

Perfluoroalkyl and Polyfluoroalkyl Substances (PFAS) and Women's Reproductive Aging

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Collaborative on Health and the Environment

Next Generation Chemical Webinar

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Reproductive Aging and Menopause

A hand holding a stethoscope over a piece of paper with the word 'menopause' written on it. The word is written in a blue, dotted font. The background is dark, and the stethoscope is silver and black.

menopause

Defined as one year without a menstrual period

Age at menopause and women's health risks

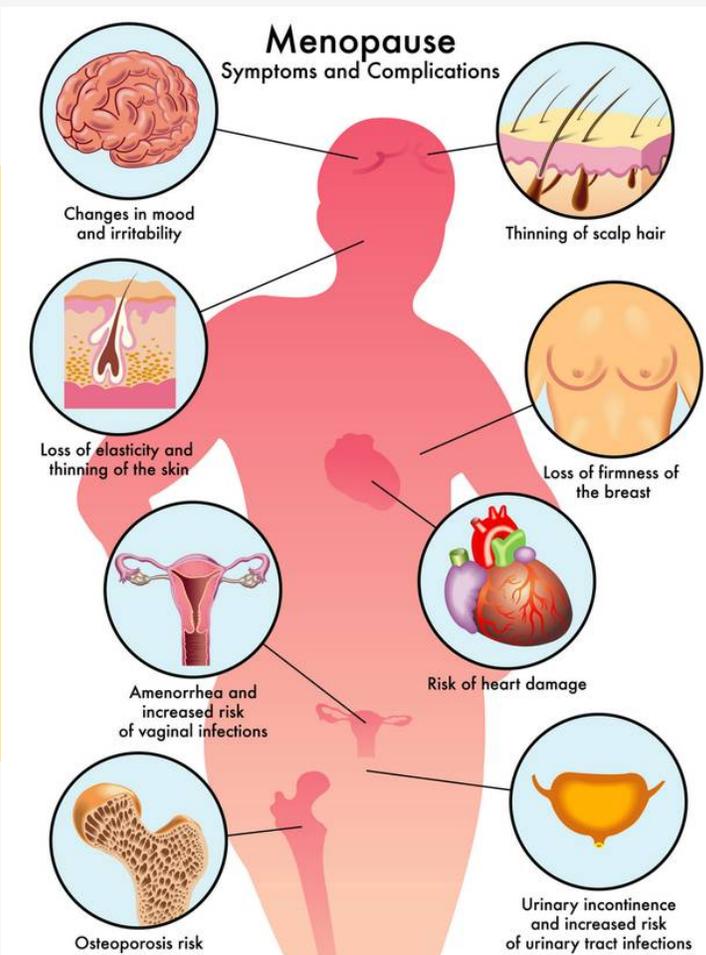
Most women reach menopause between 45 and 55, with a median age between 50 and 52.

Earlier onset

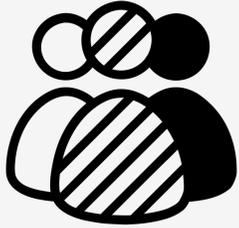
- Increased **overall mortality**
- Higher risks of **cardiovascular disease**
- Lower **bone density**
- Higher risks of **osteoporosis**
- Higher risks of **neurological disease**

Later onset

- Increased risks of **breast, endometrial, and ovarian cancer**

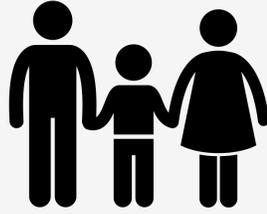


Factors related to age at menopause



Created by MRFA from Noun Project

Race/ethnicity



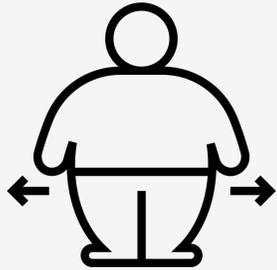
Created by Gan Khoon Lay from Noun Project

