The relationship between physical activity and inflammatory markers over 10 years has been recently examined in *Circulation*. The last author of this article is Mika Kivimäki, PhD, professor of social epidemiology, Department of Epidemiology and Public Health, University College London, London, England. He says, “The anti-inflammatory effects of exercise are thought to be one of the mechanisms that explains the well-documented cardioprotective effects of physical activity. This is supported by experimental studies, which, however, have truncated follow-up periods, typically not >6 months. Supportive epidemiological evidence also exists, but in those studies inflammatory markers have usually been measured only once. To address these limitations in research, we examined the association between physical activity and inflammatory markers over a 10-year follow-up period using a well characterised, population-based cohort study of middle-aged adults. We found that physically active participants at baseline had lower C-reactive protein and interleukin 6 levels, and that this difference remained stable over time.”

Previously, Professor Kivimäki has published articles on work-related stress and the risk of cardiovascular disease, and he has developed this theme to cardiovascular risk prediction, including an Individual-Participant-Data (IPD) meta-analysis on this topic. He explains, “Pooling of published and unpublished studies allowed us to investigate the association between coronary heart disease and exposure to job strain, defined by high work demands and low decision control, with greater precision than has been previously possible. Our findings from almost 200,000 adults indicate that job strain is associated with a small, but consistent, increased risk of experiencing a first coronary heart disease event such as a heart attack. It was the first IPD meta-analysis to examine the link between job strain and coronary heart disease. More fundamentally, to the best of my knowledge, it represents the first attempt to pool raw data at the level of the individual in the field of psychological factors as risk indices for somatic health.” He adds that this work provides a “relatively definite answer to the question of the status of work stress as a risk factor for coronary heart disease.”

Over the past decade, Professor Kivimäki has had a number of roles, including research professor at the Institute of Occupational Health, Helsinki, Finland, associate professor in the Department of Psychology, University of Helsinki from 1998 to 1999; Academy of Finland fellow from 1999 to 2001; professor of applied psychology from 2001 to 2003, and then professor of occupational health from 2003 to 2006 at the Institute of
Behavioural Sciences, University of Helsinki. He is now professor of social epidemiology in the Department of Epidemiology and Public Health at University College London, where he leads the Whitehall II study. In this role, he is an Economic and Social Research Council professor, and his work is funded by the Medical Research Council, the British Heart Foundation, the US National Institutes of Health, and the European Union New and Emerging Risks in Occupational Safety and Health Coordination Action research programme. Professor Kivimäki also receives Academy of Finland funding.

A Principal Investigator of the Finnish Public Sector Study Which Provides a Prospective Regularly Updated Follow-Up of >50000 Employees With a Questionnaire Survey Repeated Every 4 Years and Linkage to National Hospitalisation and Mortality Registers

Professor Kivimäki was born in Espoo, Finland, in 1961, and he graduated from the University of Helsinki in 1987 with an MA in psychology. The topic for his thesis was episodic stress. He completed a PhD in 1997 on chronic stress. Professor Kivimäki then found his interest shifting from psychology to epidemiology, with a desire to focus on diseases with major public health importance. From 1990 onwards, his colleague Professor Jussi Vahtera, MD, PhD, had been following up a cohort of 800 public sector workers in a small town in Western Finland where he had been an occupational physician. In 1997, Professor Kivimäki and Professor Vahtera decided to significantly expand the study and recruited >10000 new public sector workers from 8 towns and 12 hospitals in those areas. The study has since expanded, and is now the Finnish Public Sector study, providing a prospective regularly updated follow-up of >50000 employees with a questionnaire survey repeated every 4 years and linkage to national hospitalisation and mortality registers. Professors Kivimäki and Vahtera are its joint principal investigators and have a particular interest in learning the effects of organisational downsizing (a work-related psychosocial stressor) on health.

