

## References

1. Serné, E. H. et al. Microvascular function relates to inulin sensitivity and blood pressure in norml subjects. *Circulation* 99, 896–902 (1999).
2. Schinzari, F. et al. Generalized impairment of vasodilator reactivity during hyperinsulinemia in patients with obesity-related metabolic syndrome. *Am. J. Physiol. - Endocrinol. Metab.* 299, E947–E952 (2010).
3. De Jongh, R. T. et al. Physiological hyperinsulinaemia increases intramuscular microvascular reactive hyperaemia and vasomotion in healthy volunteers. *Diabetologia* 47, 978–986 (2004).
4. De Jongh, R. T. et al. Visceral and truncal subcutaneous adipose tissue are associated with impaired capillary recruitment in healthy individuals. *J. Clin. Endocrinol. Metab.* 91, 5100–5106 (2006).
5. De Jongh, R. T., Serné, E. H., IJzerman, R. G. & Stehouwer, C. D. A. Microvascular function: a potential link between salt sensitivity, insulin resistance and hypertension. *J. Hypertens.* 25, 1887–1893 (2007).
6. De Jongh, R. T., Serné, E. H., IJzerman, R. G., De Vries, G. & Stehouwer, C. D. A. Impaired microvascular function in obesity: implications for obesity-associated microangiopathy, hypertension, and insulin resistance. *Circulation* 109, 2529–2535 (2004).
7. Eringa, E. C. et al. Regulation of vascular function and insulin sensitivity by adipose tissue: focus on perivascular adipose tissue. *Microcirc.* New York NY 1994 14, 389–402 (2007).
8. De Boer, M. P. et al. Microvascular dysfunction: a potential mechanism in the pathogenesis of obesity-associated insulin resistance and hypertension. *Microcirculation.* 19, 5–18 (2012).
9. Levy, B. I., Ambrosio, G., Pries, A. R. & Struijker-Boudier, H. A. J. Microcirculation in hypertension: A new target for treatment? *Circulation* 104, 736–741 (2001).
10. Serné, E. H. et al. Capillary recruitment is impaired in essential hypertension and relates to insulin's metabolic and vascular actions. *Cardiovasc. Res.* 49, 161–168 (2001).
11. De Jongh, R. T., Serné, E. H., IJzerman, R. G., Jørstad, H. T. & Stehouwer, C. D. A. Impaired local microvascular vasodilatory effects of insulin and reduced skin microvascular vasomotion in obese women. *Microvasc. Res.* 75, 256–262 (2008).
12. Clark, M. G. Impaired microvascular perfusion: a consequence of vascular dysfunction and a potential cause of insulin resistance in muscle. *Am. J. Physiol. Endocrinol. Metab.* 295, E732–E750 (2008).
13. Barrett, E. J. et al. The vascular actions of insulin control its delivery to muscle and regulate the rate-limiting step in skeletal muscle insulin action. *Diabetologia* 52, 752–764 (2009).
14. Serné, E. H. et al. Impaired skin capillary recruitment in essential hypertension is caused by both functional and structural capillary rarefaction. *Hypertension* 38, 238–242 (Am Heart Assoc, 2001).
15. Meijer, R. I. et al. Insulin-Induced Microvascular Recruitment in Skin and Muscle are Related and Both are Associated with Whole-Body Glucose Uptake. *Microcirculation* 19, 494–500 (2012).
16. Seidell, J. in *Semin. Vasc. Med.* 3–14 (Thieme Medical Publishers, Inc, 2005). at <<https://www.thieme-connect.com/ejournals/abstract/10.1055/s-2005-871737>>

17. Popkin, B. Does global obesity represent a global public health challenge? *Am. J. Clin. Nutr.* 93, 232–233 (2011).
18. Lago, F., Gómez, R., Gómez-Reino, J. J., Dieguez, C. & Gualillo, O. Adipokines as novel modulators of lipid metabolism. *Trends Biochem. Sci.* 34, 500–510 (2014).
19. De Boer, M. P. et al. Body mass index is related to microvascular vasomotion, this is partly explained by adiponectin. *Eur. J. Clin. Invest.* n/a–n/a (2014). doi:10.1111/eci.12284
20. Lee, C. M. Y., Huxley, R. R., Wildman, R. P. & Woodward, M. Indices of abdominal obesity are better discriminators of cardiovascular risk factors than BMI: a meta-analysis. *J. Clin. Epidemiol.* 61, 646–653 (2008).
21. Janssen, I., Heymsfield, S. B., Allison, D. B., Kotler, D. P. & Ross, R. Body mass index and waist circumference independently contribute to the prediction of nonabdominal, abdominal subcutaneous, and visceral fat. *Am. J. Clin. Nutr.* 75, 683–688 (2002).
22. Snijder, M. B., van Dam, R. M., Visser, M. & Seidell, J. C. What aspects of body fat are particularly hazardous and how do we measure them? *Int. J. Epidemiol.* 35, 83–92 (2006).
23. Weiner, J. & Lourie, J. A guide to field methods, handbook nr 9. (Blackwell Science Inc, 1986).
24. Després, J.-P. Body Fat Distribution and Risk of Cardiovascular Disease: An Update. *Circ.* 126, 1301–1313 (2012).
25. Welschen, L. M. et al. The effectiveness of adding cognitive behavioural therapy aimed at changing lifestyle to managed diabetes care for patients with type 2 diabetes: design of a randomised controlled trial. *BMC Public Health* 8, 1–10 (2007).
26. Wijnstok, N. J., Hoekstra, T., van Mechelen, W., Kemper, H. C. G. & Twisk, J. W. R. Cohort profile: the Amsterdam Growth and Health Longitudinal Study. *Int. J. Epidemiol.* 42, 422–9 (2013).
27. Van 't Riet, E. et al. Relationship Between A1C and Glucose Levels in the General Dutch Population: The New Hoorn Study. *Diabetes Care* 33, 61–66 (2010).
28. IJzerman, R. G. et al. Individuals at increased coronary heart disease risk are characterized by an impaired microvascular function in skin. *Eur. J. Clin. Invest.* 33, 536–542 (2003).
29. Czernichow, S. et al. Microvascular dysfunction in healthy insulin-sensitive overweight individuals. *J. Hypertens.* 28, 325–332 (2010).
30. Irving, R. J. et al. Microvascular correlates of blood pressure, plasma glucose, and insulin resistance in health. *Cardiovasc. Res.* 53, 271–276 (2002).
31. Kemper, H. & Hof, M. Design of a multiple longitudinal study of growth and health in teenagers. *Eur. J. Pediatr.* 129, 147–155. (1978).
32. Kemper, H., Post, G., Twisk, J. & van Mechelen, W. Lifestyle and obesity in adolescence and young adulthood: results from the Amsterdam growth and health longitudinal study (AGAHLS). *Int. J. Obes.* 23, S34–S40 (1999).
33. Kemper, H. Growth, Health and Fitness of Teenagers: Logitudinal Research in International Perspective. (Karger, 1985).
34. Kemper, H. The Amsterdam Growth Study: A Longitudinal Analysis of Health, Fitness, and Lifestyle. (Human Kinetics, 1995).
35. Kemper, H., Snel, J., Verschuur, R. & Strom-van Essen, L. Tracking of health and risk indicators of cardiovascular diseases from teenager to adult: The Amsterdam Growth and Health Study. *Prev. Med. (Baltim).* 19, 642–655 (1990).