Family history



Created by Fater from Noun Project

Socioeconomic



Created by Vectors Point from Noun Project

Obesity



Created by Chattapat from Noun Project

Physical inactivity



Created by Pi from Noun Project

Unhealthy diet



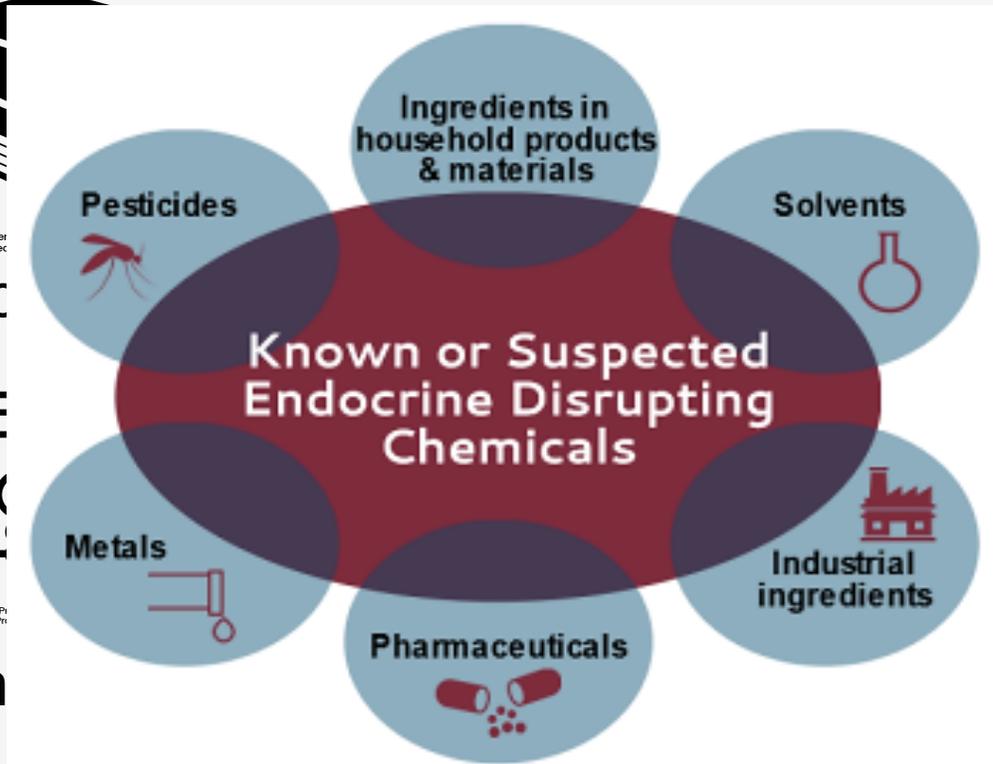
Created by Luis Prado from Noun Project

Surgery



Created by Gan Khoon Lay from Noun Project

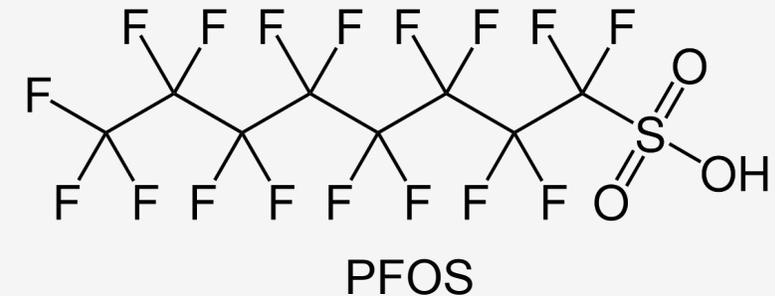
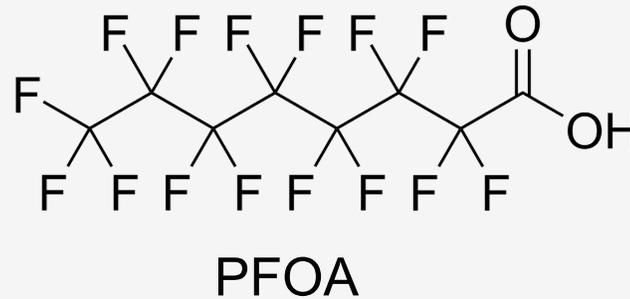
Smoking



Source: <https://www.healthandenvironment.org>

PFAS are potential EDCs and 'forever chemicals'

- Anthropogenic chemicals
- Two main groups
 - **Carboxylates:** perfluorooctanoic acid (PFOA)
 - **Sulfonates:** perfluorooctane sulfonate (PFOS)



- Sources



Non-stick cookware



Waterproof clothing



Furniture and carpeting



Personal care products



Food packaging

A hand is pouring clear water from a glass pitcher into a glass. The background is a bright, out-of-focus indoor setting with windows. The text '200,000,000+' is overlaid in large, bold, black font across the center of the image.

