atherosclerosis in men*. *Eur J Clin Invest*, 2000. 30(1): p. 18-25.
51. Corsetti, J.P., et al, *LPL polymorphism (D9N) predicts cardiovascular disease risk directly and through interaction with CETP polymorphism (TaqIB) in women with high HDL cholesterol and CRP*. *Atherosclerosis*, 2011. 214(2): p. 373-6.
52. Langsted, A., J.J. Freiberg, and B.G. Nordestgaard, *Fasting and nonfasting lipid levels: influence of normal food intake on lipids, lipoproteins, apolipoproteins, and cardiovascular risk prediction*. *Circulation*, 2008. 118(20): p. 2047-56.
53. Zilversmit, D.B., *Atherogenesis: a postprandial phenomenon*. *Circulation*, 1979. 60(3): p. 473-85.
54. Seidell, J.C. and C. Bouchard, *Visceral fat in relation to health: is it a major culprit or simply an innocent bystander? International Journal of Obesity*, 1997. 21(8): p. 626-631.
55. Lemieux, S., et al, *Are Gender Differences in Cardiovascular-Disease Risk-Factors Explained by the Level of Visceral Adipose-Tissue*. *Diabetologia*, 1994. 37(8): p. 757-764.

56. Appelman, Y., et al., *Sex differences in cardiovascular risk factors and disease prevention. Atherosclerosis*, 2015. 241(1): p. 211-218.
57. Greenland, S. and H. Morgenstern, *Confounding in health research. Annual Review of Public Health*, 2001. 22: p. 189-212.
58. Burgess, S. and S.G. Thompson, *Multivariable Mendelian Randomization: The Use of Pleiotropic Genetic Variants to Estimate Causal Effects. American Journal of Epidemiology*, 2015. 181(4): p. 251-260.
59. de Mutsert, R., et al., *The Netherlands Epidemiology of Obesity (NEO) study: study design and data collection. Eur J Epidemiol*, 2013. 28(6): p. 513-23.
60. Korn, E.L. and B.I. Graubard, *Epidemiologic studies utilizing surveys: accounting for the sampling design. Am J Public Health*, 1991. 81(9): p. 1166-73.
61. Nikpay, M., et al., *A comprehensive 1000 Genomes-based genome-wide association meta-analysis of coronary artery disease. Nature Genetics*, 2015. 47(10): p. 1121-+.
62. Lab, N. September 25, 2018]; Available from: <http://www.nealelab.is/uk-biobank/>.
63. Kilpelainen, T.O., et al., *Genome-wide meta-analysis uncovers novel loci influencing circulating leptin levels. Nature Communications*, 2016. 7.
64. Dastani, Z., et al., *Novel Loci for Adiponectin Levels and Their Influence on Type 2 Diabetes and Metabolic Traits: A Multi-Ethnic Meta-Analysis of 45,891 Individuals. Plos Genetics*, 2012. 8(3).
65. Johansson, A., et al., *Genome-wide association and Mendelian randomization study of NT-proBNP in patients with acute coronary syndrome. Human Molecular Genetics*, 2016. 25(7): p. 1447-1456.
66. Wild, P.S., et al., *Large-scale genome-wide analysis identifies genetic variants associated with cardiac structure and function. Journal of Clinical Investigation*, 2017. 127(5): p. 1798-1812.
67. Willer, C.J., et al., *Discovery and refinement of loci associated with lipid levels. Nat Genet*, 2013. 45(11): p. 1274-1283.
68. Dale, C.E., et al., *Causal Associations of Adiposity and Body Fat Distribution With Coronary Heart Disease, Stroke Subtypes, and Type 2 Diabetes Mellitus A Mendelian Randomization Analysis. Circulation*, 2017. 135(24): p. 2373-+.
69. Recio-Rodriguez, J.I., et al., *Abdominal obesity vs general obesity for identifying arterial stiffness, subclinical atherosclerosis and wave reflection in healthy, diabetics and hypertensive. BMC Cardiovasc Disord*, 2012. 12: p. 3.
70. Fontes, J.D., et al., *Clinical correlates of change in inflammatory biomarkers: The Framingham Heart Study. Atherosclerosis*, 2013. 228(1): p. 217-23.
71. Gregor, M.F. and G.S. Hotamisligil, *Inflammatory mechanisms in obesity. Annu Rev Immunol*, 2011. 29: p. 415-45.
72. Brooks, G.C., M.J. Blaha, and R.S. Blumenthal, *Relation of C-reactive protein to abdominal adiposity. Am J Cardiol*, 2010. 106(1): p. 56-61.
73. Otvos, J.D., et al., *GlycA: A Composite Nuclear Magnetic Resonance Biomarker of Systemic Inflammation. Clinical Chemistry*, 2015. 61(5): p. 714-723.
74. Lawler, P.R., et al., *Circulating N-Linked Glycoprotein Acetyls and Longitudinal Mortality Risk. Circulation Research*, 2016. 118(7): p. 1106-1115.