36. Bakker, I. Affectors of adult lumbar bone: genetics, body composition and lifestyle. Results from the Amsterdam Growth and Health Study. (2003).
37. Ferreira, I. et al. The metabolic syndrome, cardiopulmonary fitness, and subcutaneous trunk fat as independent determinants of arterial stiffness: the Amsterdam Growth and Health Longitudinal Study. *Arch. Intern. Med.* 165, 875–882 (2005).
38. Ferreira, I. et al. Current and adolescent body fatness and fat distribution: relationships with carotid intima-media thickness and large artery stiffness at the age of 36 years. *J. Hypertens.* 22, 145–155 (2004).
39. Stam, C. Use of Magnetoencephalography (MEG) to study functional brain networks in neurodegenerative disorders. *J. Neurol. Sci.* 15, 125–134 (2010).
40. Douw, L. et al. Cognition is related to resting-state small-world network topology: a magnetoencephalographic study. *Neuroscience* 23, 169–177 (2011).
41. Twisk, J., Kemper, H., Van Mechelen, W. & Post, G. Tracking of risk factors for coronary heart disease over a 14-year period: a comparison between lifestyle and biologic risk factors with data from the Amsterdam Growth and Health Study. *American J. Epidemiol.* 145, 888–898 (1997).
42. Twisk, J., Staal, B., Brinkman, M., Kemper, H. & Van Mechelen, W. Tracking of lung function parameters and the longitudinal relationship with lifestyle. *Eur. Respir. J.* 12, 627–634 (1998).
43. Hoekstra, T., Barbosa-Leiker, C., Koppes, L. L. J. & Twisk, J. W. R. Developmental trajectories of body mass index throughout the life course: an application of Latent Class Growth (Mixture) Modelling. *Longit. Life Course Stud.* 2, 319–330 (2011).
44. Kemper, H. C., de Vente, W., Van Mechelen, W. & Twisk, J. W. Adolescent motor skill and performance: is physical activity in adolescence related to adult physical fitness? *Am. J. Hum. Biol.* 13, 180–189 (2001).
45. Post, B., Kemper, H. C. & Strom-Van Essen, L. Longitudinal changes in nutritional habits of teenagers: differences in intake between schooldays and weekend days. *Br. J. Nutr.* 57, 161–176 (1987).
46. Beal, V. The nutritional history in longitudinal research. *J. Am. Diet. Assoc.* 57, 161–176 (1987).
47. Marr, J. Individual dietary surveys: purpose and methods. *World Rev. Nutr. Diet.* 13, 105–164 (1971).
48. Bakker, I., Twisk, J. W. R., Van Mechelen, W., Mensink, G. B. M. & Kemper, H. C. G. Computerization of a dietary history interview in a running cohort: evaluation within the Amsterdam Growth and Health Longitudinal Study. *J. Clin. Nutr.* 57, 394–404 (2003).
49. Kemper, H. C. G. et al. Effects of health information in youth and young adulthood on risk factors for chronic diseases: 20-year study results from the Amsterdam Growth and Health Longitudinal Study. *Prev. Med. (Baltim.)* 35, 533–539 (2002).
50. Twisk, J. Different statistical models to analyze epidemiological observational longitudinal data: an example from the Amsterdam Growth and Health Longitudinal Study. *Int. J. Sports Med.* 18, S216–224 (1997).
51. Bornaards, C. M., Twisk, J. J. W. R., Snel, J., Van Mechelen, W. & Kemper, H. C. G. H. In a prospective study in young people, associations between changes in smoking behavior and risk factors for cardiovascular disease were complex. *J. Clin. Epidemiol.* 58, 1165–1171 (2005).

52. Bernaards, C. M. et al. Smoking and quantitative ultrasound parameters in the calcaneus in 36-year-old men and women. *Osteoporos. Int. a J. Establ. as result Coop. between Eur. Found. Osteoporos. Natl. Osteoporos. Found. USA* 15, 735–741 (2004).
53. Bernaards, C. et al. Smoking and quantitative ultrasound parameters in the calcaneus in 36-year old men and women. *Osteoporos. Int.* 15, 735–741 (2004).
54. Ketel, I. J. G. et al. Superiority of skinfold measurements and waist over waist-to-hip ratio for determination of body fat distribution in a population-based cohort of Caucasian Dutch adults. *Eur. J. Endocrinol. Eur. Fed. Endocr. Soc.* 156, 655–661 (2007).
55. Wijnstok, N. et al. The relationship of body fatness and body fat distribution with microvascular recruitment: The Amsterdam Growth and Health Longitudinal Study. *Microcirculation* 19, 273–9 (2012).
56. Van Lenthe, F. J., Van Mechelen, W., Kemper, H. C. & Twisk, J. W. Associations of a central pattern of body fat with blood pressure and lipoproteins from adolescence into adulthood: The Amsterdam Growth and Health Study. *Am. J. Epidemiol.* 1, 40–48 (1998).
57. Schouten, F. et al. Increases in central fat mass and decreases in peripheral fat mass are associated with accelerated arterial stiffening in healthy adults: The Amsterdam Growth and Health Longitudinal Study. *Am. J. Clin. Nutr.* 94, 40–48 (2011).
58. Te Velde, S. et al. Birthweight and arterial stiffness and blood pressure in adulthood: results from the Amsterdam Growth and Health Longitudinal Study. *Int. J. Epidemiol.* 33, 154–161 (2004).
59. Welten, D. C. et al. Weight-bearing activity during youth is a more important factor for peak bone mass than calcium intake. *J. bone Miner. Res. Off. J. Am. Soc. Bone Miner. Res.* 10, 1089–1096 (1995).
60. Twisk, J. W., Kemper, H. C., Van Mechelen, W. & Post, G. B. Clustering of risk factors for coronary heart disease. the longitudinal relationship with lifestyle. *Ann. Epidemiol.* 11, 157–165 (2001).
61. Van Bussel, B. C. et al. Endothelial dysfunction and low-grade inflammation are associated with greater arterial stiffness over a 6-year period. *Hypertension* 58, 588–595 (2011).
62. Bernaards, C. M., Twisk, J. W. R., Van Mechelen, W., Snel, J. & Kemper, H. C. G. A longitudinal study on smoking in relationship to fitness and heart rate response. *Med. Sci. Sport. Exerc.* 35, 793–800 (2003).
63. Hanewald, G. CES-D De Nederlandse versie. Een onderzoek naar betrouwbaarheid en validiteit. *Vakgr. Klin. Psychol. Univ. van Amsterdam* (1987).
64. Vingerhoets, A. J. & Flohr, P. J. Type A behaviour and self-reports of coping preferences. *Br. J. Med. Psychol.* 57 ( Pt 1), 15–21 (1984).
65. Sarason, I. G., Johnson, J. H. & Siegel, J. M. Assessing the impact of life changes: development of the Life Experiences Survey. *J. Consult. Clin. Psychol.* 46, 932–946 (1978).
66. Van Veldhoven, M. & Broersen, S. Measurement quality and validity of the “need for recovery scale”. *Occup. Environ. Med.* 60 Suppl 1, i3–i9 (2003).
67. Luteijn, E., Starren, J. & van Dijk, H. *The Manual for Dutch Personality Inventory.* (Swets&Zeitlinger Press, 1985).
68. Ware, J. E. & Sherbourne, C. D. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med. Care* 30, 473–483 (1992).