200,000,000+

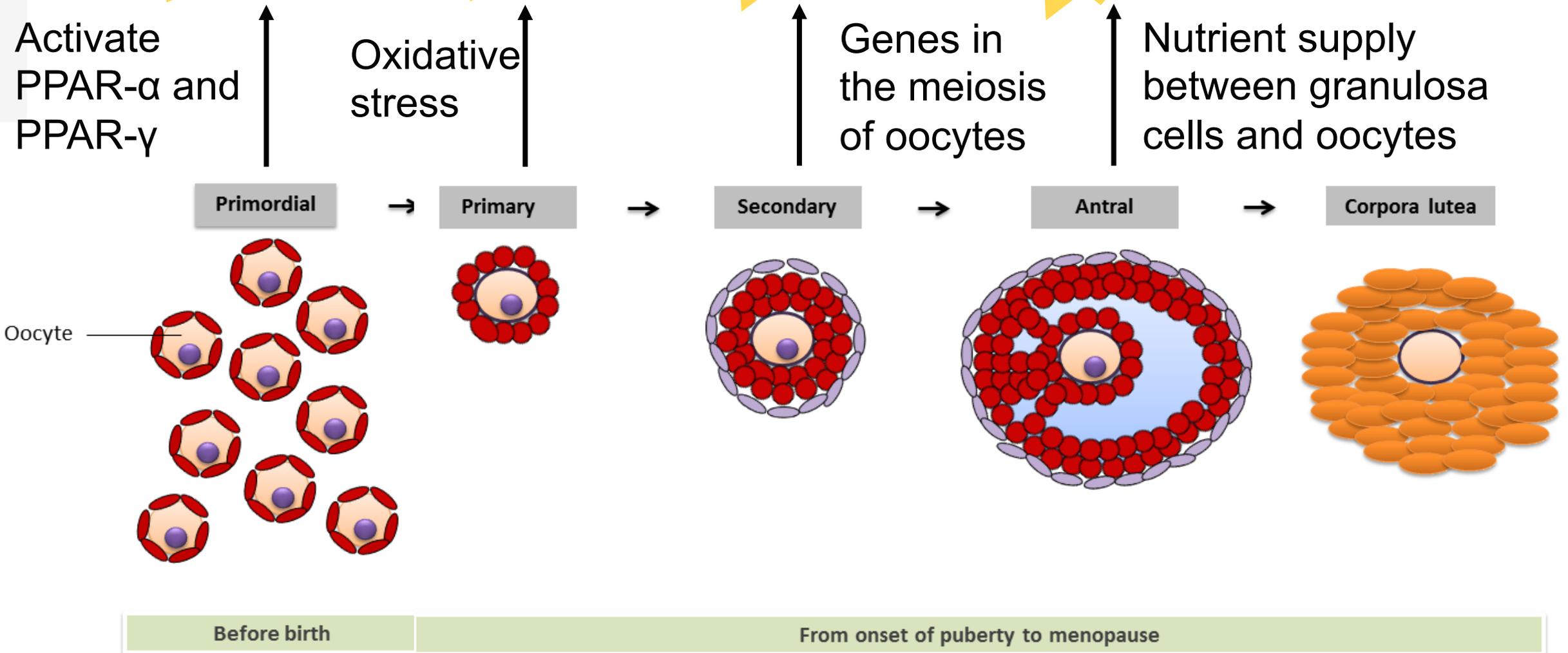
Americans consume drinking water contaminated by PFAS

PFAS and their effects on the ovary



- Higher PFAS were associated with:
 - Later menarche
 - Irregular menstrual cycles
 - Reduced levels of estrogen
- Folliculogenesis and steroidogenesis

PFAS may deplete the ovarian reserve.



PFAS and their effects on the ovary



Perfluoroalkyl and polyfluoroalkyl substances (PFAS) and their effects on the ovary

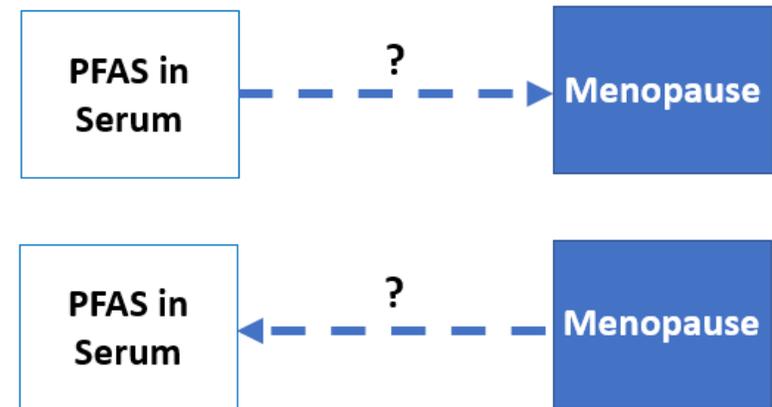
Ning Ding¹, Siobán D. Harlow¹, John F. Randolph Jr², Rita Loch-Caruso³, and Sung Kyun Park^{1,3,*}

¹Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI 48109, USA, ²Department of Obstetrics and Gynecology, School of Medicine, University of Michigan, Ann Arbor, MI 48109, USA, ³Department of Environmental Health Sciences, School of Public Health, University of Michigan, Ann Arbor, MI 48109, USA