75. Sattar, N., et al., *C-reactive protein and prediction of coronary heart disease and global vascular events in the prospective study of pravastatin in the elderly at risk (PROSPER)*. *Circulation*, 2007. 115(8): p. 981-989.
76. Yasmin, et al., *C-reactive protein is associated with arterial stiffness in apparently healthy individuals*. *Arterioscler Thromb Vasc Biol*, 2004. 24(5): p. 969-74.
77. Elliott, P., et al., *Genetic Loci Associated With C-Reactive Protein Levels and Risk of Coronary Heart Disease*. *Jama-Journal of the American Medical Association*, 2009. 302(1): p. 37-48.
78. Zacho, J., et al., *Genetically elevated C-reactive protein and ischemic vascular disease*. *New England Journal of Medicine*, 2008. 359(18): p. 1897-1908.
79. Jette, M., K. Sidney, and G. Blumchen, *Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity*. *Clin Cardiol*, 1990. 13(8): p. 555-65.
80. Christen, T., et al., *Mendelian randomization analysis of cholesteryl ester transfer protein and subclinical atherosclerosis: A population-based study*. *J Clin Lipidol*, 2017.
81. Soininen, P., et al., *Quantitative serum nuclear magnetic resonance metabolomics in cardiovascular epidemiology and genetics*. *Circ Cardiovasc Genet*, 2015. 8(1): p. 192-206.
82. McConkey, B., et al., *Effects of gold, dapsone, and prednisone on serum C-reactive protein and haptoglobin and the erythrocyte sedimentation rate in rheumatoid arthritis*. *Ann Rheum Dis*, 1979. 38(2): p. 141-4.
83. Tarp, S., et al., *Effect of nonsteroidal antiinflammatory drugs on the C-reactive protein level in rheumatoid arthritis: a meta-analysis of randomized controlled trials*. *Arthritis Rheum*, 2012. 64(11): p. 3511-21.
84. Baron, R.M. and D.A. Kenny, *The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations*. *J Pers Soc Psychol*, 1986. 51(6): p. 1173-82.
85. le Cessie, S., et al., *Quantification of bias in direct effects estimates due to different types of measurement error in the mediator*. *Epidemiology*, 2012. 23(4): p. 551-60.
86. Forouhi, N.G., N. Sattar, and P.M. McKeligue, *Relation of C-reactive protein to body fat distribution and features of the metabolic syndrome in Europeans and South Asians*. *International Journal of Obesity*, 2001. 25(9): p. 1327-1331.
87. Wensley, F., et al., *Association between C reactive protein and coronary heart disease: mendelian randomisation analysis based on individual participant data*. *British Medical Journal*, 2011. 342.
88. Gabay, C. and I. Kushner, *Mechanisms of disease: Acute-phase proteins and other systemic responses to inflammation*. *New England Journal of Medicine*, 1999. 340(6): p. 448-454.
89. Lu, Y., et al., *Mediators of the effect of body mass index on coronary heart disease: decomposing direct and indirect effects*. *Epidemiology*, 2015. 26(2): p. 153-62.
90. VanderWeele, T.J., L. Valeri, and E.L. Ogburn, *The Role of Measurement Error and Misclassification in Mediation Analysis Mediation and Measurement Error*. *Epidemiology*, 2012. 23(4): p. 561-564.
91. Chai, S.B., et al., *Leptin and coronary heart disease: a systematic review and meta-analysis*. *Atherosclerosis*, 2014. 233(1): p. 3-10.
92. Nigro, E., et al., *New insight into adiponectin role in obesity and obesity-related diseases*. *Biomed Res Int*, 2014. 2014: p. 658913.
93. Rajkovic, N., et al., *Relationship between obesity, adipocytokines and inflammatory mark-*

- ers in type 2 diabetes: relevance for cardiovascular risk prevention. *Int J Environ Res Public Health*, 2014. 11(4): p. 4049-65.
94. Yaghootkar, H., et al, Mendelian randomisation studies do not support a causal role for reduced circulating adiponectin levels in fasting based measures of insulin resistance and Type 2 diabetes. *Diabetic Medicine*, 2013. 30: p. 30-30.
95. Gao, H., et al, Evidence of a Causal Relationship between Adiponectin Levels and Insulin Sensitivity: A Mendelian Randomization Study. *Circulation*, 2012. 126(21).
96. Koh, K.K., S.M. Park, and M.J. Quon, Leptin and cardiovascular disease - Response to therapeutic interventions. *Circulation*, 2008. 117(25): p. 3238-3249.
97. Lubkowska, A., et al, Serum Adiponectin and Leptin Concentrations in Relation to Body Fat Distribution, Hematological Indices and Lipid Profile in Humans. *International Journal of Environmental Research and Public Health*, 2015. 12(9): p. 11528-11548.
98. Lee, J.J., et al, Cross-Sectional Associations of Computed Tomography (CT)-Derived Adipose Tissue Density and Adipokines: The Framingham Heart Study. *J Am Heart Assoc*, 2016. 5(3): p. e002545.
99. Bidulescu, A., et al, Gender differences in the association of visceral and subcutaneous adiposity with adiponectin in African Americans: the Jackson Heart Study. *Bmc Cardiovascular Disorders*, 2013. 13.
100. Elbers, J.M.H., et al, Reversal of the sex difference in serum leptin levels upon cross-sex hormone administration in transsexuals. *Journal of Clinical Endocrinology & Metabolism*, 1997. 82(10): p. 3267-3270.
101. Rosenbaum, M., et al, Sexual dimorphism in circulating leptin concentrations is not accounted for by differences in adipose tissue distribution. *Int J Obes Relat Metab Disord*, 2001. 25(9): p. 1365-71.
102. Turer, A.T., et al, Adipose tissue mass and location affect circulating adiponectin levels. *Diabetologia*, 2011. 54(10): p. 2515-2524.
103. Bidulescu, A., et al, Gender differences in the association of visceral and subcutaneous adiposity with adiponectin in African Americans: the Jackson Heart Study. *BMC Cardiovasc Disord*, 2013. 13: p. 9.
104. Genomes Project, C., et al, An integrated map of genetic variation from 1,092 human genomes. *Nature*, 2012. 491(7422): p. 56-65.
105. Marchini, J., et al, A new multipoint method for genome-wide association studies by imputation of genotypes. *Nat Genet*, 2007. 39(7): p. 906-13.
106. Considine, R.V., et al, Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N Engl J Med*, 1996. 334(5): p. 292-5.
107. Clement, K., et al, A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. *Nature*, 1998. 392(6674): p. 398-401.
108. Lonsdale, J., et al, The Genotype-Tissue Expression (GTEx) project. *Nature Genetics*, 2013. 45(6): p. 580-585.
109. Blauw, L.L., et al, Genome-wide Association Study of Circulating CETP Combined With Mendelian Randomization on Serum Lipids and Coronary Artery Disease. (submitted for publication), 2017.
110. Iglesias, M.J., et al, [Gender differences in adiponectin and leptin expression in epicardial and subcutaneous adipose tissue. Findings in patients undergoing cardiac surgery]. *Rev Esp Car-*