69. Van Diest, R., Milius, H., Markusse, R. & Snel, J. De slaap-waak-ervaring lijst. *Tijdschr. Soc. Geneeskd.* 10, 343–347 (1989).
70. Koppes, L. L. J. et al. Personality characteristics in adolescence predict long-term changes in body fatness. *Diabetes Res. Clin. Pract.* 79, e10–e13 (2008).
71. Koppes, L. L. J., Twisk, J. W. R., Van Mechelen, W., Snel, J. & Kemper, H. C. G. Cross-sectional and longitudinal relationships between alcohol consumption and lipids, blood pressure and body weight indices. *J. Stud. Alcohol* 66, 713–721 (2005).
72. Koppes, L. L. J., Twisk, J. W. R., Snel, J. & Kemper, H. C. G. Concurrent validity of alcohol consumption measurement in a “healthy” population; quantity-frequency questionnaire versus dietary history interview. *Br. J. Nutr.* 88, 427–434 (2002).
73. Twisk, J. & De Vente, W. Attrition in longitudinal studies. How to deal with missing data. *J. Clin. Epidemiol.* 55, 329–337 (2002).
74. Boreham, C. et al. Tracking of physical activity, fitness, body composition and diet from adolescence to young adulthood: The Young Hearts Project, Northern Ireland. *Int. J. Behav. Nutr. Phys. Act.* 1, 14 (2004).
75. Monyeki, M. A., Koppes, L. L. J., Monyeki, K. D., Kemper, H. C. G. & Twisk, J. W. R. Longitudinal relationships between nutritional status, body composition, and physical fitness in rural children of South Africa: The Ellisras longitudinal study. *Am. J. Hum. Biol. Off. J. Hum. Biol. Council.* 19, 551–558 (2007).
76. Ekelund, U., Sardinha, L. & Anderssen, S. Associations between objectively assessed physical activity and indicators of body fatness in 9- to 10-year old European children: a population-based study from 4 distinct regions in Europe (the European Youth Heart Study). *Am. J. Clin. Nutr.* 80, 584–590 (2004).
77. Grundy, S. M., Brewer, H. B., Cleeman, J. I., Smith, S. C. & Lenfant, C. Definition of Metabolic Syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition. in *Clin. Biochem. Rev.* 109, e13–e18 (The Australian Association of Clinical Biochemists, 2004).
78. Levy, B. I. et al. Impaired tissue perfusion: a pathology common to hypertension, obesity, and diabetes mellitus. *Circulation* 118, 968–976 (2008).
79. Jonk, A. M. et al. Microvascular dysfunction in obesity: a potential mechanism in the pathogenesis of obesity-associated insulin resistance and hypertension. *Physiol. Bethesda Md* 22, 252–260 (2007).
80. Wiernsperger, N., Nivoit, P., De Aguiar, L. G. K. & Bouskela, E. Microcirculation and the metabolic syndrome. *Microcirc. New York NY* 1994 14, 403–438 (2007).
81. Khan, F. et al. Impaired microvascular function in normal children: effects of adiposity and poor glucose handling. *J. Physiol.* 551, 705–711 (2003).
82. Ketel, I. J. G. et al. Obese but not normal-weight women with polycystic ovary syndrome are characterized by metabolic and microvascular insulin resistance. *J. Clin. Endocrinol. Metab.* 93, 3365–3372 (2008).
83. Steinberg, H. O. et al. Obesity/insulin resistance is associated with endothelial dysfunction. Implications for the syndrome of insulin resistance. *J. Clin. Invest.* 97, 2601–10 (1996).
84. De Jongh, R. T., Serné, E. H., Ijzerman, R. G., De Vries, G. & Stehouwer, C. D. A. Free fatty acid levels modulate microvascular function: relevance for obesity-associated insulin resistance, hypertension, and microangiopathy. *Diabetes* 53, 2873–2882 (2004).

85. Laine, H. et al. Preserved relative dispersion but blunted stimulation of mean flow, absolute dispersion, and blood volume by insulin in skeletal muscle of patients with essential hypertension. *Circulation* 97, 2146–2153 (1998).
86. Serne, E. H. et al. Direct evidence for insulin-induced capillary recruitment in skin of healthy subjects during physiological hyperinsulinemia. *Diabetes* 51, 1515–1522 (2002).
87. Lillioja, S. et al. Skeletal muscle capillary density and fiber type are possible determinants of in vivo insulin resistance in man. *J. Clin. Invest.* 80, 415–424 (1987).
88. Wong, T. Y. et al. Associations between the metabolic syndrome and retinal microvascular signs: the Atherosclerosis Risk In Communities study. *Invest. Ophthalmol. Vis. Sci.* 45, 2949–2954 (2004).
89. Schelbert, H. R. Coronary circulatory function abnormalities in insulin resistance: insights from positron emission tomography. *J. Am. Coll. Cardiol.* 53, S3–S8 (2009).
90. Debbabi, H. et al. Increased skin capillary density in treated essential hypertensive patients. *Am. J. Hypertens.* 19, 477–483 (2006).
91. Wang, L. et al. Coronary Risk Factors and Myocardial Perfusion in Asymptomatic Adults The Multi-Ethnic Study of Atherosclerosis ( MESA ). *J. Am. Coll. Cardiol.* 47, 565–572 (2006).
92. Wong, T. Y. et al. Retinal arteriolar narrowing and risk of diabetes mellitus in middle-aged persons. *Jama J. Am. Med. Assoc.* 287, 2528–2533 (2002).
93. Wong, T. Y. et al. Retinal arteriolar diameter and risk for hypertension. *Ann. Intern. Med.* 140, 248–255 (2004).
94. Nguyen, T. T. et al. Retinal arteriolar narrowing predicts incidence of diabetes: the Australian Diabetes, Obesity and Lifestyle (AusDiab) Study. *Diabetes* 57, 536–539 (2008).
95. Ikram, M. K. et al. Retinal vessel diameters and risk of hypertension: the Rotterdam Study. *Hypertension* 47, 189–194 (2006).
96. Antonios, T. F., Singer, D. R., Markandu, N. D., Mortimer, P. S. & MacGregor, G. A. Rarefaction of skin capillaries in borderline essential hypertension suggests an early structural abnormality. *Hypertension* 33, 998–1001 (1999).
97. Noon, J. P. et al. Impaired microvascular dilatation and capillary rarefaction in young adults with a predisposition to high blood pressure. *J. Clin. Invest.* 99, 1873–1879 (1997).
98. Hedman, A., Reneland, R. & Lithell, H. O. Alterations in skeletal muscle morphology in glucose-tolerant elderly hypertensive men: relationship to development of hypertension and heart rate. *J. Hypertens.* 18, 559–565 (2000).
99. Levy, B. I. Blood pressure as a potential biomarker of the efficacy angiogenesis inhibitor. *Ann. Oncol.* 20, 20–203 (2009).
100. De Boer, M. P. et al. Sunitinib-induced reduction in skin microvascular density is a reversible phenomenon. *Ann. Oncol.* 21, 1923–1924 (2010).
101. Greene, A. S., Tonellato, P. J., Lui, J., Lombard, J. H. & Cowley, A. W. Microvascular rarefaction and tissue vascular resistance in hypertension. *Am. J. Physiol.* 256, H126–H131 (1989).
102. Hudetz, A. G. Percolation phenomenon: the effect of capillary network rarefaction. *Microvasc. Res.* 45, 1–10 (1993).
103. Jacobsen, J. C. B., Gustafsson, F. & Holstein-Rathlou, N.-H. A model of physical factors in the structural adaptation of microvascular networks in normotension and hypertension. *Physiol. Meas.* 24, 891–912 (2003).

