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LETTER

Potential confounders in the association between per- and polyfluoroalkyl substance exposure and diabetes

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Abbreviations
FPG Fasting plasma glucose
PFAS Per- and polyfluoroalkyl substances

To the Editor: We read with interest the recent article by Park et al in *Diabetologia* [1]. Per- and polyfluoroalkyl substances (PFAS) are a class of contaminants of concern in public health because of their widespread use [2]. The chemical structure of PFAS is similar to that of fatty acids, which have been implicated in 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 using 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 by the authors. As the authors point out, previous studies have shown that blood PFAS concentrations are affected by impaired renal function, including diabetic nephropathy [1]. The study by Park et al 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 risk of developing diabetes, and biases from these baseline variables may affect blood PFAS concentrations. For example, eGFR, history of hypertension or dyslipidaemia, and fasting plasma glucose (FPG) levels were not provided by Park et al. eGFR influences blood PFAS concentrations because renal clearance is an important excretion pathway for PFAS [3]; in addition, eGFR can be related to insulin resistance [4]. A decreased eGFR would increase blood PFAS levels and insulin resistance and the association between PFAS and diabetes onset could be overestimated. eGFR is influenced not only by diabetes but also by many lifestyle-related diseases, including hypertension [5]. In the study by Park et al, short-chain and branched-chain PFAS, whose blood levels are predominantly affected by renal function, showed associations with diabetes risk [1]. Hence, potential confounding by eGFR may lead to overestimation of the risks of PFAS.

In addition, higher FPG levels even within the normal range (<5.5 mmol/l) have been reported to be associated with a higher risk of diabetes [6, 7]; it would therefore be important to look for any differences in FPG levels between the PFAS tertiles analysed by Park et al [1]. Of course, if the FPG level is an intermediate variable for diabetes onset, there may be no need to adjust for it as a total effect, as some studies have shown that PFAS affect FPG levels. However, if there is a difference in FPG levels at baseline by potential differences in background variables, confounding must be considered.

Park et al adjusted for parity and menopause [1]. 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 authors' statistical model, decreases blood PFAS levels [8] and also diabetes risk [9], implying that adjustment for breastfeeding may result in a weaker association than in the original analysis.

Taking this information together, a possible directed acyclic graph of PFAS exposure and diabetes risk is shown in Fig. 1. This graph may not be all-inclusive but should be

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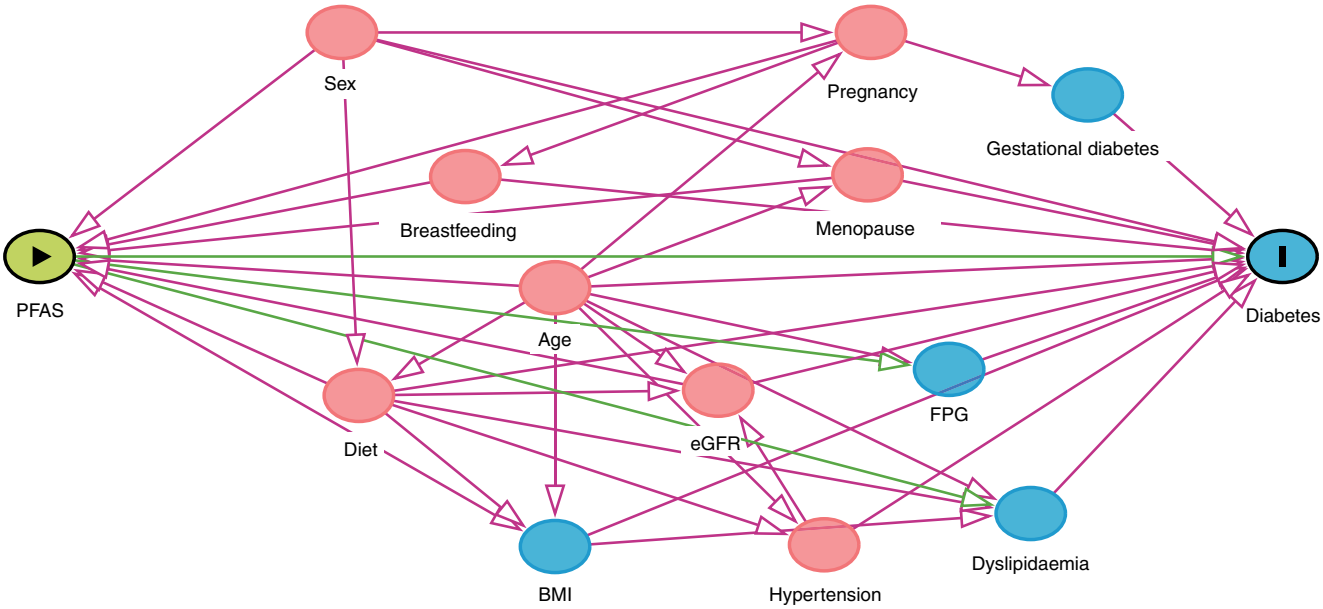

Fig. 1 Possible directed acyclic graph of the causal network between PFAS exposure and diabetes risk including potential confounders. Exposure (green circle): PFAS; outcome (blue circle with black outline): diabetes. Blue circles: ancestors of the outcome; pink circles: ancestors of the exposure and outcome. Green arrows: causal paths; pink arrows: biasing paths. Graph created using DAGitty version 3.0 (http://www.dagitty.net/; accessed 17 May 2022)

considered as background information in future studies and to help evaluate previous studies.

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

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