Professor Kivimäki says, “In those days, stress was almost exclusively measured by self-administered questionnaire. Organisational downsizing provided us with a more objective stress exposure. We found that those working in heavily downsized work units tend to have a higher morbidity rate. This association was graded; the greater the degree of downsizing, the greater the increase in disease risk.”

Increases in perceived stress to a large extent explained this association. A further article on cause-specific mortality suggested that organisational downsizing may trigger a coronary or stroke event in vulnerable individuals.

“The Whitehall II Data Provided Me With an Opportunity to Learn More About the Aetiological Aspects of Cardiovascular Diseases”

In 2000, Professor Kivimäki began a collaboration with Jane Ferrie, PhD, an occupational epidemiologist working on the Whitehall II study, a cohort of 10308 working men and women that was established in 1985 by Professor Sir Michael Marmot, MD, PhD, director, University College London Institute of Health Equity (Marmot Institute) and his team to investigate the biological, behavioural, and psychological mechanisms explaining the socioeconomic gradient in cardiovascular morbidity and mortality. Professor Kivimäki recalls, “This was a turning point in my career. The Whitehall II data are uniquely rich and provided me with an opportunity to learn more about the aetiological aspects of cardiovascular diseases.”

Professor Kivimäki began working with the members of the Whitehall II team, first as a visiting fellow and then as an honorary professor. In 2006, Professor Marmot, who at that time chaired the World Health Organization commission on socioeconomic determinants of health, invited him to take the scientific lead of Whitehall II. Professor Kivimäki was delighted to accept the invitation, and moved to London with his family. His role involves developing specific topics within the research programme in collaboration with other key figures of the Whitehall II team: cognition with Archana Singh-Manoux, PhD, diet with Eric Brunner, PhD, diabetes mellitus with Adam Tabak, MD, PhD, and genetics with Meena Kumari, PhD, as well as securing funding and planning and implementing screenings with the administrative and data coordination group (Eugenia Dahm-Vicker, Aida Sanchez, Stephanie Smith, and Bev Milne) and writing articles.
Professor Kivimäki comments, “Michael Marmot, who set up the study, is doing a great job in the policy field translating Whitehall II findings into health policy nationally, internationally, and globally.”

Professor Kivimäki advises people wanting to follow a career in medicine or cardiology to heed the following quotes from Nobel Prize winners at a seminar series at University College London. Professor Barry Marshall, AC, FRS, FAA, the co-discoverer of Helicobacter pylori, the bacterium that causes stomach ulcers, for which he won the 2005 Nobel Prize in Medicine, quoted historian Daniel Boorstin and said, “The greatest obstacle to discovery is not ignorance; it is the illusion of knowledge.” Similarly, Sir Martin John Evans, FRS, who made a series of groundbreaking discoveries concerning embryonic stem cells and was awarded the Nobel Prize for Medicine 2007, said, “Do not necessarily believe anything.”

“We Are Examining the Importance of Midlife Vascular Factors on Old-Age Outcomes, and Our Plan Is to Continue Active Data Collection Until 2030”

Professor Kivimäki has been “privileged to have had the opportunity to work with several great scientists” who have helped shape his career. These scientists include Professor George Davey Smith, MD, DSc, FRCP, FFPH, FMedSci, from the Department of Social Medicine at Bristol University, Bristol, England, who co-wrote a critical commentary to Professor Kivimäki’s 2002 article on work stress and cardiovascular mortality. Professor Kivimäki was invited to give a seminar at Bristol, and this was the start of a continuing collaboration with Professor Davey Smith, who had published his seminal article on Mendelian randomisation, an innovative method of using genetic variants to reduce confounding and bias in observational studies of modifiable risk factors. Professors Kivimäki and Davey Smith and their colleagues then wrote several early Mendelian randomisation articles on the causal role of C-reactive protein and obesity in cardiovascular disease.12,13

At University College London, genetic cardiologist Professor Aroon Hingorani, PhD, FRCP, FESC, has developed Mendelian randomisation as a method for identifying potential drug targets for the Whitehall II research. His group has shown that genetic differences in inflammatory markers and coronary heart disease risk are consistent with the effects of the interleukin 6 receptor inhibitor tocilizumab, which is used to treat rheumatoid arthritis,11 and point to opportunities for new preventive strategies that target inflammatory processes. Professor Kivimäki says, “I have learnt a lot from Aroon’s way of building collaborative consortia to achieve robust findings and statistical power through data pooling.”