104. Jacobsen, J. C. B., Hornbech, M. S. & Holstein-Rathlou, N.-H. A tissue in the tissue: models of microvascular plasticity. *Eur. J. Pharm. Sci. Off. J. Eur. Fed. Pharm. Sci.* 36, 51–61 (2009).
105. Frisbee, J. C. Hypertension-independent microvascular rarefaction in the obese Zucker rat model of the metabolic syndrome. *Microcirc. New York NY* 1994 12, 383–392 (2005).
106. De Boer, M. P. et al. Birth weight relates to salt sensitivity of blood pressure in healthy adults. *Hypertension* 51, 928–932 (2008).
107. Johnson, R., Herrera-Acosta, J., Schreiner, G. & Rodriguez-Iturbe, B. Subtle acquired renal injury as a mechanism of salt-sensitivity hypertension. *N. Engl. J. Med.* 346, 913–923 (2002).
108. Le Noble, F., Stassen, F., Hacking, W. & Struijker-Boudier, H. A. J. Angiogenesis and hypertension. *J. Hypertens.* 16, 1563–1572 (1998).
109. Galletti, F. et al. NaCl sensitivity of essential hypertensive patients is related to insulin resistance. *J. Hypertens.* 15, 1485–1491 (1997).
110. Baron, A. D. Hemodynamic actions of insulin. *Am. J. Physiol. Metab.* 267, E187–E202 (1994).
111. Yki-Järvinen, H. & Utriainen, T. Insulin-induced vasodilation: physiology or pharmacology? *Diabetologia* 41, 369–379 (1998).
112. Shankar, S. S., Considine, R. V., Gorski, J. C. & Steinberg, H. O. Insulin sensitivity is preserved despite disrupted endothelial function. *Am. J. Physiol. - Endocrinol. Metab.* 291, E691–E696 (2006).
113. Vincent, M. A., Clerk, L. H., Rattigan, S., Clark, M. G. & Barrett, E. J. Active role for the vasculature in the delivery of insulin to skeletal muscle. *Clin. Exp. Pharmacol. Physiol.* 32, 302–307 (2005).
114. Wallis, M. G. et al. Insulin-mediated hemodynamic changes are impaired in muscle of Zucker obese rats. *Diabetes* 51, 3492–3498 (2002).
115. Ellmerer, M. et al. Physiological hyperinsulinemia in dogs augments access of macromolecules to insulin-sensitive tissues. *Diabetes* 53, 2741–2747 (2004).
116. Ellmerer, M. et al. Reduced access to insulin-sensitive tissues in dogs with obesity secondary to increased fat intake. *Diabetes* 55, 1769–1775 (2006).
117. Bonadonna, R. C. et al. Role of tissue-specific blood flow and tissue recruitment in insulin-mediated glucose uptake of human skeletal muscle. *Circulation* 98, 234–241 (1998).
118. Clerk, L. H. et al. Obesity blunts insulin-mediated microvascular recruitment in human forearm muscle. *Diabetes* 55, 1436–1442 (2006).
119. Gudbjörnsdóttir, S., Sjöstrand, M., Strindberg, L. & Lönnroth, P. Decreased muscle capillary permeability surface area in type 2 diabetic subjects. *J. Clin. Endocrinol. Metab.* 90, 1078–1082 (2005).
120. Sjöstrand, M. et al. Delayed transcapillary transport of insulin to muscle interstitial fluid in obese subjects. *Diabetes* 51, 2742–2748 (2002).
121. Murdolo, G. et al. Effects of Intrabrachial metacholine infusion on muscle capillary recruitment and forearm glucose uptake during physiological hyperinsulinemia in obese, insulin-resistant individuals. *J. Clin. Endocrinol. Metab.* 93, 2764–2773 (2008).
122. Weinhandl, H. et al. Physiological hyperinsulinemia has no detectable effect on access of macromolecules to insulin-sensitive tissues in healthy humans. *Diabetes* 56, 2213–2217 (2007).

123. Stefanovska, A., Bracic, M. & Kvernmo, H. D. Wavelet analysis of oscillations in the peripheral blood circulation measured by laser Doppler technique. *IEEE Trans. Biomed. Eng.* 46, 1230–1239 (1999).
124. Rucker, M., Strobel, O., Vollmar, B., Roesken, F. & Menger, M. D. Vasomotion in critically perfused muscle protects adjacent tissues from capillary perfusion failure. *Am. J. Physiol. Hear. Circ. Physiol.* 279, H550–H558 (2000).
125. Kvernmo, H. D., Stefanovska, A., Kirkeboen, K. A. & Kvernebo, K. Oscillations in the human cutaneous blood perfusion signal modified by endothelium-dependent and endothelium-independent vasodilators. *Microvasc. Res.* 57, 298–309 (1999).
126. Rossi, M., Maurizio, S. & Carpi, A. Skin blood flowmotion response to insulin iontophoresis in normal subjects. *Microvasc. Res.* 70, 17–22 (2005).
127. Newman, J. M. B. et al. Decreased microvascular vasomotion and myogenic response in rat skeletal muscle in association with acute insulin resistance. *J. Physiol.* 587, 2579–2588 (2009).
128. Jonk, A. M. et al. Meal related increases in microvascular vasomotion are impaired in obese individuals: a potential mechanism in the pathogenesis of obesity related insulin resistance. *Diabetes Care* 34, S342–348 (2011).
129. Keske, M. A., Clerk, L. H., Price, W. J., Jahn, L. A. & Barrett, E. J. Obesity Blunts Microvascular Recruitment in Human Forearm Muscle After a Mixed Meal. *Diabetes Care* 32, 1672–1677 (2009).
130. Wang, H., Wang, A. X. & Barrett, E. J. Caveolin-1 is required for vascular endothelial insulin uptake. *Am. J. Physiol. - Endocrinol. Metab.* 300, E134–E144 (2011).
131. Muniyappa, R., Montagnani, M., Koh, K. K. & Quon, M. J. Cardiovascular actions of insulin. *Endocr. Rev.* 28, 463–491 (2007).
132. Kubota, T. et al. Impaired insulin signaling in endothelial cells reduces insulin-induced glucose uptake by skeletal muscle. *Cell Metab.* 13, 294–307 (2011).
133. Li, R. et al. Vascular insulin resistance in prehypertensive rats: role of PI3-kinase/Akt/eNOS signaling. *Eur. J. Pharmacol.* 628, 140–147 (2010).
134. Eringa, E. C., Stehouwer, C. D. A., Roos, M. H., Westerhof, N. & Sipkema, P. Selective resistance to vasoactive effects of insulin in muscle resistance arteries of obese Zucker (fa/fa) rats. *Am. J. Physiol. - Endocrinol. Metab.* 293, E1134–E1139 (2007).
135. Jiang, Z. Y. et al. Characterization of selective resistance to insulin signaling in the vasculature of obese Zucker (fa/fa) rats. *J. Clin. Invest.* 104, 447–457 (1999).
136. Kim, J., Montagnani, M., Koh, K. K. & Quon, M. J. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. *Circulation* 113, 1888–1904 (2006).
137. Symons, J. D. et al. Contribution of insulin and Akt1 signaling to endothelial nitric oxide synthase in the regulation of endothelial function and blood pressure. *Circ. Res.* 104, 1085–1094 (2009).
138. Cardillo, C. et al. Insulin stimulates both endothelin and nitric oxide activity in the human forearm. *Circulation* 100, 820–825 (1999).
139. Gudbjörnsdottir, S., Elam, M., Sellgren, J. & Anderson, E. A. Insulin increases forearm vascular resistance in obese, insulin-resistant hypertensives. *J. Hypertens.* 14, 91–97 (1996).
140. Cardillo, C., Campia, U., Iantorno, M. & Panza, J. A. Enhanced Vascular Activity of Endogenous Endothelin-1 in Obese Hypertensive Patients. *Vascular* 43, 36–40 (2004).



