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Reproductive Aging Amplifies Immune-Metabolic Vulnerability to Environmental and Nutritional Stress: A KNHANES 2010-2022 Analysis with Planned Experimental Validation

Yean Jung Choi [a,b], Seungpil Jeong [c,*]

[a] Department of Food and Nutrition, Sahmyook University, Seoul 01795, Republic of Korea
[b] Institute of Nutritional Physiology and Molecular Nutrition, Sahmyook University, Seoul 01795, Republic of Korea
[c] Institute of Convergence Medicine, Ewha Womans University Mokdong Hospital, Seoul, Republic of Korea

Abstract

Reproductive aging is accompanied by endocrine, metabolic, immune, and vascular remodeling, yet its role in modifying susceptibility to environmental and nutritional stressors remains insufficiently understood. We reorganized the present work as a Nature Aging-oriented translational framework in which menopause is conceptualized not simply as a demographic subgroup, but as a life-course inflection point that may reduce immune-metabolic resilience. This study aims to determine whether reproductive aging amplifies the association of climate-sensitive air pollution and nutritional vulnerability with metabolic aging burden among Korean adults, and to establish a mechanistic basis for this susceptibility through planned experimental validation.

The human component will use repeated cross-sectional data from the Korea National Health and Nutrition Examination Survey from 2010 to 2022, linked with environmental exposure data and national cause-of-death statistics. Environmental exposures will include PM10, PM2.5, SO2, CO, O3, temperature, humidity, rainfall, and derived climate-stress indicators where available. Nutritional resilience and vulnerability will be characterized using energy intake, water intake, protein, fat, carbohydrate, dietary fibre, sodium, potassium, calcium, iron, vitamin A, carotene, retinol, thiamine, riboflavin, niacin, vitamin C, dietary therapy status, and usual intake status. Participants will be classified by sex, menopausal status, reproductive lifespan, and years since menopause. Primary outcomes will include adiposity, vascular, glycaemic, and lipid phenotypes integrated into an immune-metabolic aging burden score. Region-year mortality statistics will be used to contextualize infectious-inflammatory aging burden and non-infectious chronic aging burden.

The analytic strategy will include survey-weighted descriptive analyses, spline-based reproductive aging trajectory models, environmental and nutritional mixture models, and interpretable machine-learning approaches. We will construct three complementary indices: an Environmental Stress Index to summarize air-pollution and meteorological exposures; a Nutritional Resilience/Vulnerability Index to capture dietary buffering capacity and dietary risk; and an Immune-Metabolic Aging Burden Score to integrate obesity, abdominal adiposity, hypertension, glycaemic dysregulation, dyslipidaemia, and functional vulnerability. Main models will evaluate whether environmental stress, nutritional vulnerability, and menopause jointly predict immune-metabolic aging burden, with particular attention to the high-risk phenotype of postmenopausal women exposed to high environmental stress and low nutritional resilience.

To validate biological mechanisms, we will conduct a mouse experiment comparing male mice, sham-operated female mice, and ovariectomized female mice as a model of postmenopausal estrogen depletion. Mice will be assigned to control or nutrition-vulnerability diets, control or environmental stress exposure, and an infection-like immune challenge using a non-replicating immune stimulant such as poly(I:C) or low-dose lipopolysaccharide. Primary experimental outcomes will include body weight, visceral adiposity, glucose tolerance, insulin sensitivity, lipid metabolism, hepatic steatosis, systemic inflammation, immune-response markers, gut-barrier dysfunction, tissue immune infiltration, oxidative stress, and cellular aging markers such as p16, p21, SASP-related cytokines, and DNA-damage markers. Planned contrasts will test whether ovariectomized females exposed to combined nutritional and environmental stress show amplified immune-metabolic dysfunction compared with sham-operated females.

This Nature Aging-aligned framework positions reproductive aging as a biological amplifier of exposome-related immune-metabolic vulnerability. By integrating national human evidence from KNHANES 2010-2022 with environmental exposure, nutritional resilience, mortality context, and planned estrogen-depletion mouse validation, the study aims to identify modifiable stressors that may accelerate metabolic aging in women. The findings could support aging-focused prevention strategies that combine environmental risk reduction, nutritional resilience, and life-course targeting to preserve metabolic healthspan after menopause.

** Corresponding author E-mail address: seungpil720@ewha.ac.kr*

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