Potential confounders in association between PFAS exposure and diabetes.

Kouji H. Harada, Mariko Harada Sassa

Department of Health and Environmental Sciences, Kyoto University Graduate School of Medicine, Kyoto, Japan

ORCID ID

Kouji H. Harada https://orcid.org/0000-0001-7319-123X

Kouji H. Harada, Department of Health and Environmental Sciences, Kyoto University Graduate School of Medicine, kharada-hes@umin.ac.jp

Mariko Harada Sassa, Department of Health and Environmental Sciences, Kyoto University Graduate School of Medicine, marikohs@kuhp.kyoto-u.ac.jp

Corresponding author: Correspondence to Kouji H. Harada.

Word count: 521 words

Keywords: per- and poly-fluoroalkyl substances, confounders, estimated glomerular filtration rate, breastfeeding

To the Editor: We read with interest the recent article by Park et al. in Diabetologia [1]. Per- and poly-fluoroalkyl substances (PFASs) are a class of contaminants of concern in public health due to their widespread contamination. Its chemical structure is similar to fatty acids, which has been suggested to affect metabolic diseases. In this context, the authors investigated the association between PFAS exposure and the risk of developing diabetes in a cohort study [1]. This is an important study that examined the impact of PFAS in a study design with a higher level of evidence than in previous case-control and cross-sectional studies.

In their statistical analysis, the authors adjusted for potential confounding factors in the regression model. However, we wonder if there are other important variables besides those included there. As the authors pointed out, previous studies have shown that blood PFAS concentrations are affected by renal function, including diabetic nephropathy. The authors' study was a cohort study, and blood PFAS concentrations were assessed before the onset of diabetes, which may reduce the influence of potential biases. However, the baseline characteristics of the cohort were not fully provided. Even before the onset of diabetes, there may be bias regarding the risks of developing diabetes, and biases from these variables might affect blood PFAS concentrations. For example, eGFR, history of hypertension or dyslipidemia, and fasting blood glucose were not given. eGFR influences blood PFAS concentrations because renal clearance is an important excretion pathway of PFAS [2], and eGFR can be related to insulin resistance [3]. Decreased eGFR would increase blood PFAS

level and insulin resistance, and the association between PFAS and diabetes onset could be overestimated. eGFR is not only influenced by diabetes but also by many lifestyle-related diseases, and hypertension is one of them [4]. In the study, short-chain, and branched-chain PFASs showed associations with diabetes risks, whose blood levels are predominantly affected by renal function. Hence, potential confounding with eGFR is possible to overestimate the risks.

In addition, even in normal fasting plasma glucose (FPG) levels (<5.5 mmol/L), higher FPG levels have been reported to be associated with higher diabetes risk [5,6]; it would be necessary to check for the differences between PFAS concentration groups. Of course, if this is an intermediate variable for diabetes onset, there may be no need to adjust for it as a total effect, since some studies have shown that PFAS affected FPG levels. However, if there was a difference in FPG at baseline by potential differences in background variables, confounding must be considered.

The authors adjusted for the history of delivery and menopause. This is because blood PFAS levels are affected by these variables and they also affect the risk of developing diabetes. In addition, breastfeeding, not included in the statistical model, decreases blood PFAS levels [7] and also diabetes risk [8], implying that the adjustment may show a weaker association than the original analysis.

Taken together, the possible directed acyclic graph between PFAS exposure and diabetes risk

is shown (Figure 1). This information may not be all-inclusive but should be considered as background information in future studies and help evaluate previous studies.

Abbreviations

PFAS: per- and poly-fluoroalkyl substances

eGFR: estimated glomerular filtration rate

FPG: fasting plasma glucose

Data availability

Not applicable

Funding

This letter was partly supported by the Japan Society for the Promotion of Science (grant numbers 22K10509; 20K23224). The funder was not involved in this work.

Authors' relationships and activities

Author information

Affiliations

Department of Health and Environmental Sciences, Kyoto University Graduate School of Medicine, Kyoto, Japan

Mariko Harada Sassa & Kouji H. Harada

Ethics declarations

Duality of interest

The authors declare that there is no duality of interest associated with this manuscript.

Contributions

MH and KHH were responsible for drafting the article. All authors approved the version to be submitted.

References

1. Park SK, Wang X, Ding N, et al.. Per- and polyfluoroalkyl substances and incident diabetes in midlife women: the Study of Women's Health Across the Nation (SWAN). Diabetologia. 2022 Apr 11. doi: 10.1007/s00125-022-05695-5. Epub ahead of print.

PMID: 35399113.