diol, 2006. 59(12): p. 1252-60.

111. Nishizawa, H., et al, Androgens decrease plasma adiponectin, an insulin-sensitizing adipocyte-derived protein. *Diabetes*, 2002. 51(9): p. 2734-41.
112. Kern, P.A., et al, Adiponectin expression from human adipose tissue: relation to obesity, insulin resistance, and tumor necrosis factor- α expression. *Diabetes*, 2003. 52(7): p. 1779-85.
113. Franklin, R.M., L. Ploutz-Snyder, and J.A. Kanaley, Longitudinal changes in abdominal fat distribution with menopause. *Metabolism*, 2009. 58(3): p. 311-5.
114. Motoshima, H., et al, Differential regulation of adiponectin secretion from cultured human omental and subcutaneous adipocytes: Effects of insulin and rosiglitazone. *Diabetes*, 2002. 51: p. A88-A88.
115. Saad, M.F., et al, Sexual dimorphism in plasma leptin concentration. *J Clin Endocrinol Metab*, 1997. 82(2): p. 579-84.
116. Magnussen, L.V., et al, MR spectroscopy of hepatic fat and adiponectin and leptin levels during testosterone therapy in type 2 diabetes: a randomized, double-blinded, placebo-controlled trial. *Eur J Endocrinol*, 2017. 177(2): p. 157-168.
117. Streed, C.G., Jr., et al, Cardiovascular Disease Among Transgender Adults Receiving Hormone Therapy: A Narrative Review. *Ann Intern Med*, 2017. 167(4): p. 256-267.
118. Hara, K., et al, Genome-wide association study identifies three novel loci for type 2 diabetes. *Human Molecular Genetics*, 2014. 23(1): p. 239-246.
119. Perry, R.J., et al, Leptin reverses diabetes by suppression of the hypothalamic-pituitary-adrenal axis. *Nature Medicine*, 2014. 20(7): p. 759-763.
120. Ostlund, R.E., Jr., et al, Relation between plasma leptin concentration and body fat, gender, diet, age, and metabolic covariates. *J Clin Endocrinol Metab*, 1996. 81(11): p. 3909-13.
121. Jurimae, T., et al, Relationships between plasma leptin levels and body composition parameters measured by different methods in postmenopausal women. *American Journal of Human Biology*, 2003. 15(5): p. 628-636.
122. Looney, S.W. and J.L. Hagan, *Analysis of Biomarker Data: A Practical Guide*. 2015: Wiley.
123. Friedman, J.M. and J.L. Halaas, Leptin and the regulation of body weight in mammals. *Nature*, 1998. 395(6704): p. 763-70.
124. Iikuni, N., et al, Leptin and Inflammation. *Curr Immunol Rev*, 2008. 4(2): p. 70-79.
125. Guagnano, M.T., et al, Leptin increase is associated with markers of the hemostatic system in obese healthy women. *J Thromb Haemost*, 2003. 1(11): p. 2330-4.
126. Fortuno, A., et al, Leptin inhibits angiotensin II-induced intracellular calcium increase and vasoconstriction in the rat aorta. *Endocrinology*, 2002. 143(9): p. 3555-60.
127. Lin, Y.C., et al, Leptin decreases heart rate associated with increased ventricular repolarization via its receptor. *American Journal of Physiology-Heart and Circulatory Physiology*, 2015. 309(10): p. H1731-H1739.
128. Friedewald, W.T., R.I. Levy, and D.S. Fredrickson, Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*, 1972. 18(6): p. 499-502.
129. Matthews, D.R., et al, Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*, 1985. 28(7): p. 412-9.