- **Research Gaps:**

- Lack of prospective cohort
- PFAS mixture

Question about reverse causality



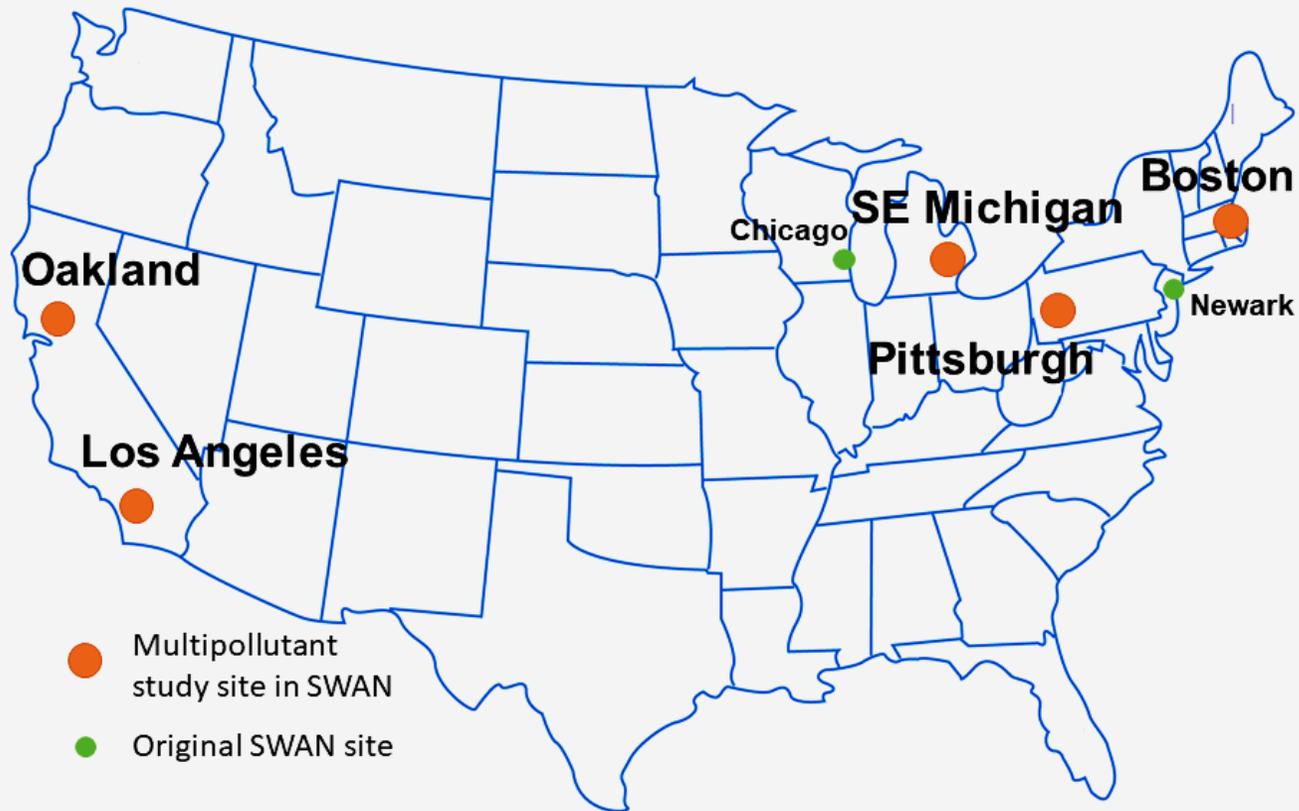
Study of Women's Health Across the Nation (SWAN)



- Initiated in 1996-97
- N=3302 women aged 42-52 y
- White from all 7 sites
- Black from Chicago, SE Michigan, Pittsburgh, Boston
- Asians from Oakland (Chinese) and Los Angeles (Japanese)
- Hispanic from Newark
- Approximately annual or biannual follow-up

SWAN Multi-Pollutant Substudy (SWAN-MPS)

PI: Dr. Sung Kyun Park



- Serum/urine samples collected at third SWAN visit, which is the baseline for SWAN-MPS (1999-2000).
- N=1,400
- 5 study sites: Boston, SE Michigan, Oakland, Los Angeles, Pittsburgh.
- White, Black, Chinese, and Japanese.



Determinants of per- and polyfluoroalkyl substances (PFAS) in midlife women: Evidence of racial/ethnic and geographic differences in PFAS exposure

Sung Kyun Park^{a,b,*}, Qing Peng^a, Ning Ding^a, Bhramar Mukherjee^c, Siobán D. Harlow^a

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Longitudinal trends in perfluoroalkyl and polyfluoroalkyl substances among multiethnic midlife women from 1999 to 2011: The Study of Women's Health Across the Nation

Ning Ding^a, Siobán D. Harlow^a, Stuart Batterman^{b,c}, Bhramar Mukherjee^d, Sung Kyun Park^{a,b,*}