141. Lteif, A. A. et al. Hyperinsulinemia fails to augment ET-1 action in the skeletal muscle vascular bed in vivo in humans. *Am. J. Physiol. Endocrinol. Metab.* 295, E1510–E1517 (2008).
142. Mather, K. J., Mirzamohammadi, B., Lteif, A., Steinberg, H. O. & Baron, A. D. Endothelin contributes to basal vascular tone and endothelial dysfunction in human obesity and type 2 diabetes. *Diabetes* 51, 3517–3523 (2002).
143. Ahlborg, G., Shemyakin, A., Böhm, F., Gonon, A. & Pernow, J. Dual endothelin receptor blockade acutely improves insulin sensitivity in obese patients with insulin resistance and coronary artery disease. *Diabetes Care* 30, 591–596 (2007).
144. Lteif, A. A., Vaishnava, P., Baron, A. D. & Mather, K. J. Endothelin limits insulin action in obese/insulin-resistant humans. *Diabetes* 56, 728–734 (2007).
145. Lee, D.-E., Kehlenbrink, S., Lee, H., Hawkins, M. & Yudkin, J. S. Getting the message across: mechanisms of physiological cross talk by adipose tissue. *Am. J. Physiol. - Endocrinol. Metab.* 296, E1210–29 (2009).
146. Meijer, R. I. et al. Perivascular Adipose Tissue and Its Role in Type 2 Diabetes and Cardiovascular Disease. *Curr. Diab. Rep.* 11, 211–217 (2011).
147. Schenk, S., Saberi, M. & Olefsky, J. M. Insulin sensitivity: modulation by nutrients and inflammation. *J. Clin. Invest.* 118, 2992–3002 (2008).
148. Shulman, G. I. Unraveling the cellular mechanism of insulin resistance in humans: new insights from magnetic resonance spectroscopy. *Physiol. Bethesda Md* 19, 183–190 (2004).
149. Kelley, D. E., Williams, K. V & Price, J. C. Insulin regulation of glucose transport and phosphorylation in skeletal muscle assessed by PET. *Am. J. Physiol.* 277, E361–E369 (1999).
150. Clerk, L. H., Rattigan, S. & Clark, M. G. Lipid infusion impairs physiologic insulin-mediated capillary recruitment and muscle glucose uptake in vivo. *Diabetes* 51, 1138–1145 (2002).
151. Liu, Z., Liu, J., Jahn, L. A., Fowler, D. E. & Barrett, E. J. Infusing Lipid Raises Plasma Free Fatty Acids and Induces Insulin Resistance in Muscle Microvasculature. *J. Clin. Endocrinol. Metab.* 94, 3543–3549 (2009).
152. Bakker, W. et al. Protein kinase C theta activation induces insulin-mediated constriction of muscle resistance arteries. *Diabetes* 57, 706–713 (2008).
153. Sarzani, R., Salvi, F., Dessì-Fulgheri, P. & Rappelli, A. Renin-angiotensin system, natriuretic peptides, obesity, metabolic syndrome, and hypertension: an integrated view in humans. *J. Hypertens.* 26, 831–843 (2008).
154. Prasad, A. & Quyyumi, A. Renin-angiotensin system and angiotensin receptor blockers in the metabolic syndrome. *Circulation* 110, 1507–1512 (2004).
155. Lu, H., Boustany-Kari, C. M., Daugherty, A. & Cassis, L. A. Angiotensin II increases adipose angiotensinogen expression. *Am. J. Physiol. - Endocrinol. Metab.* 292, E1280–E1287 (2007).
156. Chai, W. et al. Angiotensin II type 1 and type 2 receptors regulate basal skeletal muscle microvascular volume and glucose use. *Hypertension* 55, 523–530 (2010).
157. Andreozzi, F., Laratta, E., Sciacqua, A., Perticone, F. & Sesti, G. Angiotensin II Impairs the Insulin Signaling Pathway Promoting Production of Nitric Oxide by Inducing Phosphorylation of Insulin Receptor Substrate-1 on Ser312 and Ser616 in Human Umbilical Vein Endothelial Cells. *Circ. Res.* 94, 1211–1218 (2004).