130. Millipore, E., Human Leptin RIA kit HL-81HK, in http://www.merckmillipore.com/NL/en/product/Human-Leptin-RIA,MM_NF-HL-81HK?bd=1. . 2015.
131. Altshuler, D.M., et al., An integrated map of genetic variation from 1,092 human genomes. *Nature*, 2012. 491(7422): p. 56-65.
132. Draisma, H.H.M., et al. LEADS: an interactive research oriented ECG/VCG analysis system. in *Computers in Cardiology*, 2005. 2005.
133. Sum-Che, M., et al. Beats: An interactive research oriented ECG analysis system. in *Computing in Cardiology*, 2010. 2010.
134. Schunkert, H., et al., Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. *Nature Genetics*, 2011. 43(4): p. 333-U153.
135. Burgess, S., N.M. Davies, and S.G. Thompson, Bias due to participant overlap in two-sample Mendelian randomization. *Genetic Epidemiology*, 2016. 40(7): p. 597-608.
136. Gibran Hemani, et al., MR-Base: a platform for systematic causal inference across the phenotype using billions of genetic associations. *bioRxiv*, 2016.
137. Burgess, S. and E. Harshfield, Mendelian randomization to assess causal effects of blood lipids on coronary heart disease: lessons from the past and applications to the future. *Current Opinion in Endocrinology Diabetes and Obesity*, 2016. 23(2): p. 124-130.
138. Bastien, M., et al., Overview of Epidemiology and Contribution of Obesity to Cardiovascular Disease. *Progress in Cardiovascular Diseases*, 2014. 56(4): p. 369-381.
139. Srikanthan, P., T.B. Horwich, and C.H. Tseng, Relation of Muscle Mass and Fat Mass to Cardiovascular Disease Mortality. *Am J Cardiol*, 2016. 117(8): p. 1355-60.
140. Rahmouni, K., et al., Intracellular mechanisms involved in leptin regulation of sympathetic outflow. *Hypertension*, 2003. 41(3): p. 763-767.
141. Schindler, C.W., JAK-STAT signaling in human disease. *Journal of Clinical Investigation*, 2002. 109(9): p. 1133-1137.
142. Rezaei-Zadeh, K., et al., Leptin receptor neurons in the dorsomedial hypothalamus are key regulators of energy expenditure and body weight, but not food intake. *Molecular Metabolism*, 2014. 3(7): p. 681-693.
143. Luo, W., et al., Leptin receptor-induced STAT3-independent signaling pathways are protective against atherosclerosis in a murine model of obesity and hyperlipidemia. *Atherosclerosis*, 2011. 214(1): p. 81-85.
144. Sharma, S., et al., Association of serum leptin with future left ventricular structure and function: The Multi-Ethnic Study of Atherosclerosis (MESA). *International Journal of Cardiology*, 2015. 193: p. 64-68.
145. Neeland, I.J., et al., Associations of visceral and abdominal subcutaneous adipose tissue with markers of cardiac and metabolic risk in obese adults. *Obesity (Silver Spring)*, 2013. 21(9): p. E439-47.
146. Christen, T., et al., Sex differences in body fat distribution are related to sex differences in serum leptin and adiponectin. *Peptides*, 2018. 107: p. 25-31.
147. Lee, S., et al., Adiponectin abates diabetes-induced endothelial dysfunction by suppressing oxidative stress, adhesion molecules, and inflammation in type 2 diabetic mice. *Am J Physiol Heart Circ Physiol*, 2012. 303(1): p. H106-15.
148. Persson, J., et al., Sex-Specific Effects of Adiponectin on Carotid Intima-Media Thickness and Incident Cardiovascular Disease. *J Am Heart Assoc*, 2015. 4(8): p. e001853.

149. Ohashi, K., et al., Adiponectin Promotes Macrophage Polarization toward an Anti-inflammatory Phenotype. *Journal of Biological Chemistry*, 2010. 285(9): p. 6153-6160.
150. Okamoto, Y., et al., Adiponectin reduces atherosclerosis in apolipoprotein E-deficient mice. *Circulation*, 2002. 106(22): p. 2767-2770.
151. Wong, W.T., et al., Adiponectin Is Required for PPAR gamma-Mediated Improvement of Endothelial Function in Diabetic Mice. *Cell Metabolism*, 2011. 14(1): p. 104-115.
152. Al-Hamodi, Z., et al., Association of adipokines, leptin/adiponectin ratio and C-reactive protein with obesity and type 2 diabetes mellitus. *Diabetol Metab Syndr*, 2014. 6(1): p. 99.
153. Weyer, C., et al., Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *J Clin Endocrinol Metab*, 2001. 86(5): p. 1930-5.
154. Borges, M.C., et al., Role of Adiponectin in Coronary Heart Disease Risk A Mendelian Randomization Study. *Circulation Research*, 2016. 119(3): p. 491-+.
155. Yaghootkar, H., et al., Mendelian Randomization Studies Do Not Support a Causal Role for Reduced Circulating Adiponectin Levels in Insulin Resistance and Type 2 Diabetes. *Diabetes*, 2013. 62(10): p. 3589-3598.
156. Lindberg, S., et al., Cardio-adipose tissue cross-talk: relationship between adiponectin, plasma pro brain natriuretic peptide and incident heart failure. *Eur J Heart Fail*, 2014. 16(6): p. 633-8.
157. Witberg, G., et al., Relation of Adiponectin to All-Cause Mortality, Cardiovascular Mortality, and Major Adverse Cardiovascular Events (from the Dallas Heart Study). *Am J Cardiol*, 2016. 117(4): p. 574-9.
158. Hernan, M.A., Invited Commentary: Selection Bias Without Colliders. *American Journal of Epidemiology*, 2017. 185(11): p. 1048-1050.
159. Menzaghi, C. and V. Trischitta, The Adiponectin Paradox for All-Cause and Cardiovascular Mortality. *Diabetes*, 2018. 67(1): p. 12-22.
160. Allison, M.A., et al., Adiponectin is independently associated with NT-proBNP: The Multi-Ethnic Study of Atherosclerosis. *Nutr Metab Cardiovasc Dis*, 2015. 25(8): p. 780-6.
161. Tsukamoto, O., et al., Natriuretic Peptides Enhance the Production of Adiponectin in Human Adipocytes and in Patients With Chronic Heart Failure. *Journal of the American College of Cardiology*, 2009. 53(22): p. 2070-2077.
162. Wang, T.J., et al., Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *New England Journal of Medicine*, 2004. 350(7): p. 655-663.
163. Lawlor, D.A., et al., Mendelian randomization: Using genes as instruments for making causal inferences in epidemiology. *Statistics in Medicine*, 2008. 27(8): p. 1133-1163.
164. Flanders, W.D., R.C. Eldridge, and W. McClellan, A nearly unavoidable mechanism for collider bias with index-event studies. *Epidemiology*, 2014. 25(5): p. 762-4.
165. Blauw, L.L., et al., CETP (Cholesteryl Ester Transfer Protein) Concentration: A Genome-Wide Association Study Followed by Mendelian Randomization on Coronary Artery Disease. *Circ Genom Precis Med*, 2018. 11(5): p. e002034.
166. Leslie, R., C.J. O'Donnell, and A.D. Johnson, GRASP: analysis of genotype-phenotype results from 1390 genome-wide association studies and corresponding open access database. *Bioinformatics*, 2014. 30(12): p. 185-194.
167. Lumley, T., Analysis of Complex Survey Samples. *Journal of Statistical Software*, 2004. 9(8): p. 1-19.