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Detection > 95%

- Linear PFOS
- Branched PFOS
- Linear PFOA
- PFNA
- PFHxS
- EtFOSAA
- MeFOSAA

Detection < 40%

- Branched PFOA
- PFDA
- PFUnDA
- PFDoDA

Determinants

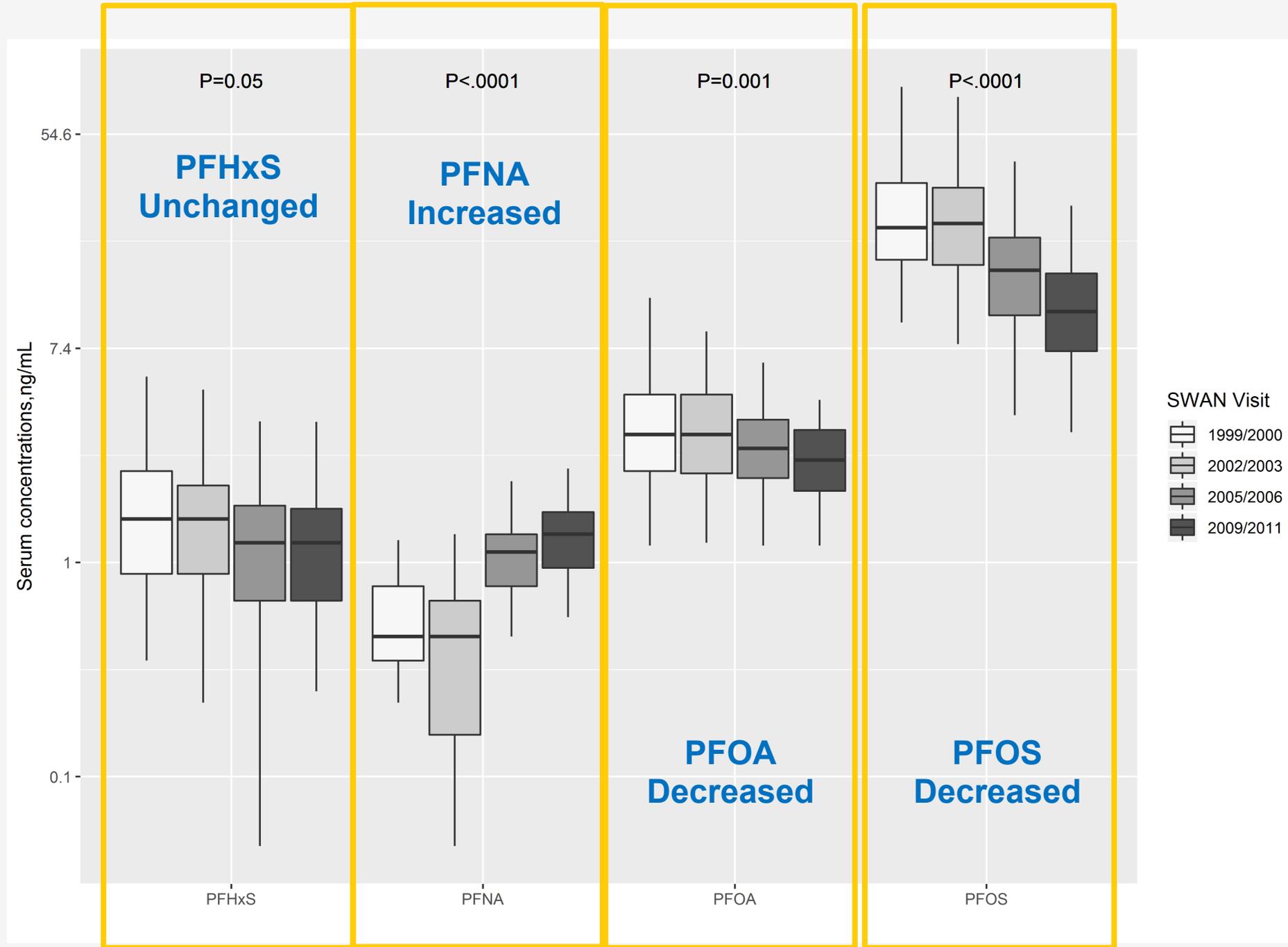
- Race/ethnicity
- Menstrual bleeding
- Parity
- Consumption of salty snacks (e.g. popcorn, chips)
- Age

Decline in PFOA and PFOS

PFHxS unchanged

PFNA increased

Concentrations of selected PFAS by study visits between 1999 and 2011 (N=75).