Professor Kivimäki is also grateful for the support of Professor Marmot and other leading occupational epidemiologists, such as Professor Töres Theorell, MD, and Professor Johannes Siegrist, PhD. Professor Andrew Steptoe, PhD, of University College London, and Professor Ichiro Kawachi, MD, PhD, of Harvard School of Public Health, have also been important scientific influences.

Professor Kivimäki particularly enjoys writing articles with other scientists. Recent examples include a review on stress and cardiovascular disease with Professor Steptoe,14 a review article on prediabetes with Dr Tabak and others,10 and an article on cardiometabolic predictors of late-life depression with David Batty, PhD, and Mark Hamer, PhD.15 Professor Kivimäki says that his work and way of thinking were greatly influenced by a 1998 article by Bruce McEwen, PhD, on stress mediators.16 He explains, “This article introduces the term ‘allostatic load,’ that is, the idea that frequent activation of the body’s stress response, essential for managing acute threats, can damage the body in the long run. Although this concept has not turned out to be as useful as originally thought, the idea that we should use repeat data to determine long-term exposure to risk factors is important.” Professor Kivimäki is also impressed by the work of Professor John Danesh, FRCP, in relation to the Emerging Risk Factor Consortium.17 His work established the physiological risk factors for vascular disease that led to Professor Kivimäki setting up the IPD Work consortium.

Professor Kivimäki’s key area of research interest in cardiovascular diseases, diabetes mellitus, and depression
is now increasingly focusing on the ageing process, with the Whitehall participants now at 65 to 85 years of age. He says, “We are examining, for example, the importance of midlife vascular factors on old-age outcomes, such as cognitive decline, late-onset depression, and physical functioning. Our plan is to continue active data collection in the study until 2030. Measurements of biological, behavioural, psychological, and behavioural factors from early midlife onwards provide us with a great opportunity to identify key determinants of old-age health and functioning. Of course, Whitehall II also contributes to a number of research consortia.”

Professor Kivimäki concludes, “In epidemiology, IPD meta-analyses will be increasingly important in testing new hypotheses. However, discoveries are likely to come from high-resolution longitudinal data sets from across the life course combined with novel biotechnology.”

References


Contact details for Professor Kivimäki: Department of Epidemiology and Public Health, University College London, 1-19 Torrington Place, WC1E 6BT London, United Kingdom. E-mail: m.kivimaki@ucl.ac.uk

Mark Nicholls is a freelance medical journalist.
Funding: British Heart Foundation Intermediate Basic Science Research Fellowships

Tom McKinnon, BSc, PhD, British Heart Foundation Intermediate Basic Science Research Fellow, Thrombosis and Haemostasis Lab, Hammersmith Campus, Imperial College London, London, England, and Emma C. Hart, PhD, British Heart Foundation Intermediate Postdoctoral Research Fellow, School of Physiology and Pharmacology, University of Bristol, Bristol, England, talk to Jennifer Taylor, BSc, MSc, MPhil.

Dr McKinnon’s fellowship is a progression from his PhD research where he investigated the role of VWF N-linked glycans in modulating the interaction of VWF with ADAMTS13 (also known as VWF-cleaving protease). His thesis demonstrated that blood group sugars presented on VWF N-linked glycans alter susceptibility to proteolysis by ADAMTS13,1,2 and that the N-linked glycan structures modulate cleavage by helping to maintain the globular structure of VWF. Most of this effect was attributed to 1 glycan close to the ADAMTS13 cleavage site.3 Dr McKinnon has since investigated further functional effects of VWF N-linked glycans and demonstrated that certain glycosylation sites modulate proper expression and folding of VWF.4 These projects mapped in detail the N- and O-linked glycocomes of VWF, where they showed for the first time that VWF O-linked glycans present the ABO blood group sugars as well as a rare disialosyl motif.5 Recently, the group published the effect of VWF O-linked glycans on the interaction with platelets under static and flow conditions.6

References
Emma C. Hart, PhD, British Heart Foundation Intermediate Postdoctoral Research Fellow, School of Physiology and Pharmacology, University of Bristol, Bristol, England.

