Testing nutritional interventions for the prevention of chronic disease

Clinician-scientist and experienced population researcher Dr JoAnn Manson discusses with *International Innovation* the wide-reaching implications of the large-scale health studies that she is leading or co-leading to explore dietary and lifestyle preventive strategies for chronic disease.

Could you introduce some of the key large-scale randomised clinical trials and observational studies for which you are a principal investigator?

As an endocrinologist and physician epidemiologist, my primary interest is in conducting randomised prevention trials of promising clinical interventions. My research interests are broad-based, and include prevention trials of nutritional, lifestyle and pharmacologic interventions for cardiovascular disease (CVD), type 2 diabetes and cancer. I serve as a principal investigator of several National Institutes of Health-funded research studies, including the Women’s Health Initiative (WHI) Clinical Center in Boston; the nationwide ViTamin D and Omega-3 Trial (VITAL); the Women’s Antioxidant and Folic Acid Cardiovascular Study; and the cardiovascular component of the Nurses’ Health Study (NHS). In addition, we are currently recruiting for the Cocolate Supplement and Multivitamins Outcomes Study (COSMOS).

What is the correlation between lifestyle and genetic factors in the prevention of CVD and diabetes?

The role of modifiable lifestyle factors in the prevention of CVD and type 2 diabetes is powerful. We've been astounded by the magnitude of association in our large-scale prospective studies, as well as in studies by other researchers. We found, that among women in the NHS, approximately 80 per cent of myocardial infarctions, 70 per cent of strokes and 90 per cent of type 2 diabetes cases could be prevented by adhering to healthy lifestyle practices such as not smoking, engaging in moderate-to-vigorous physical activity for at least 30 minutes per day, maintaining a healthy weight, and following a dietary pattern high in fruits, vegetables, legumes, whole grains, fish, nuts and healthy fats, and low in red meat and trans fats. However, genetic factors also play a pivotal role, and what’s particularly important is the interaction between genes and environmental/lifestyle factors. For example, some people are genetically predisposed to develop obesity or type 2 diabetes with Western diets and others appear prone to develop CVD if they don’t exercise or become overweight.

Which biochemical and genetic markers for CVD and diabetes have you found through your collaborative research endeavours?

We’ve studied a large number of biomarkers to assess their role in predicting risk of CVD, type 2 diabetes and cancer. Our main interests have been in the role of inflammatory cytokines and other markers of systemic inflammation, such as high-sensitivity C-reactive protein, interleukin 6, tumour necrosis factor α, and adipokines such as adiponectin, leptin, retinol binding protein-4, resistin and others. These biomarkers are highly predictive of cardiometabolic disorders and insulin resistance. We also have a strong interest in biomarkers of vitamin D status, including 25(OH) vitamin D, vitamin D binding protein, bioavailable and free 25(OH) vitamin D and parathyroid hormone, as well as biomarkers of fatty acid composition. Based on long-term follow-up of our large-scale cohorts, we’ve also developed genetic risk scores for obesity, type 2 diabetes, vascular disease and other chronic disease outcomes. Finally, we have a strong interest in telomere biology and metabolomic markers, including the gut flora metabolites that have been linked to risk of type 2 diabetes, CVD and cancer.

You have won a number of prestigious awards and been elected to membership of many renowned organisations, such as the Institute of Medicine (National Academy of Medicine). For early-career researchers and students, how important is it that there are prominent role models? Has the situation for underrepresented groups in science improved since you were a student?

Despite these recognitions and career successes, my greatest satisfaction and gratification come from mentoring students and junior investigators, and helping to support their career goals. It is very rewarding to work with the next generation of scientists and researchers in this field and provide resources that help to foster their careers. I do think it’s important for students and junior faculty to have role models. Progress for women faculty and underrepresented groups has been steady, but at a slower pace than we had hoped.

Where do you plan to focus your efforts in the next five to 10 years?

Our current focus is to complete the VITAL and COSMOS randomised trials; continue long-term follow-up in the WHI, NHS and other cohorts; and launch new randomised trials that include testing promising behavioural interventions, such as increasing physical activity, testing dietary patterns and reducing stress. We also have a strong interest in expanding our biomarker research, including genomics, metabolomics, telomere biology and studies of gene-environment interactions. Finally, we hope to become more involved in comparative effectiveness research and pragmatic clinical trials in patient care settings.

**Dr JoAnn Manson and her VITAL study colleagues.**
One prominent example of this sterling work is the VITamin D and OmegA-3 TriaL (VITAL) randomised placebo-controlled study on which Manson is currently focusing her efforts. Its aim is to gauge the capacity of vitamin D and omega-3 supplements in preventing cancer and CVD.

"Vitamin D supplementation has looked very promising in observational studies, but the randomised trial evidence to date is mixed and inconsistent," reveals Manson. "This may be because most previous trials have tested low doses of vitamin D and have been underpowered to address cancer, CVD and other nonskeletal outcomes. We hope that VITAL and other large ongoing trials will finally provide conclusive answers about the benefits and risks of high-dose vitamin D supplementation." A challenging endeavour, Manson and her colleagues recruited 25,874 men and women aged 50 and over to the study. They will now follow the progress of these participants for around five years, observing differences in their health as they take capsules containing extra vitamin D and/or omega-3 fatty acids, or placebo. "VITAL is, to our knowledge, the largest trial of either vitamin D or omega-3 supplementation in a usual-risk population," Manson elucidates.

Nearly 17,000 participants have provided baseline blood samples, and 6,000 are also providing follow-up samples. A subset of 1,054 patients have in-clinic visits with in-depth phenotyping at baseline and two years, including anthropometry, spirometry, DXA imaging and 2D echocardiograms, as well as blood pressure, glucose tolerance and physical performance tests. The population recruited to the study also includes a diversity of races and ethnicities, with significant representation of African Americans, offering the potential to examine important racial disparities in health.