168. Hemani, G., et al., *The MR-Base platform supports systematic causal inference across the human phenome*. *Elife*, 2018. 7.
169. Tsukamoto, O., et al., *Natriuretic peptides enhance the production of adiponectin in human adipocytes and in patients with chronic heart failure*. *J Am Coll Cardiol*, 2009. 53(22): p. 2070-7.
170. Wannamethee, S.G., et al., *High adiponectin and increased risk of cardiovascular disease and mortality in asymptomatic older men: does NT-proBNP help to explain this association?* *European Journal of Cardiovascular Prevention & Rehabilitation*, 2011. 18(1): p. 65-71.
171. Galasko, G.I.W., et al., *What is the normal range for N-terminal pro-brain natriuretic peptide? How well does this normal range screen for cardiovascular disease?* *European Heart Journal*, 2005. 26(21): p. 2269-2276.
172. Withers, S.B., et al., *Mechanisms of adiponectin-associated perivascular function in vascular disease*. *ArteriosclerThromb Vasc Biol*, 2014. 34(8): p. 1637-42.
173. Li, S., et al., *Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis*. *JAMA*, 2009. 302(2): p. 179-88.
174. Yamamoto, K., et al., *Production of adiponectin, an anti-inflammatory protein, in mesenteric adipose tissue in Crohn's disease*. *Gut*, 2005. 54(6): p. 789-796.
175. Hemani, G., J. Bowden, and G.D. Smith, *Evaluating the potential role of pleiotropy in Mendelian randomization studies*. *Human Molecular Genetics*, 2018. 27(R2): p. R195-R208.
176. Zhong, S., et al., *Increased coronary heart disease in Japanese-American men with mutation in the cholesteryl ester transfer protein gene despite increased HDL levels*. *J Clin Invest*, 1996. 97(12): p. 2917-23.
177. Ritsch, A. and J.R. Patsch, *Cholesteryl ester transfer protein: gathering momentum as a genetic marker and as drug target*. *Current opinion in lipidology*, 2003. 14(2): p. 173-9.
178. Inazu, A., et al., *Increased high-density lipoprotein levels caused by a common cholesteryl-ester transfer protein gene mutation*. *N Engl J Med*, 1990. 323(18): p. 1234-8.
179. Okamura, T., et al., *Cholesteryl ester transfer protein, coronary calcium, and intima-media thickness of the carotid artery in middle-age Japanese men*. *Am J Cardiol*, 2009. 104(6): p. 818-22.
180. Boekholdt, S.M., et al., *Plasma levels of cholesteryl ester transfer protein and the risk of future coronary artery disease in apparently healthy men and women: the prospective EPIC (European Prospective Investigation into Cancer and nutrition)-Norfolk population study*. *Circulation*, 2004. 110(11): p. 1418-23.
181. Barter, P.J. and K.A. Rye, *Cholesteryl Ester Transfer Protein Inhibition Is Not Yet Dead--Pro*. *ArteriosclerThromb Vasc Biol*, 2016. 36(3): p. 439-41.
182. Ordovas, J.M., *Genetic polymorphisms and activity of cholesterol ester transfer protein (CETP): should we be measuring them?* *Clin Chem Lab Med*, 2000. 38(10): p. 945-9.
183. Inazu, A., J. Koizumi, and H. Mabuchi, *Cholesteryl ester transfer protein and atherosclerosis*. *Curr Opin Lipidol*, 2000. 11(4): p. 389-96.
184. Boekholdt, S.M. and J.F. Thompson, *Natural genetic variation as a tool in understanding the role of CETP in lipid levels and disease*. *J Lipid Res*, 2003. 44(6): p. 1080-93.
185. Parra, E.S., et al., *The I405V and Taq1B polymorphisms of the CETP gene differentially affect sub-clinical carotid atherosclerosis*. *Lipids Health Dis*, 2012. 11: p. 130.
186. Wu, Z., et al., *Association of cholesteryl ester transfer protein (CETP) gene polymorphism,*

high density lipoprotein cholesterol and risk of coronary artery disease: a meta-analysis using a Mendelian randomization approach. *BMC Med Genet*, 2014. 15: p. 118.