Dr Hart received her fellowship in the 2010/11 funding round to investigate the mechanisms that lead to the onset of hypertension in humans. Blood pressure remains uncontrolled in around 30% to 50% of patients being treated for hypertension, suggesting that therapeutic interventions have limitations. In addition, the mechanisms that lead to the development of high blood pressure are not fully understood. Dr Hart says, “We know that hypertension is associated with elevated sympathetic nerve activity, which results in the typical profile of hypertension where peripheral and renovascular resistance is elevated and cardiac contractility is augmented.”

Dr Hart is carrying out her research to test the hypothesis that reductions in cerebral blood flow (e.g., due to atherosclerosis) cause reflex increases in sympathetic nerve activity, and thus blood pressure, to maintain cerebral perfusion with Professor Julian F. R. Paton, PhD, at the University of Bristol. The main goal is to measure whether vascular resistance and blood flow (using magnetic resonance angiography and functional magnetic resonance imaging) are altered in the cerebral arteries of the brain stem in 3 groups of hypertensive patients (borderline, untreated, and resistant hypertensives) compared with age-matched normotensive controls. The relationship between the level of sympathetic nerve activity (using microneurography) and cerebral vessel remodelling in these patients will also be examined. In addition, the effect of current pharmacological therapies for hypertension (such as angiotensin-converting enzyme inhibitors) on cerebral vessel structure and blood flow will be measured to help determine causality, that is, whether sympathetic activation occurs before or after decreases in cerebral perfusion.

“We hope to discover that hypertension is related to alterations in cerebral blood flow and structure of the arteries in the brain stem that supply regions critical in human blood pressure regulation,” says Dr Hart. “We think that cerebral blood flow and structure will be characteristically different between the borderline, untreated, and resistant hypertensive patients.”

She adds, “We think that typical chronic pharmacological treatment of high blood pressure in patients who have previously been untreated will result in remodelling of the cerebral vessels. Additionally, we hope to demonstrate that the level of sympathetic activity is related to cerebral vascular resistance in hypertensive humans.”

Dr Hart’s previous research, completed at the Mayo Clinic, Minnesota, MN, with Professor Michael J. Joyner, MD, and Nisha Charkoudian, PhD, focused on sex differences in resting blood pressure control and how this changed with the onset of menopause. The research revealed that, in young men, a balance between sympathetic activity, cardiac output, and total peripheral resistance appears to be critical in maintaining the level of resting blood pressure, and this disappears as men age.1 Interestingly, this balance observed in young men did not exist in young women,2 in whom other factors were more important than sympathetic nerve activity in maintaining total peripheral resistance.

The research also demonstrated that vascular β-adrenergic receptors offset the transfer of sympathetic activity into vasoconstrictor tone in young women, but not in young men.3 Furthermore, when the β-adrenergic receptors are blocked in young women, the resting level of sympathetic nerve activity becomes directly related to resting blood pressure levels. “This suggests that β-adrenergic receptors prevent young women with higher levels of sympathetic nerve activity from having higher levels of resting blood pressure,” says Dr Hart. In postmenopausal women, the ability of the β-adrenergic receptors to offset high levels of sympathetic nerve activity is lost.3 Thus, the level of sympathetic nerve activity becomes directly related to the level of overall blood pressure in older women.

Dr Hart concludes, “The current fellowship builds on the principles of blood pressure regulation in normotensive individuals that we learnt from my previous studies.”

References


Jennifer Taylor is a freelance medical journalist.