Due to the viral nature of information dissemination today, nutrition and lifestyle ‘tips’ often infiltrate the mainstream media – whether this information is evidence-based or unsubstantiated can be difficult to discern. In order to provide the public with decisive, reliable and relevant data, large-scale studies that focus on usual-risk subjects for relevant diseases are required – only with such a large and broad sample will it be possible to obtain an accurate understanding of the role of lifestyle and dietary factors in preventing major diseases.

JoAnn Manson, MD, DrPH, is Chief of the Division of Preventive Medicine at Brigham and Women’s Hospital and Professor of Medicine at Harvard Medical School; she has played a significant role in some of the largest nutritional prevention trials in the world. With a particular interest in cardiovascular disease (CVD), type 2 diabetes, cancer and other chronic afflictions, Manson and her team are dedicated to discovering the lifestyle/behavioural factors that can influence the progression of disease. "Some associations are so strong or so compelling that randomised trials aren’t needed, but trials have a powerful role in proving cause-and-effect relationships and informing clinical and public health recommendations," she explains.

Manson’s work spans from observational research to rigorous testing of micronutrients, nutritional supplements and dietary patterns in randomised clinical trials.

Medical researchers at Harvard Medical School in the US are working in close collaboration with clinicians to complete some of the largest and longest-running randomised clinical trials ever performed; their results will shed new light on the nutrients and health habits that are beneficial to human health.

CANCER, CVD AND BEYOND

Participant outcomes in terms of diagnoses of cancer and CVD will be monitored over the five years of the trial – but the study will not stop there. It will also examine a huge range of additional outcomes in ancillary studies on disorders like diabetes, hypertension, cognitive decline, depression, respiratory disease, infectious diseases, autoimmune disease and anaemia, to name but a few. In total, 21 ancillary studies will be performed, maximising the potential of this unique resource. Manson and her collaborators expect to see the fruits of their labour in concrete results in late 2017. This is a huge study, and a significant undertaking – but it is only one of a range led or co-led by Manson as Principal Investigator.
OBJECTIVE
To conduct randomised controlled trials of promising nutritional and behavioural interventions to reduce risk of chronic diseases and assess mechanistic and genetic factors that influence treatment response.

KEY COLLABORATORS
Dr Julie Buring, Dr Howard Sesso, Dr Paul Ridker, Dr I-Min Lee, and many other researchers at Brigham and Women’s Hospital, Harvard Medical School, USA

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Women’s Health Initiative investigators
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DR JOANN MANSON is Professor of Medicine and the Michael and Lee Bell Professor of Women’s Health at Harvard Medical School. She is also Chief of the Division of Preventive Medicine and Co-Director of the Connors Center for Women’s Health and Gender Biology at Brigham and Women’s Hospital. Her primary research interests include randomised clinical prevention trials; the role of lifestyle and nutritional factors, including vitamin D and omega-3s, in the prevention of CVD, cancer and diabetes; effects of endogenous and exogenous sex steroid hormones on cardiovascular disease, diabetes and other chronic diseases; benefits and risks of oestrogen therapy; the benefits and risks of aspirin; effects of moderate-intensity versus vigorous exercise; and the role of biochemical and genetic factors in predicting chronic disease risk.

RISK FACTORS FOR CARDIOVASCULAR DISEASE IN WOMEN
This epidemiological study of the determinants of coronary heart disease (CHD) among women has had a recent focus on the biochemical and genetic predictors of CHD. It has thus far resulted in over 300 CVD-related publications, including the benefits of both moderate-intensity and vigorous exercise, dietary patterns high in fruits/vegetables and whole grains, and low in trans fats and red or processed meats; elucidating the complex pattern of benefits and risks of reproductive factors and exogenous hormone use; and the role of inflammatory cytokines, adipokines, genetic factors, telomere length and metabolomic and other biomarkers in predicting CVD risk. The cohort for this research is the Harvard Nurses’ Health Study.

WOMEN’S ANTIOXIDANT AND FOLIC ACID CARDIOVASCULAR STUDY
Antioxidant micronutrients include vitamins C, E and beta carotene, and have been proposed as a secondary preventive of cardiovascular events; for this reason, Manson and her colleagues initiated a trial in 1995 to determine the effect of these dietary factors on 8,000 high-risk women with prior CVD history. The Women’s Antioxidant and Folic Acid Cardiovascular Study (WAFACS) was also updated a couple years later, when a combination of folic acid and vitamins B6 and B12 was introduced to lower homocysteine. Now completed, significant findings of the WAFACS concerned the potential benefits of the folic acid/B vitamin intervention for age-related macular degeneration and cognition, while effects on CVD events were neutral.

COCOA SUPPLEMENT AND MULTIVITAMINS OUTCOMES STUDY
The COocoa Supplement and Multivitamins Outcomes Study (COSMOS) aims to evaluate the efficacy of a purported superfood: cocoa extract. This four-year, placebo-controlled randomised trial will test a cocoa extract supplement containing 600mg of flavanols daily. The 18,000 participating men and women, aged 60 and over, will then be monitored with particular attention to the development of CVD and cancer, to assess the ability of the cocoa extract as a dietary preventive. Multivitamins will also be tested, primarily for cancer prevention. Recruitment for COSMOS began earlier this year, and the results are expected in 2019-20.

Manson also collaborates on the following studies:

WOMEN’S HEALTH STUDY
NURSES’ HEALTH STUDY I AND II
PHYSICIANS’ HEALTH STUDY I AND II

Blood repository in the Division of Preventive Medicine, Harvard Medical School, USA