187. Niu, W.Q. and Y. Qi, Circulating Cholesteryl Ester Transfer Protein and Coronary Heart Disease Mendelian Randomization Meta-Analysis. *Circulation-Cardiovascular Genetics*, 2015. 8(1): p. 114-U232.
188. Johannsen, T.H., et al., Genetic Inhibition of CETP, Ischemic Vascular Disease and Mortality, and Possible Adverse Effects. *Journal of the American College of Cardiology*, 2012. 60(20): p. 2041-2048.
189. Ference, B.A., et al., Association of Genetic Variants Related to CETP Inhibitors and Statins With Lipoprotein Levels and Cardiovascular Risk. *JAMA*, 2017. 318(10): p. 947-956.
190. Postmus, I., et al., Meta-analysis of genome-wide association studies of HDL cholesterol response to statins. *J Med Genet*, 2016. 53(12): p. 835-845.
191. Silverman, M.G., et al., Association Between Lowering LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions A Systematic Review and Meta-analysis. *Jama-Journal of the American Medical Association*, 2016. 316(12): p. 1289-1297.
192. D'Agostino, R.B., et al., General cardiovascular risk profile for use in primary care - The Framingham Heart Study. *Circulation*, 2008. 117(6): p. 743-753.
193. Expert Panel on Detection, E. and A. Treatment of High Blood Cholesterol in, Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA*, 2001. 285(19): p. 2486-97.
194. Nordestgaard, B.G., et al., Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points-a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine. *Eur Heart J*, 2016.
195. Expert Committee on the, D. and M. Classification of Diabetes, Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care*, 2003. 26 Suppl 1: p. S5-20.
196. Alssema, M., et al., Elevated cholesteryl ester transfer protein concentration is associated with an increased risk for cardiovascular disease in women, but not in men, with Type 2 diabetes: the Hoorn Study. *Diabet Med*, 2007. 24(2): p. 117-23.
197. Krauss, R.M., et al., Changes in lipoprotein subfraction concentration and composition in healthy individuals treated with the CETP inhibitor anacetrapib. *J Lipid Res*, 2012. 53(3): p. 540-7.
198. Langsted, A. and B.G. Nordestgaard, Nonfasting Lipids, Lipoproteins, and Apolipoproteins in Individuals with and without Diabetes: 58 434 Individuals from the Copenhagen General Population Study. *Clinical Chemistry*, 2011. 57(3): p. 482-489.
199. Barter, P.J., et al., Effects of torcetrapib in patients at high risk for coronary events. *New England Journal of Medicine*, 2007. 357(21): p. 2109-2122.
200. Kannel, W.B. and P.W.F. Wilson, Risk-Factors That Attenuate the Female Coronary-Disease Advantage. *Archives of Internal Medicine*, 1995. 155(1): p. 57-61.
201. Peters, S.A.E., et al., Total cholesterol as a risk factor for coronary heart disease and stroke in women compared with men: A systematic review and meta-analysis. *Atherosclerosis*, 2016. 248: p. 123-131.

202. Bairey Merz, C.N., et al., Hypoestrogenemia of hypothalamic origin and coronary artery disease in premenopausal women: a report from the NHLBI-sponsored WISE study. *J Am Coll Cardiol*, 2003. 41(3): p. 413-9.
203. Lorenz, M.W., et al., Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation*, 2007. 115(4): p. 459-67.
204. Cao, G., et al., Evacetrapib is a novel, potent, and selective inhibitor of cholesteryl ester transfer protein that elevates HDL cholesterol without inducing aldosterone or increasing blood pressure. *J Lipid Res*, 2011. 52(12): p. 2169-76.
205. Schwartz, G.G., et al., Rationale and design of the dal-OUTCOMES trial: efficacy and safety of dalcetrapib in patients with recent acute coronary syndrome. *Am Heart J*, 2009. 158(6): p. 896-901 e3.
206. Clark, R.W., et al., Description of the torcetrapib series of cholesteryl ester transfer protein inhibitors, including mechanism of action. *J Lipid Res*, 2006. 47(3): p. 537-52.
207. Anderson, K.M., W.P. Castelli, and D. Levy, Cholesterol and mortality. 30 years of follow-up from the Framingham study. *JAMA*, 1987. 257(16): p. 2176-80.
208. Yang, C., et al., The correlation between serum lipid profile with carotid intima-media thickness and plaque. *BMC Cardiovasc Disord*, 2014. 14: p. 181.
209. Richardson, T.G., et al., Apolipoprotein B underlies the causal relationship of circulating blood lipids with coronary heart disease. *medRxiv*, 2019.
210. McNamara, J.R., et al., Remnant-like particle (RLP) cholesterol is an independent cardiovascular disease risk factor in women: results from the Framingham Heart Study. *Atherosclerosis*, 2001. 154(1): p. 229-36.
211. Nordestgaard, B.G., Triglyceride-Rich Lipoproteins and Atherosclerotic Cardiovascular Disease: New Insights From Epidemiology, Genetics, and Biology. *Circ Res*, 2016. 118(4): p. 547-63.
212. Patsch, J.R., et al., Inverse relationship between blood levels of high density lipoprotein subfraction 2 and magnitude of postprandial lipemia. *Proc Natl Acad Sci U S A*, 1983. 80(5): p. 1449-53.
213. Pruneta, V., et al., VLDL-bound lipoprotein lipase facilitates the cholesteryl ester transfer protein-mediated transfer of cholesteryl esters from HDL to VLDL. *Journal of Lipid Research*, 1999. 40(12): p. 2333-2339.
214. Wang, Y.N., et al., CETP expression reverses the reconstituted HDL-induced increase in VLDL. *Journal of Lipid Research*, 2011. 52(8): p. 1533-1541.
215. Ibi, D., et al., Common genetic variation in hepatic lipase (LIPC) is associated with postprandial triglyceride metabolism independent from fasting triglyceride levels. (unpublished), 2019.
216. Willer, C.J., et al., Newly identified loci that influence lipid concentrations and risk of coronary artery disease. *Nature Genetics*, 2008. 40(2): p. 161-169.
217. Preuss, M., et al., Design of the Coronary ARtery Disease Genome-Wide Replication And Meta-Analysis (CARDIoGRAM) Study: A Genome-wide association meta-analysis involving more than 22 000 cases and 60 000 controls. *Circ Cardiovasc Genet*, 2010. 3(5): p. 475-83.
218. Rees, J.M.B., A.M. Wood, and S. Burgess, Extending the MR-Egger method for multivariable Mendelian randomization to correct for both measured and unmeasured pleiotropy. *Stat Med*, 2017. 36(29): p. 4705-4718.