158. Velloso, L. A. et al. Cross-talk between the insulin and angiotensin signaling systems. *Proc. Natl. Acad. Sci. U. S. A.* 93, 12490–12495 (1996).
159. Vincent, M. A. et al. Mixed meal and light exercise each recruit muscle capillaries in healthy humans. *Am. J. Physiol. - Endocrinol. Metab.* 290, E1191–E1197 (Am Physiological Soc, 2006).
160. Liu, Z. The renin-angiotensin system and vascular insulin resistance. *Curr. Diab. Rep.* 7, 34–42 (2007).
161. Jandeleit-Dahm, K. A. M., Tikellis, C., Reid, C. M., Johnston, C. I. & Cooper, M. E. Why blockade of the renin-angiotensin system reduces the incidence of new-onset diabetes. *J. Hypertens.* 23, 463–73 (2005).
162. McMurray, J. et al. Effects of valsartan on the incidence of diabetes and cardiovascular events. *N. Engl. J. Med.* 362, 1477–1490 (2010).
163. Jamerson, K. A., Nesbitt, S. D., Amerena, J. V, Grant, E. & Julius, S. Angiotensin mediates forearm glucose uptake by hemodynamic rather than direct effects. *Hypertension* 27, 854–858 (1996).
164. Buchanan, T. A. et al. Angiotensin II increases glucose utilization during acute hyperinsulinemia via a hemodynamic mechanism. *J. Clin. Invest.* 92, 720–726 (1993).
165. Goossens, G. H., Blaak, E. E., Saris, W. H. M. & Van Baak, M. A. Angiotensin II-induced effects on adipose and skeletal muscle tissue blood flow and lipolysis in normal-weight and obese subjects. *J. Clin. Endocrinol. Metab.* 89, 2690–2696 (2004).
166. Jonk, A. M. et al. Angiotensin II enhances insulin-stimulated whole-body glucose disposal but impairs insulin-induced capillary recruitment in healthy volunteers. *J. Clin. Endocrinol. Metab.* 95, 3901–3908 (2010).
167. Jonk, A. M. et al. Acute angiotensin II receptor blockade improves insulin-induced microvascular function in hypertensive individuals. *Microvasc. Res.* 82, 77–83 (2011).
168. Van Der Zijl, N. J. et al. Valsartan-induced improvement in insulin sensitivity is not paralleled by changes in microvascular function in individuals with impaired glucose metabolism. *J. Hypertens.* 29, 1955–1962 (2011).
169. Shoelson, S. E., Lee, J. & Goldfine, A. B. Inflammation and insulin resistance. *J. Clin. Invest.* 116, 2308 (2006).
170. Steinberg, G. R. et al. Tumor necrosis factor alpha-induced skeletal muscle insulin resistance involves suppression of the AMPK-kinase signalling. *Cell Metab.* 4, 465–474 (2006).
171. Youd, J., Rattigan, S. & Clark, M. G. Acute impairment of insulin mediated capillary recruitment and glucose uptake in rat skeletal muscle in vivo by TNF-alpha. *Diabetes* 49, 1904–1909 (2000).
172. Eringa, E. C. et al. Physiological concentrations of insulin induce endothelin-dependent vasoconstriction of skeletal muscle resistance arteries in the presence of tumor necrosis factor-alpha dependence on c-Jun N-terminal kinase. *Arterioscler. Thromb. Vasc. Biol.* 26, 274–280 (2006).
173. Hirosumi, J. et al. A central role for JNK in obesity and insulin resistance. *Nature* 420, 333–336 (2002).
174. Pausova, Z. et al. Role of tumor necrosis factor-alpha gene locus in obesity and obesity-associated hypertension in French Canadians. *Hypertension* 36, 14–19 (2000).
175. Kiortsis, D. N. et al. Effects of infliximab treatment on insulin resistance in patients with rheumatoid arthritis and ankylosing spondylitis. *Ann. Rheum. Dis.* 64, 921–3 (2006).

176. Van Eijk, I. C. et al. Microvascular function is impaired in ankylosing spondylitis and improves after tumour necrosis factor alpha blockade. *Ann. Rheum. Dis.* 68, 362–366 (2009).
177. Hotamisligil, G. S. & Spiegelman, B. M. Tumor necrosis factor alpha: a key component of the obesity-diabetes link. *Diabetes* 43, 1271–1278 (1994).
178. Bruun, J. M., Lihn, A. S., Pedersen, S. B. & Richelsen, B. Monocyte chemoattractant protein-1 release is higher in visceral than subcutaneous human adipose tissue (AT): implication of macrophages resident in the AT. *J. Clin. Endocrinol. Metab.* 90, 2282–2289 (2005).
179. Ijzerman, R. et al. TNF-alpha levels are associated with skin capillary recruitment in humans: a potential explanation for the relationship between TNF-alpha and insulin resistance. *Clin. Sci. London Engl.* 1979 110, 361–368 (2006).
180. Hotamisligil, G. S., Arner, P., Caro, J. F., Atkinson, R. L. & Spiegelman, B. M. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. *J. Clin. Invest.* 95, 2409–2415 (1995).
181. Chatterjee, T. K. et al. Proinflammatory phenotype of perivascular adipocytes: influence of high-fat feeding. *Circ. Res.* 104, 541–549 (2009).
182. Mazurek, T. et al. Human epicardial adipose tissue is a source of inflammatory mediators. *Circulation* 108, 2460–2466 (2003).
183. Yudkin, J. S., Eringa, E. & Stehouwer, C. D. A. “Vasocrine” signalling from perivascular fat: a mechanism linking insulin resistance to vascular disease. *Lancet* 365, 1817–1820 (2005).
184. Greenstein, A. S. et al. Local inflammation and hypoxia abolish the protective anticontractile properties of perivascular fat in obese patients. *Circulation* 119, 1661–1670 (2009).
185. Eringa, E. C. et al. Adiponectin uncovers insulin-mediated vasodilatation by activating AMPK in microvascular endothelium and inhibiting insulin’s vasoconstrictor effects. *Diabetes* 57, A385–A385 (2008).
186. Sowers, J. Obesity as a cardiovascular risk factor\*1. *Am. J. Med.* 115, 37–41 (2003).
187. Wilson, P. W. F. & Meigs, J. B. Cardiometabolic risk: a Framingham perspective. *Int. J. Obes.* 2005 32 Suppl 2, S17–S20 (2008).
188. The Emerging Risk Factors Collaboration. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. *Lancet* 377, 1085–1095 (2011).
189. Serné, E. H., de Jongh, R. T., Eringa, E. C., IJzerman, R. G. & Stehouwer, C. D. A. Microvascular Dysfunction: A Potential Pathophysiological Role in the Metabolic Syndrome. *Hypertens.* 50, 204–211 (2007).
190. Cholesterol, N. & Program, E. 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) final report. *Circulation* 106, 3143–3421 (2002).
191. Nederlands Huisartsen Genootschap. Cardiovasculair risicomanagement. (2006).
192. Ketel, I. J. G. et al. Microvascular function has no menstrual-cycle-dependent variation in healthy ovulatory women. *Microcirc.* New York NY 1994 16, 714–724 (2009).
193. Schokker, D. F., Visscher, T. L. S., Nooyens, A. C. J., Van Baak, M. A. & Seidell, J. C. Prevalence of overweight and obesity in the Netherlands. *Obes. Rev. an Off. J. Int. Assoc. Study Obes.* 8, 649–652 (2007).

