Can precision medicine get us through menopause?

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Women spend up to three decades in the postmenopausal phase of life, which is often accompanied by a wide variety of life-disrupting symptoms, including vasomotor symptoms, sleep disturbances, cognitive decline, mood disorders, and metabolic dysfunction.[1] Regarding the latter, while ageing associates with weight gain, shifts in body composition, and metabolic dysfunction in both sexes, the abrupt shifts in hormones associated with the menopause transition coincides with a stark increase in metabolic risk,[1] resulting in an alarming increase in cardiovascular disease and diabetes prevalence among postmenopausal women. It remains unclear how much of this increase in cardiometabolic risk is due to behavioural changes, like dietary patterns and exercise, versus hormonal changes. Indeed, as we approach 2023, we still have very little declarative insight on the biological and/or neuro-behavioural mechanisms causing menopausal symptoms, and thus clinicians have a difficult time advising women on how best to achieve optimal health following menopause. Moreover, there are few pharmacological treatments available that are without perceived potential health risks.[2] New research supports that it is an interaction between hormonal/physiological and dietary factors that ultimately determines metabolic risk, and that the gut may play an important mediating role in that interaction.

Over thirty years ago, the then National Institute of Health director, Bernadine Healy helped to obtain funding for the Women's Health Initiative (WHI), a would-be historical series of clinical trials, which included dietary intervention trials as well as hormone replacement therapy (HRT) trials.[3] At least in the medical community, the HRT trials have received much more attention than have the dietary/behavioural trials. As a nutrition researcher who studies menopause, I only recently became aware that such studies were part of the original WHI. One of the first nutritional trials associated with the WHI was the "dietary modification" trial, where women were randomized to a control or a diet group.[4] Participants were instructed to adopt a low-fat diet and encouraged to consume more fruits, vegetables, and grains. This was just around the time when preclinical studies were associating diets high in fat with chronic diseases, like cancer and obesity, an idea that would go on to be largely disproved in human studies,[5] but still one that is not without controversy. The researchers were interested in whether a low-fat diet would improve overall health and prevent disease among postmenopausal women. Following that 9-month intervention, women in the intervention group weighted ~2.2 kg less on average than those in the control group and modestly reduced energy intake. Noteworthy are factors that changed among those women other than dietary fat consumption—in addition to consuming less fat, the intervention group consumed more fibre, vitamins and minerals, dairy products and fish.[4,6] Along with these dietary changes, the women saw a reduction in ER+ breast cancers that approached statistical significance. There were also minor protective effects on total deaths and diabetes, findings that were strongest for women who were obese at the beginning of the trial.[7,8]

Later, between 2004 and 2006, owing to the limitations to dietary analyses based on self-report, the WHI expanded its trials to include biomarker studies, which included precise assessments of energy expenditure, and urinary nitrogen to validate protein consumption. Then, between 2010 and 2014 a feeding study was conducted to identify important biomarkers of dietary patterns and how such patterns influence health and disease status.[3] A major epiphany from those carefully-controlled studies was not at all surprising—self-reported dietary and physical activity data are not reliable. However, those more sophisticated analytic studies supported another obvious correlation between energy surplus (*mediated through excess energy intake or reduced energy expenditure*) and increased adiposity, metabolic dysfunction, and ultimately, increased disease risk. As pointed out by the authors of a recent review on the history of nutrition-focused research conducted under the WHI,[3] the future nutritional epidemiology research agenda needs to capitalize on both self-report and biomarker measures of nutritional intake and disease status, and should include additional outcomes such as metabolomic profiles from blood and urine. Such studies, they conclude, will lend critical insight about the best strategies for dietary modification to improve health among our growing population of postmenopausal women.

Published in the November 2022 issue of *eBioMedicine*, The ZOE PREDICT study[9] takes the field in that positive direction, carefully assessing not only dietary patterns in a large sample of ageing women, but also

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indicators of postprandial metabolism, metabolic health and lifestyle factors. The study was unique in that they assessed metabolic responses to specific meal challenges, and measured an impressive battery of potential mediating factors, most notably, gut microbiome changes. In addition, they were thorough in their assessments of a broad spectrum of menopausal symptoms, with assessments ranging from psychological (*e.g., feelings of sadness*), to metabolic (*e.g., hormonal responses to macronutrients, body composition changes*), to neurophysiological (*e.g., sleep*), to dietary changes (*e.g., sugar versus fat consumption*). Another critically important and novel component of the study was the assessment of the effects of HRT on metabolic outcomes with statistical adjustments for factors such as smoking and age. This is a controversial, yet vitally important element of the discussion of how to best advise and treat ageing women to foster optimal health-span. This discussion should be viewed through the lens of precision medicine/nutrition, which is where we are heading. This study moves the field in that direction.

Part of the ZOE PREDICT project, this was a large cohort study which included premenopausal women, postmenopausal women, and age-matched men. Controlling for important factors such as age and BMI, independent effects of menopause on aspects of metabolic health were identified, mostly supporting prior studies. However, findings were extended to show that menopause also adversely affected postprandial metabolism and glycemic variability (*subjects wore continuous glucose monitors*). Independent effects of menopause also included sleep quality (*12% worse sleep among menopausal women*) and dietary added sugar intake (*12% more added sugar among menopausal women*). Regarding HRT, a favourable association was found for visceral adiposity (*a major cardiometabolic risk factor*), as well as fasting and postprandial metabolic indicators. Finally, using the comprehensive broad database generated, statistical mediation analyses were performed to lend insight into mechanisms driving the observed changes. These analyses revealed some novel and potentially important associations between diet, gut microbial changes, and health indicators. Such analyses do not allow one to make causal determinations, but do support additional work to identify more precise approaches to best treat and prevent age-related disease among aging women. Importantly, this study highlights the profound impact that diet and lifestyle have on protecting aging women, and supports a closer look at HRT, especially for women at high susceptibility for metabolic disease who do not have contraindicated health risks, such as history of reproductive cancers.

Contributors
VV-P is the sole author.

Declaration of interests
No conflicts to report.

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