219. Nagata, T., et al., Fasting remnant lipoproteins can predict postprandial hyperlipidemia. *Lipids Health Dis*, 2012. 11: p. 146.
220. Varbo, A., M. Benn, and B.G. Nordestgaard, Remnant cholesterol as a cause of ischemic heart disease: evidence, definition, measurement, atherogenicity, high risk patients, and present and future treatment. *Pharmacol Ther*, 2014. 141(3): p. 358-67.
221. Kolovou, G.D., et al., Cholesterol Ester Transfer Protein (CETP), Postprandial Lipemia and Hypolipidemic Drugs. *Current Medicinal Chemistry*, 2009. 16(33): p. 4345-4360.
222. Li, Y., et al., Lipoprotein lipase: from gene to atherosclerosis. *Atherosclerosis*, 2014. 237(2): p. 597-608.
223. Schaap, F.G., et al., ApoAV reduces plasma triglycerides by inhibiting very low density lipoprotein-triglyceride (VLDL-TG) production and stimulating lipoprotein lipase-mediated VLDL-TG hydrolysis. *J Biol Chem*, 2004. 279(27): p. 27941-7.
224. Goldberg, I.J., R.H. Eckel, and R. McPherson, Triglycerides and Heart Disease Still a Hypothesis? *Arteriosclerosis Thrombosis and Vascular Biology*, 2011. 31(8): p. 1716-1725.
225. Patsch, J.R., Triglyceride-rich lipoproteins and atherosclerosis. *Atherosclerosis*, 1994. 110 Suppl: p. S23-6.
226. Khan, I.M., et al., Postprandial Monocyte Activation in Individuals With Metabolic Syndrome. *Journal of Clinical Endocrinology & Metabolism*, 2016. 101(11): p. 4195-4204.
227. Wang, Y.L., et al., Endothelial inflammation correlates with subject triglycerides and waist size after a high-fat meal. *American Journal of Physiology-Heart and Circulatory Physiology*, 2011. 300(3): p. H784-H791.
228. Chung, B.H., et al., Lipolytic Surface Remnants of Triglyceride-Rich Lipoproteins Are Cytotoxic to Macrophages but Not in the Presence of High-Density Lipoprotein - a Possible Mechanism of Atherogenesis. *Journal of Clinical Investigation*, 1989. 83(4): p. 1363-1374.
229. Kume, N., M.I. Cybulsky, and M.A. Gimbrone, Lysophosphatidylcholine, a Component of Atherogenic Lipoproteins, Induces Mononuclear Leukocyte Adhesion Molecules in Cultured Human and Rabbit Arterial Endothelial-Cells. *Journal of Clinical Investigation*, 1992. 90(3): p. 1138-1144.
230. Zhang, W.Y., et al., Elevated concentrations of nonesterified fatty acids increase monocyte expression of CD11b and adhesion to endothelial cells. *Arteriosclerosis Thrombosis and Vascular Biology*, 2006. 26(3): p. 514-519.
231. Boekholdt, S.M., et al., Levels and changes of HDL cholesterol and apolipoprotein A-I in relation to risk of cardiovascular events among statin-treated patients: a meta-analysis. *Circulation*, 2013. 128(14): p. 1504-12.
232. Sarwar, N., et al., Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. *Lancet*, 2010. 375(9726): p. 1634-1639.
233. Do, R., et al., Common variants associated with plasma triglycerides and risk for coronary artery disease. *Nature Genetics*, 2013. 45(11): p. 1345-+.
234. Erbel, R., et al., Signs of subclinical coronary atherosclerosis in relation to risk factor distribution in the Multi-Ethnic Study of Atherosclerosis (MESA) and the Heinz Nixdorf Recall Study (HNR). *Eur Heart J*, 2008. 29(22): p. 2782-91.
235. Fernandez-Friera, L., et al., Prevalence, Vascular Distribution, and Multiterritorial Extent of Subclinical Atherosclerosis in a Middle-Aged Cohort: The PESA (Progression of Early Subclinical Atherosclerosis) Study. *Circulation*, 2015. 131(24): p. 2104-13.