194. Adair, L. S. Child and adolescent obesity: epidemiology and developmental perspectives. *Physiol. Behav.* 94, 8–16 (2008).
195. Finucane, M. M. et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet* 377, 557–567 (2011).
196. Ezzati, M., Lopez, A. D., Rodgers, A., Vander Hoorn, S. & Murray, C. J. L. Selected major risk factors and global and regional burden of disease. *Lancet* 360, 1347–1360 (2002).
197. Alberga, A. S., Sigal, R. J., Goldfield, G., Prud Homme, D. & Kenny, G. P. Overweight and obese teenagers: why is adolescence a critical period? *Pediatr. Obes.* (2012). doi:10.1111/j.2047-6310.2011.00046.x
198. Barker, D. J. P., Osmond, C., Forsén, T. J., Kajantie, E. & Eriksson, J. G. Trajectories of growth among children who have coronary events as adults. *N. Engl. J. Med.* 353, 1802–9 (2005).
199. Ferraro, K. F., Thorpe, R. J. & Wilkinson, J. A. The life course of severe obesity: does childhood overweight matter? *Journals Gerontol. Ser. B Psychol. Sci. Soc. Sci.* 58, S110–S119 (2003).
200. Ovesen, L. Adolescence: a critical period for long-term tracking of risk for coronary heart disease? *Ann. Nutr. Metab.* 50, 317–324 (2006).
201. Stovitz, S. D., Demerath, E. W., Hannan, P. J., Lytle, L. A. & Himes, J. H. Growing into obesity: Patterns of height growth in those who become normal weight, overweight, or obese as young adults. *Am. J. Hum. Biol. Off. J. Hum. Biol. Council.* 23, 635–641 (2011).
202. Nonnemaker, J. M., Morgan-Lopez, A. A., Pais, J. M. & Finkelstein, E. A. Youth BMI trajectories: evidence from the NLSY97. *Obes. Silver Spring Md* 17, 1274–1280 (2009).
203. Pryor, L. E. et al. Developmental Trajectories of Body Mass Index in Early Childhood and Their Risk Factors. *Arch. Pediatr.* 165, 906–912 (2011).
204. Rajaleid, K., Janszky, I. & Hallqvist, J. Small birth size, adult overweight, and risk of acute myocardial infarction. *Epidemiol. Cambridge Mass* 22, 138–147 (2011).
205. Tirosh, A. et al. Adolescent BMI trajectory and risk of diabetes versus coronary disease. *N. Engl. J. Med.* 364, 1315–1325 (2011).
206. Must, A. & Strauss, R. S. Risks and consequences of childhood and adolescent obesity. *Int. J. Obes. Relat. Metab. Disord. J. Int. Assoc. Study Obes.* 23 Suppl 2, S2–11 (1999).
207. Kuk, J. L. & Lee, S. Independent associations between cardiorespiratory fitness and abdominal obesity with metabolic risk in adolescents and adults. *Obes. Silver Spring Md* 18, 2061–2063 (2010).
208. Stoner, L., Stoner, K. R., Young, J. M. & Fryer, S. Preventing a cardiovascular disease epidemic among indigenous populations through lifestyle changes. *Int. J. Prev. Med.* 3, 230–240 (2012).
209. Twisk, J. W., Kemper, H. C. & Van Mechelen, W. Tracking of activity and fitness and the relationship with cardiovascular disease risk factors. *Med. Sci. Sport. Exerc.* 32, 1455–1461 (2000).
210. Aeberli, I., Kaspar, M. & Zimmermann, M. B. Dietary intake and physical activity of normal weight and overweight 6 to 14 year old Swiss children. *Swiss Med. Wkly. Off. J. Swiss Soc. Infect. Dis. Swiss Soc. Intern. Med. Swiss Soc. Pneumol.* 137, 424–430 (2007).
211. Druet, C. & Ong, K. K. Early childhood predictors of adult body composition. *Best Pract. Res. Clin. Endocrinol. Metab.* 22, 489–502 (2008).

212. Wijnstok, N., Serne, E., Hoekstra, T., Smulders, Y. & Twisk, J. The relationship between 30-year developmental patterns of body fat and body fat distribution and its vascular properties: The Amsterdam Growth and Health Longitudinal Study. *Nutr. Diabetes* in press, (2013).
213. Muthén, B. O. & Muthén, L. K. Integrating person-centered and variable centered analyses: Growth Mixture Modeling with latent trajectory classes. *Alcohol. Clin. Exp. Res.* 24, 882–891 (2000).
214. Nagin, D. S. & Odgers, C. L. Group-based trajectory modeling in clinical research. *Annu. Rev. Clin. Psychol.* 6, 109–138 (2010).
215. Henneberg, M. & Ulijaszek, S. J. Body frame dimensions are related to obesity and fatness: Lean trunk size, skinfolds, and body mass index. *Am. J. Hum. Biol. Off. J. Hum. Biol. Counc.* 91, 83–91 (2010).
216. Kriemler, S. et al. Estimation of percentage body fat in 6- to 13-year-old children by skinfold thickness, body mass index and waist circumference. *Br. J. Nutr.* 104, 1565–1572 (2010).
217. Freedman, D. S. & Sherry, B. The validity of BMI as an indicator of body fatness and risk among children. *Pediatrics* 124 Suppl , S23–S34 (2009).
218. Lohman, T. G. & Going, S. B. Body composition assessment for development of an international growth standard for preadolescent and adolescent children. *Food Nutr. Bull.* 27, S314–325 (2006).
219. Perkins, K. A. Effects of tobacco smoking on caloric intake. *Br. J. Addict.* 87, 193–205 (1992).
220. Must, A. et al. Behavioral risk factors in relation to visceral adipose tissue deposition in adolescent females. *Int. J. Pediatr. Obes. IJPO an Off. J. Int. Assoc. Study Obes.* 3 Suppl 1, 28–36 (2008).
221. Laitinen, J., Pietiläinen, K., Wadsworth, M., Sovio, U. & Järvelin, M.-R. Predictors of abdominal obesity among 31-y-old men and women born in Northern Finland in 1966. *Eur. J. Clin. Nutr.* 58, 180–190 (2004).
222. Association, A. H. et al. Dietary Recommendations for Children and Adolescents: A Guide for Practitioners. *Pediatr.* 117 , 544–559 (2006).
223. Ferreira, I., Van De Laar, R. J., Prins, M. H., Twisk, J. W. & Stehouwer, C. D. Carotid stiffness in young adults: a life-course analysis of its early determinants: the Amsterdam Growth and Health Longitudinal Study. *Hypertension* 59, 54–61 (2012).
224. Baird, J. et al. Being big or growing fast: systematic review of size and growth in infancy and later obesity. *BMJ Br. Med. J.* 331, 929 (2005).
225. Huang, D., Brecht, M.-L., Hara, M. & Hser, Y.-I. Influences of a covariate on growth mixture modeling. *J. Drug Issues* 40, 173–194 (2010).
226. Ostbye, T., Malhorta, R. & Landerman, L. R. Body mass trajectories through adulthood: results from the National Longitudinal Survey of Youth 1979 Cohort (1981–2006). *Int. J. Epidemiol.* 40, 240–250 (2011).
227. Pryor, L. E. et al. Developmental trajectories of body mass index in early childhood and their risk factors: An 8-year longitudinal study. *Arch. Pediatr. Adolesc. Med.* 165, 906–912 (2011).
228. Nagin, D. S. & Odgers, C. L. Group-based trajectory modelling in clinical research. *Annu. Rev. Clin. Psychol.* 6, 109–138 (2010).
229. Jung, T. & Wickrama, K. A. S. An introduction to Latent Class Growth Analysis and Growth Mixture Modeling. *Soc. Personal. Psychol. Compass* 2, 302–317 (2008).