Associations of Perfluoroalkyl Substances with Incident Natural Menopause: The Study of Women's Health Across the Nation

Ning Ding,¹ Siobán D. Harlow,¹ John F. Randolph Jr,² Antonia M. Calafat,³ Bhramar Mukherjee,⁴ Stuart Batterman,^{5,6} Ellen B. Gold,⁷ and Sung Kyun Park^{1,5}

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PFAS and Incident Natural Menopause in Midlife Women.

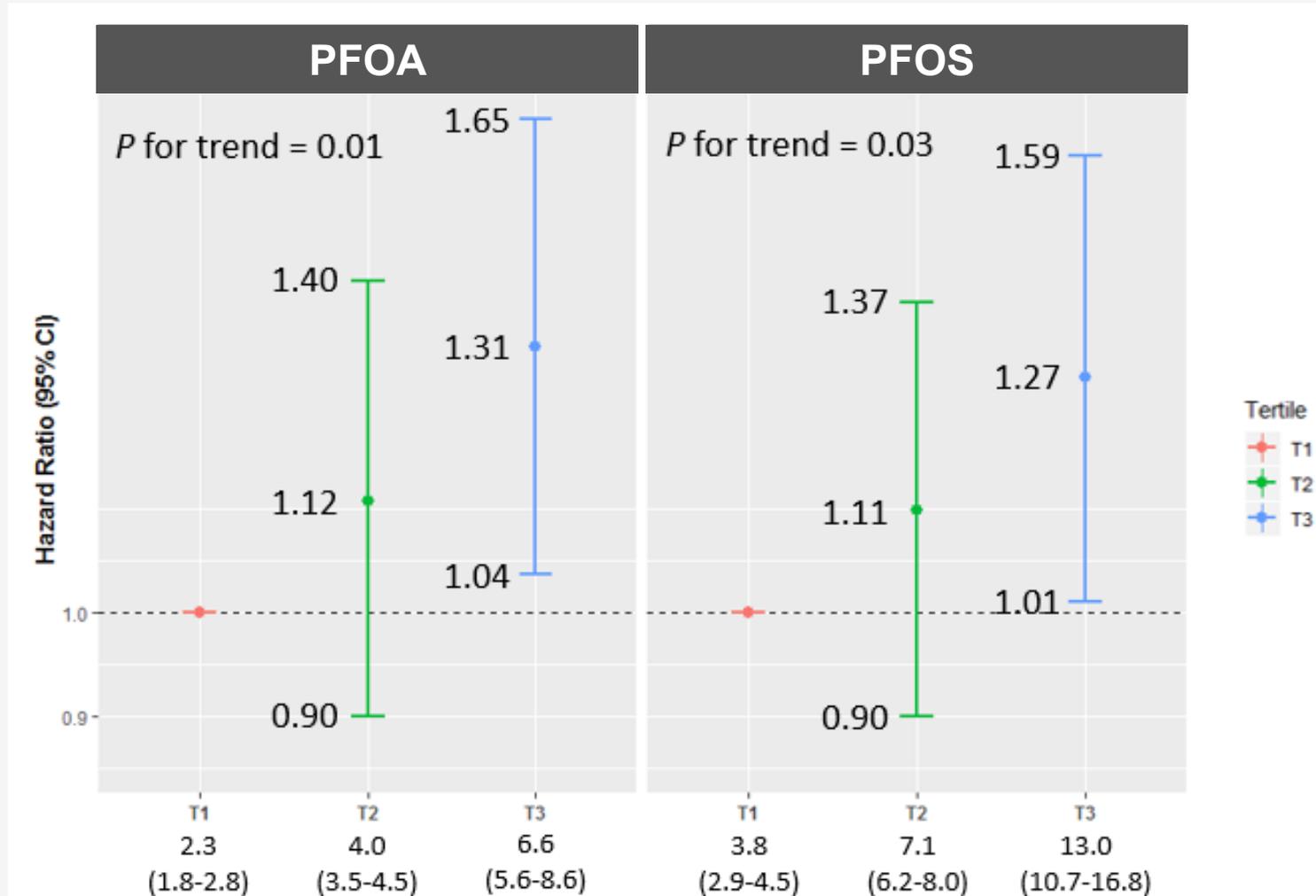
Study population and statistical methods