236. Levi, F., et al., Mortality from cardiovascular and cerebrovascular diseases in Europe and other areas of the world: an update. *Eur J Cardiovasc Prev Rehabil*, 2009. 16(3): p. 333-50.
237. Klop, B., et al., A physician's guide for the management of hypertriglyceridemia: the etiology of hypertriglyceridemia determines treatment strategy. *Panminerva Med*, 2012. 54(2): p. 91-103.
238. Havel, R., McCollum Award Lecture, 1993: triglyceride-rich lipoproteins and atherosclerosis--new perspectives. *Am J Clin Nutr*, 1994. 59(4): p. 795-6.
239. Benlian, P., et al., Premature atherosclerosis in patients with familial chylomicronemia caused by mutations in the lipoprotein lipase gene. *N Engl J Med*, 1996. 335(12): p. 848-54.
240. Howard, G., et al., Cigarette smoking and progression of atherosclerosis: The Atherosclerosis Risk in Communities (ARIC) Study. *JAMA*, 1998. 279(2): p. 119-24.
241. Nakamura, A., et al., Effect of glycemic state on postprandial hyperlipidemia and hyperinsulinemia in patients with coronary artery disease. *Heart Vessels*, 2015.
242. Schrezenmeir, J., et al., The phenomenon of a high triglyceride response to an oral lipid load in healthy subjects and its link to the metabolic syndrome. *Ann NY Acad Sci*, 1993. 683: p. 302-14.
243. de Hollander, E.L., et al., The SQUASH was a more valid tool than the OBiN for categorizing adults according to the Dutch physical activity and the combined guideline. *Journal of clinical epidemiology*, 2012. 65(1): p. 73-81.
244. Wendel-Vos, G.C., et al., Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. *J Clin Epidemiol*, 2003. 56(12): p. 1163-9.
245. Feunekes, G.I., et al., Relative and biomarker-based validity of a food-frequency questionnaire estimating intake of fats and cholesterol. *Am J Clin Nutr*, 1993. 58(4): p. 489-96.
246. NEVO, S., NEVO: Dutch food database 2011. Den Haag: Voedingscentrum 2011, 2011.
247. Boquist, S., et al., Alimentary lipemia, postprandial triglyceride-rich lipoproteins, and common carotid intima-media thickness in healthy, middle-aged men. *Circulation*, 1999. 100(7): p. 723-8.
248. Sharrett, A.R., et al., Association of postprandial triglyceride and retinyl palmitate responses with asymptomatic carotid artery atherosclerosis in middle-aged men and women. The Atherosclerosis Risk in Communities (ARIC) Study. *Arterioscler Thromb Vasc Biol*, 1995. 15(12): p. 2122-9.
249. Bansal, S., et al., Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. *JAMA*, 2007. 298(3): p. 309-16.
250. Perk, J., et al., European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J*, 2012. 33(13): p. 1635-701.
251. Li, S., et al., Cigarette smoking exacerbates the adverse effects of age and metabolic syndrome on subclinical atherosclerosis: the Bogalusa Heart Study. *PLoS One*, 2014. 9(5): p. e96368.
252. Ebong, I.A., et al., Association of lipids with incident heart failure among adults with and without diabetes mellitus: Multiethnic Study of Atherosclerosis. *Circ Heart Fail*, 2013. 6(3): p. 371-8.
253. Klop, B., et al., Understanding postprandial inflammation and its relationship to lifestyle be-

haviour and metabolic diseases. *Int J Vasc Med*, 2012. 2012: p. 947417.

254. Iso, H., et al., Serum triglycerides and risk of coronary heart disease among Japanese men and women. *Am J Epidemiol*, 2001. 153(5): p. 490-9.
255. Njolstad, I., E. Arnesen, and P.G. Lund-Larsen, Smoking, serum lipids, blood pressure, and sex differences in myocardial infarction. A 12-year follow-up of the Finnmark Study. *Circulation*, 1996. 93(3): p. 450-6.
256. Ludwig, D.S. and C.B. Ebbeling, Type 2 diabetes mellitus in children - Primary care and public health considerations. *Jama-Journal of the American Medical Association*, 2001. 286(12): p. 1427-1430.
257. Vaartjes, I., et al., Coronary heart disease mortality trends in the Netherlands 1972-2007. *Heart*, 2011. 97(7): p. 569-573.
258. Scherer, P.E., et al., A novel serum protein similar to C1q, produced exclusively in adipocytes. *J Biol Chem*, 1995. 270(45): p. 26746-9.
259. Lonnqvist, F., et al., Overexpression of the Obese (Ob) Gene in Adipose-Tissue of Human Obese Subjects. *Nature Medicine*, 1995. 1(9): p. 950-953.
260. Ruan, H. and L.Q. Dong, Adiponectin signaling and function in insulin target tissues. *Journal of Molecular Cell Biology*, 2016. 8(2): p. 101-109.
261. Norvik, J.V., et al., Low adiponectin is associated with diastolic dysfunction in women: a cross-sectional study from the Tromso Study. *Bmc Cardiovascular Disorders*, 2017. 17.
262. Sakura, T., et al., The association of serum adiponectin with abdominal aortic calcification in Japanese male hemodialysis patients: a cross-sectional observational study. *Sci Rep*, 2017. 7(1): p. 6434.
263. Vavrouch, C., et al., Serum leptin levels are independently related to the incidence of ischemic heart disease in a prospective study of patients with type 2 diabetes. *Cardiovascular Diabetology*, 2015. 14.
264. Kettunen, T., et al., Polymorphism in the C-reactive protein (CRP) gene affects CRP levels in plasma and one early marker of atherosclerosis in men: The Health 2000 Survey. *Scandinavian Journal of Clinical & Laboratory Investigation*, 2011. 71(5): p. 353-361.
265. Groenwold, R.H., [Bias in observational research: 'confounding']. *Ned Tijdschr Geneeskd*, 2012. 156(13): p. A4221.
266. VanderWeele, T.J., et al., Methodological Challenges in Mendelian Randomization. *Epidemiology*, 2014. 25(3): p. 427-435.
267. le Cessie, S., Bias Formulas for Estimating Direct and Indirect Effects When Unmeasured Confounding Is Present. *Epidemiology*, 2016. 27(1): p. 125-32.
268. Taguri, M., J. Featherstone, and J. Cheng, Causal mediation analysis with multiple causally non-ordered mediators. *Stat Methods Med Res*, 2015.
269. VanderWeele, T.J., *Mediation Analysis: A Practitioner's Guide*. *Annu Rev Public Health*, 2016. 37: p. 17-32.
270. Tardif, J.C., et al., Genotype-Dependent Effects of Dalcetrapib on Cholesterol Efflux and Inflammation Concordance With Clinical Outcomes. *Circulation-Cardiovascular Genetics*, 2016. 9(4): p. 340-348.