230. Nylund, K., Asparouhov, T. & Muthén, B. O. Deciding on the number of classes in Latent Class Analysis and Growth Mixture Modelling: A Monte Carlo Simulation Study. *Struct. Equ. Model.* 14, 535–569 (2007).
231. Muthén, L. K. & Muthén, B. O. *Mplus user's guide*. Seventh edition. (2012).
232. Mitchell, G. et al. Cross-sectional relations of peripheral microvascular function, cardiovascular disease risk factors, and aortic stiffness. *Circulation* 112, 3722–3728 (2005).
233. Strandberg, T. E. et al. Explaining the obesity paradox: cardiovascular risk, weight change, and mortality during long-term follow-up in men. *Eur. Heart J.* 30, 1720–1727 (2009).
234. Hassan, A. A. & Tooke, J. E. Mechanism of the postural vasoconstrictor response in the human foot. *Clin. Sci. London Engl.* 1979 75, 379–387 (1988).
235. Feihl, F., Liaudet, L., Waerber, B. & Levy, B. I. Hypertension: A Disease of the Microcirculation? *Hypertens.* 48, 1012–1017 (2006).
236. Park, J. B. & Schiffrin, E. L. Small artery remodeling is the most prevalent (earliest?) form of target organ damage in mild essential hypertension. *J. Hypertens.* 19, 921–930 (2001).
237. Struijker-Boudier, H. A. J., Heijnen, B. F. J., Liu, Y.-P. & Staessen, J. A. Phenotyping the Microcirculation. *Hypertens.* 60, 523–527 (2012).
238. Dijk, J. M., Algra, A., Van Der Graaf, Y., Grobbee, D. E. & Bots, M. L. Carotid stiffness and the risk of new vascular events in patients with manifest cardiovascular disease. The SMART study. *Eur. Heart J.* 26, 1213–1220 (2005).
239. WHO | Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. at <[http://www.who.int/diabetes/publications/diagnosis\\_diabetes2006/en/index.html#Ugzgna2Z3x4.mendeley](http://www.who.int/diabetes/publications/diagnosis_diabetes2006/en/index.html#Ugzgna2Z3x4.mendeley)>
240. Baron, R. & Kenny, D. The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *J. Pers. Soc. Psychol.* 51, 1173–1182 (1986).
241. MacKinnon, D., Krull, J. & Lockwood, C. Equivalence of the Mediation, Confounding and Suppression Effect. *Prev. Sci.* 1, 173–181 (2000).
242. Sobel, M. in *Common Probl. Solut. (LongJS)* 46–64 (Sage Publications, 1988).
243. Martina, B., Dieterle, T., Weinbacher, M. & Battagay, E. Effects of losartan titrated to losartan/hydrochlorothiazide and amlodipine on left ventricular mass in patients with mild-to-moderate hypertension : A double-blind randomized controlled study. *Cardiology* 92, 110–114
244. Ferrannini, E. & Mari, A. How to measure insulin sensitivity. *J. Hypertens.* 16, 895–906
245. Bonora, E. et al. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care* 23, 57–63 (2000).
246. Mather, K. J. et al. Repeatability Characteristics of Simple Indices of Insulin Resistance: Implications for Research Applications. *J. Clin. Endocrinol. Metab.* 86, 5457–5464 (2001).
247. Matsuda, M. & DeFronzo, R. A. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care* 22, 1462–1470 (1999).
248. Holowatz, L. A., Thompson-Torgerson, C. S. & Kenney, W. L. The human cutaneous circulation as a model of generalized microvascular function. *J. Appl. Physiol.* 105, 370–372 (2008).

249. Sabanayagam, C. & Shankar, A. Sleep duration and cardiovascular disease: results from the National Health Interview Survey. *Sleep* 33, 1037–1042 (2010).
250. Hayes, A. L., Xu, F., Babineau, D. & Patel, S. R. Sleep duration and circulating adipokine levels. *Sleep* 34, 147–152 (2011).
251. Wolk, R., Gami, A. S., Garcia-Touchard, A. & Somers, V. K. Sleep and cardiovascular disease. *Curr. Probl. Cardiol.* 30, 625–662 (2005).
252. Hoevenaer-Blom, M. P., Spijkerman, A. M., Kromhout, D., van den Berg, J. F. & Verschuren, W. M. Sleep duration and sleep quality in relation to 12-year cardiovascular disease incidence: the MORGEN study. *Sleep* 34, 1487–1492 (2011).
253. Spiegel, K., Knutson, K., Leproult, R., Tasali, E. & van Cauter, E. Sleep loss: a novel risk factor for insulin resistance and Type 2 diabetes. *J. Appl. Physiol.* 99, 2008–2019 (2005).
254. Spiegel, K., Leproult, R. & van Cauter, E. Impact of sleep debt on metabolic and endocrine function. *Lancet* 354, 1435–1439 (1999).
255. Tochikubo, O., Ikeda, A., Miyajima, E. & Ishii, M. Effects of insufficient sleep on blood pressure monitored by a new multibiomedical recorder. *Hypertension* 27, 1318–1324 (1996).
256. Bansil, P., Kuklina, E. V., Merritt, R. K. & Yoon, P. W. Associations between sleep disorders, sleep duration, quality of sleep, and hypertension: results from the National Health and Nutrition Examination Survey, 2005 to 2008. *J. Clin. Hypertens.* 13, 739–743 (2011).
257. Meier-Ewert, H. K. et al. Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. *J. Am. Coll. Cardiol.* 43, 678–683 (2004).
258. Vgontzas, A. N. et al. Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. *J. Clin. Endocrinol. Metab.* 89, 2119–2126 (2004).
259. Penev, P. D. Short sleep and circulating adipokine concentrations: does the fat hit the fire? *Sleep* 34, 131–132 (2011).
260. Galarraga, B., Khan, F., Kumar, P., Pullar, T. & Belch, J. J. C-reactive protein: the underlying cause of microvascular dysfunction in rheumatoid arthritis. *Rheumatol.* 47, 1780–1784 (2008).
261. Kemper, H. in (Borms, J., Hebbelink, M. & Hills, A. P.) 47, (Karger, 2004).
262. Van Diest, R. Subjective sleep characteristics as coronary risk factors, their association with Type A behaviour and vital exhaustion. *J. Psychosom. Res.* 34, 415–426 (1990).
263. Wendel-Vos, G. C., Schuit, A. J., Saris, W. H. & Kromhout, D. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. *J. Clin. Epidemiol.* 56, 1163–1169 (2003).
264. Bernaards, C. M., Twisk, J. W. R., van Mechelen, W., Snel, J. & Kemper, H. C. G. Comparison between self-report and a dipstick method (NicCheck 1) to assess nicotine intake. *Eur. Addict. Res.* 10, 163–167 (2004).
265. Van Bussel, B. C. et al. Fish consumption in healthy adults is associated with decreased circulating biomarkers of endothelial dysfunction and inflammation during a 6-year follow-up. *J. Nutr.* 141, 1719–1725 (2011).
266. Meisinger, C., Heier, M., Lowel, H., Schneider, A. & Doring, A. Sleep duration and sleep complaints and risk of myocardial infarction in middle-aged men and women from the general population: the MONICA/KORA Augsburg cohort study. *Sleep* 30, 1121–1127 (2007).

267. Kronholm, E., Laatikainen, T., Peltonen, M., Sippola, R. & Partonen, T. Self-reported sleep duration, all-cause mortality, cardiovascular mortality and morbidity in Finland. *Sleep Med.* 12, 215–221 (2011).
268. Sites, C. K. et al. Menopause-related differences in inflammation markers and their relationship to body fat distribution and insulin-stimulated glucose disposal. *Fertil. Steril.* 77, 128–135 (2002).
269. Ferrie, J. E., Kumari, M., Salo, P., Singh-Manoux, A. & Kivimäki, M. Sleep epidemiology—a rapidly growing field. *Int. J. Epidemiol.* 40, 1431–1437 (2011).
270. Snijder, M. B. et al. Trunk fat and leg fat have independent and opposite associations with fasting and postload glucose levels: the Hoorn study. *Diabetes Care* 27, 372–377 (2004).
271. Voors, A. W., Webber, L. S., Frerichs, R. R. & Berenson, G. S. Body height and body mass as determinants of basal blood pressure in children-The Bogalusa Heart Study. *Am. J. Epidemiol.* 106, 101–108 (1977).