- **Incident natural menopause:** amenorrhea for at least 12 months not due to hormone therapy, oophorectomy and/or hysterectomy,
- **Cox proportional hazards model** adjusting for age at baseline, race/ethnicity, study site, education, parity, BMI at baseline, physical activity, smoking status and prior hormone use at baseline.

Earlier natural menopause with PFOA and PFOS

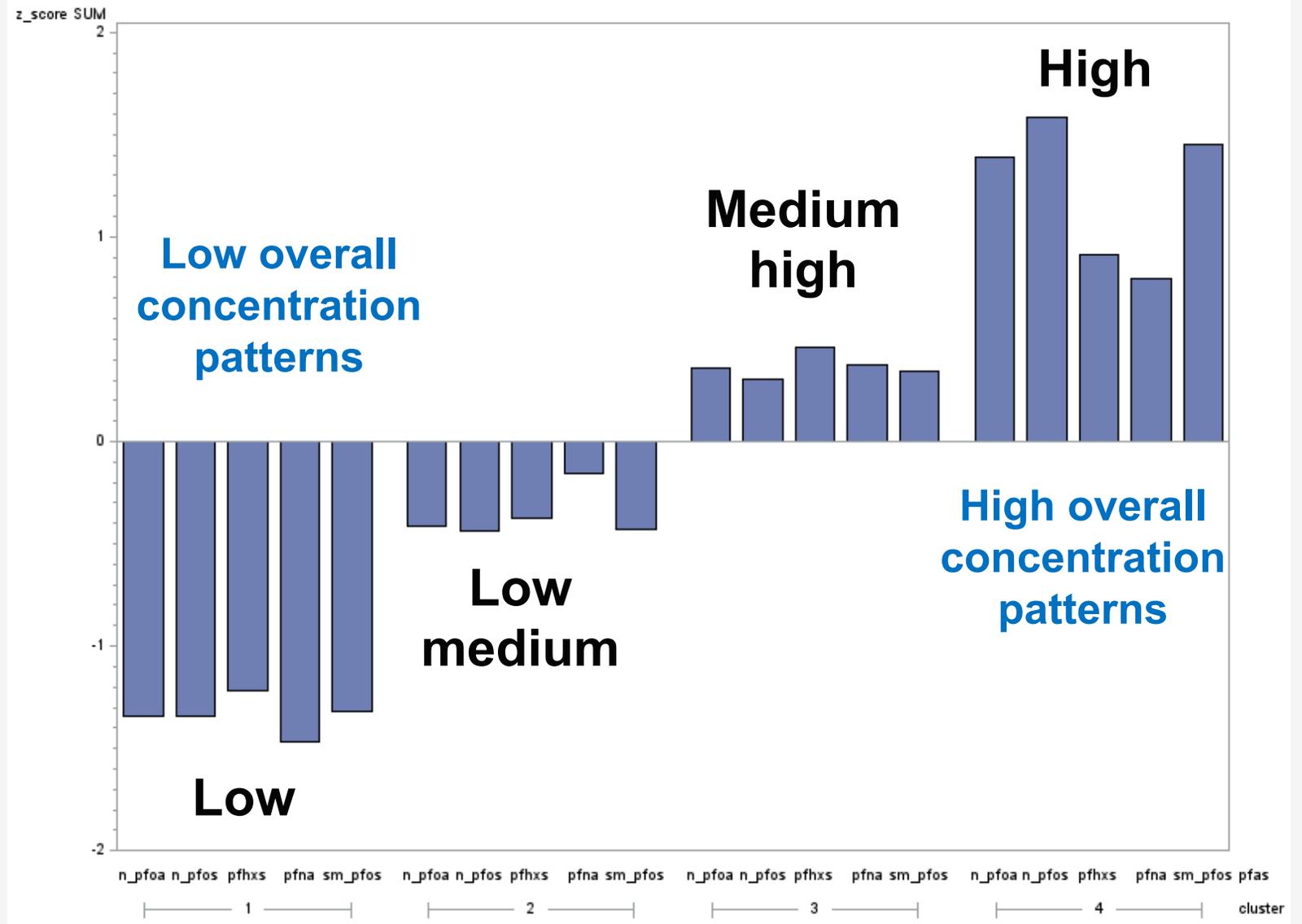
1.1 years earlier

0.9 years earlier

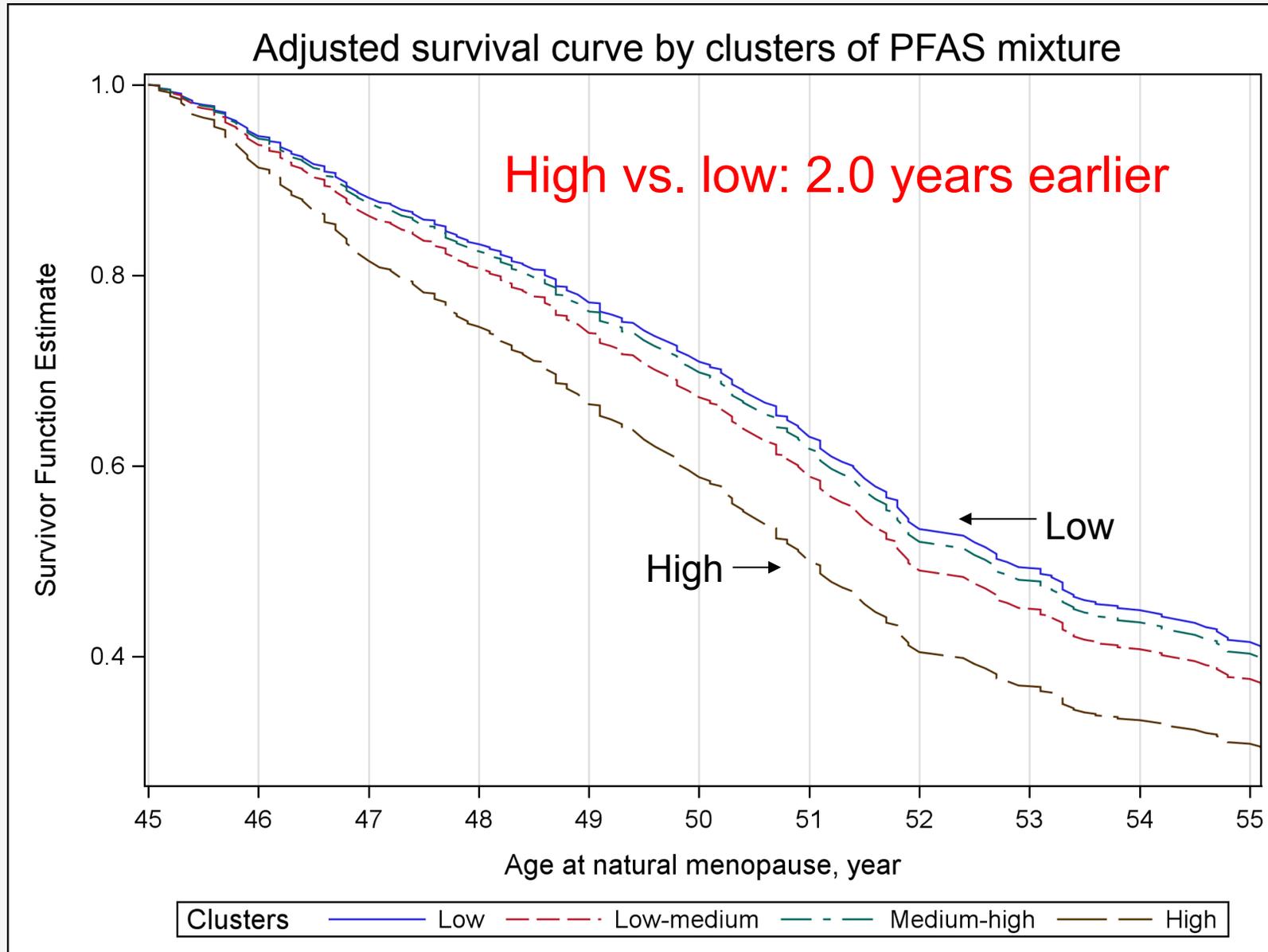


PFAS Mixture

- Unsupervised learning method:
K-means clustering
- Minimize within-cluster sum of squares.
- Number of cluster determined using cubic clustering criterion, pseudo F statistic (i.e. the ratio of between-cluster variance to within-cluster variance), and r-squared statistics.