2. Harada K, Inoue K, Morikawa A, Yoshinaga T, Saito N, Koizumi A. Renal clearance of perfluorooctane sulfonate and perfluorooctanoate in humans and their species-specific excretion. Environ Res. 2005 Oct;99(2):253-61. doi: 10.1016/j.envres.2004.12.003. Epub 2005 Jan 18. PMID: 16194675.

3. Pham H, Robinson-Cohen C, Biggs ML, et al.. Chronic kidney disease, insulin resistance, and incident diabetes in older adults. Clin J Am Soc Nephrol. 2012 Apr;7(4):588-94. doi: 10.2215/CJN.11861111. Epub 2012 Mar 1. PMID: 22383749; PMCID: PMC3315343.

4. Yoshida T, Takei T, Shirota S, et al.. Risk factors for progression in patients with early-stage chronic kidney disease in the Japanese population. Intern Med. 2008;47(21):1859-64. doi: 10.2169/internalmedicine.47.1171. Epub 2008 Nov 4. PMID: 18981628.

5. Nichols GA, Hillier TA, Brown JB. Normal fasting plasma glucose and risk of type 2 diabetes diagnosis. Am J Med. 2008 Jun;121(6):519-24. doi: 10.1016/j.amjmed.2008.02.026. PMID: 18501234.

6. Dowse GK, Zimmet PZ, Collins VR. Insulin levels and the natural history of glucose intolerance in Nauruans. Diabetes. 1996 Oct;45(10):1367-72. doi: 10.2337/diab.45.10.1367. PMID: 8826973.

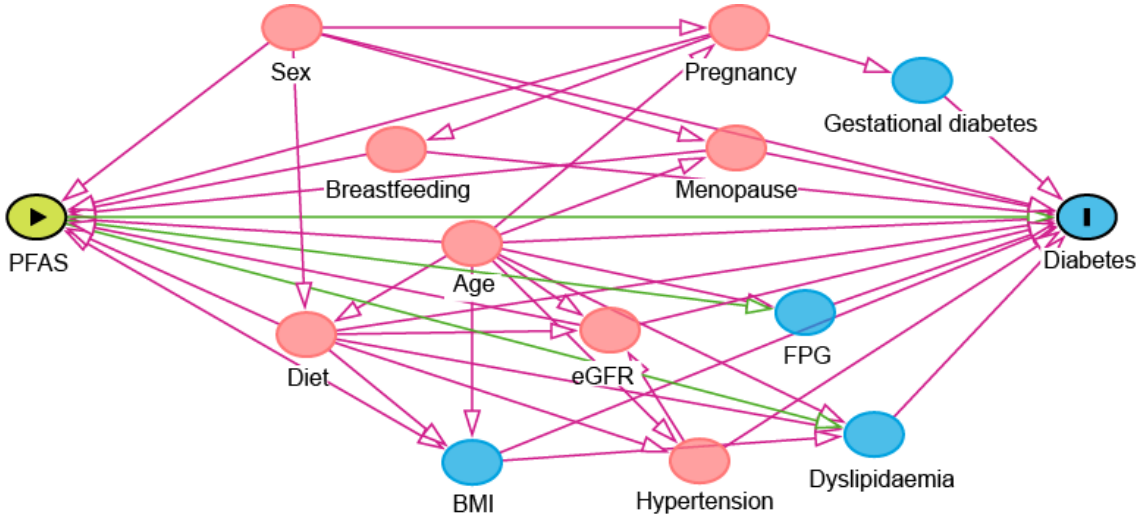
7. Kato K, Wong LY, Chen A, et al.. Changes in serum concentrations of maternal poly- and perfluoroalkyl substances over the course of pregnancy and predictors of exposure in a

multiethnic cohort of Cincinnati, Ohio pregnant women during 2003-2006. Environ Sci Technol. 2014 Aug 19;48(16):9600-8. doi: 10.1021/es501811k. Epub 2014 Jul 29. PMID: 25026485; PMCID: PMC4140533.

8. Stuebe AM, Rich-Edwards JW, Willett WC, Manson JE, Michels KB. Duration of lactation and incidence of type 2 diabetes. JAMA. 2005 Nov 23;294(20):2601-10. doi: 10.1001/jama.294.20.2601. PMID: 16304074.

Figure legend

Figure 1. Possible directed acyclic graph of the causal network between PFAS exposure and diabetes risk with potential confounders. PFAS: exposure; Diabetes: outcome; Blue circles: ancestor of outcome; Pink circles: ancestor of exposure and outcome. Green arrows: causal paths; Pink arrows: biasing paths. This graph is made by 'dagitty' (http://www.dagitty.net/).


Sex
Pregnancy
Gestational diabetes
Breastfeeding
Menopause
PFAS
Diabetes
Age
FPG
Diet
eGFR
Dyslipidaemia
BMI
Hypertension

129