High vs. low overall concentrations patterns: 2.0 years earlier natural menopause



HR (95% CI) comparing High vs. Low: 1.66 (1.17-2.36)

Predicted median age at menopause:

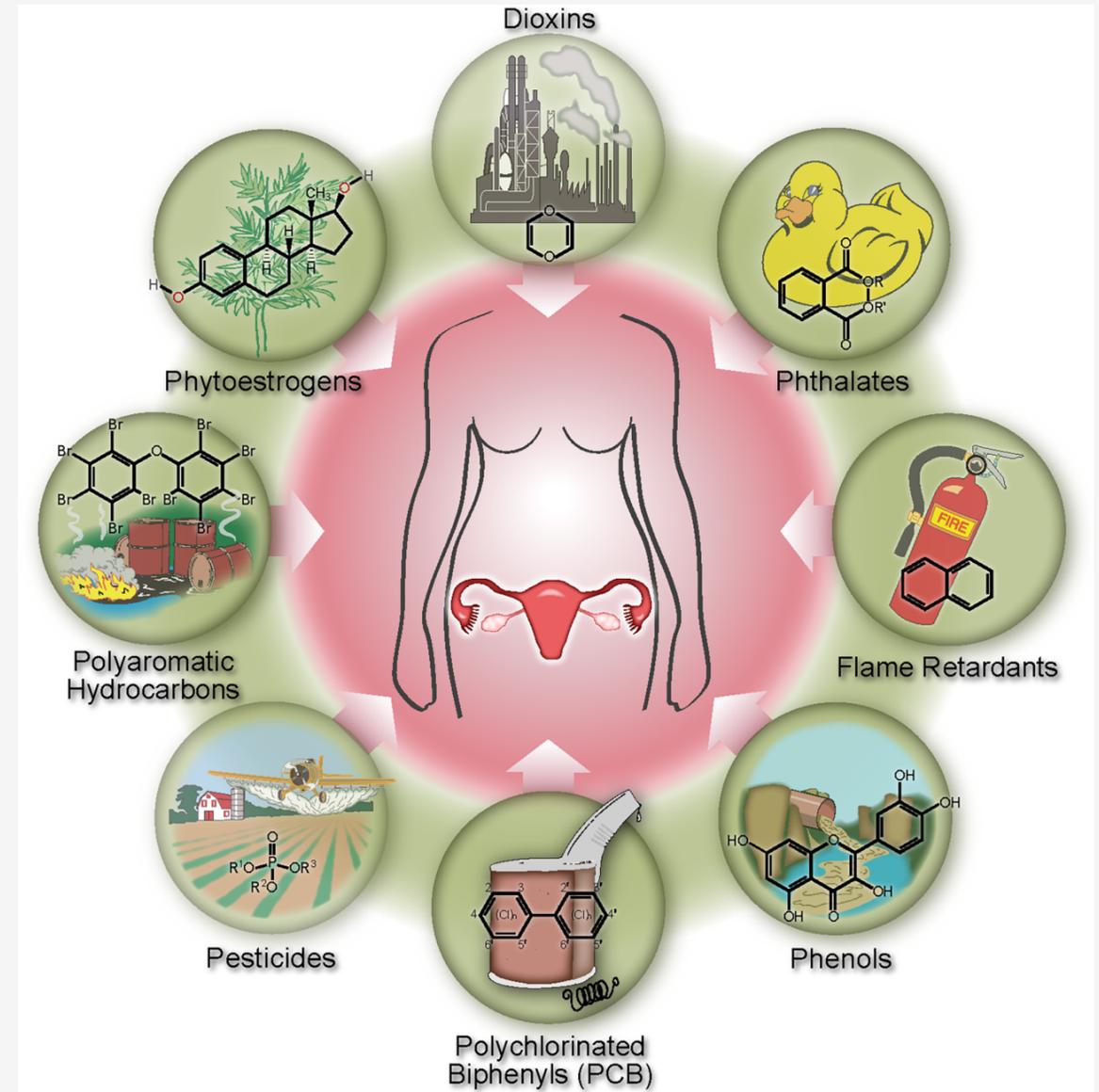
- **Low: 52.7 (95% CI: 51.8-54.6) years**
- Medium low: 51.9 (95% CI: 51.5-52.7) years
- Medium high: 52.6 (95% CI: 51.8-53.3) years
- **High: 50.7 (95% CI: 50.4-51.7) years**

Summary: PFAS were associated with earlier natural menopause, a risk factor for overall health.

- PFAS are potential EDCs and ovarian toxicants (Ding et al. 2020).
- Determinants and temporal trends of PFAS
- 2.0 years earlier natural menopause was associated with **shorter life expectancy (HR=1.04, 95% CI: 1.02-1.07)** in a cohort of 12,134 postmenopausal women followed for an average of 17 years (Ossewaarde et al. 2005).

Future directions

- Linking natural menopause to health conditions.
- Other EDCs and mixture analysis;



(Grindler et al. 2015)

On-going projects

SWAN-MPS (PI: Sung Kyun Park):

- Chemicals: PFAS, metals, PCBs, flame retardants, pesticides, phthalates, phenols, and parabens in serum or urine
- Evaluation of chemicals and their relationships to reproductive traits:
 - Age at natural menopause
 - Hormone profiles
 - Menstrual cycle characteristics
 - ...
- Evaluation of metal exposures and their relationship to metabolic traits:
 - Body composition
 - Diabetes
 - Metabolic syndrome and its components
 - ...

Thank you !

Questions / Comments

Acknowledgement

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Participants in SWAN.

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