



Full length article

Substantial decrease of PFAS with anion exchange resin treatment – A clinical cross-over trial

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ABSTRACT

Background: Per- and polyfluoroalkyl substances (PFAS) are heat and stain resisting chemicals. They are persistent, bioaccumulating and spread ubiquitously. Many hotspots where humans are exposed to high levels of PFAS have been reported. A few small observational studies in humans suggest that treatment with an Anion Exchange Resin (AER) decreases serum PFAS. This first clinical controlled crossover study aimed to assess whether AER decreases perfluorooctanesulfonic acid (PFOS) in highly exposed adults.

Methods: An open label 1:1 randomized treatment sequence crossover study with allocation to oral AER (cholestyramine 4 g three times daily) or observation for 12 weeks was conducted among citizens from a PFAS hotspot. Main inclusion criteria was serum PFOS > 21 ng/mL. Primary endpoint was change in serum PFOS levels between treatment and observational period.

Results: In total, 45 participants were included with a mean age of 50 years (SD 13). Serum PFOS baseline median was 191 ng/mL (IQR: 129–229) and decreased with a mean of 115 ng/mL (95 % CI: 89–140) on treatment, and 4.3 ng/mL in observation period corresponding to a decrease of 60 % (95 % CI: 53–67; $p < 0.0001$). PFHxS, PFOA, PFNA and PFDA decreased during treatment between 15 and 44 %. No serious adverse events were reported.

Conclusions: Oral treatment with AER significantly lowered serum PFOS concentrations suggesting a possible treatment for enhancing elimination of PFOS in highly exposed adults.

1. Introduction

Per- and polyfluoroalkyl substances (PFAS) have been widely used in industrial and consumer products since the middle of the 20th century, due to their heat resisting and water- and grease-repelling properties (EFSA CONTAM PANEL *et al.*, 2020). PFAS are persistent, bioaccumulating and found in human biomonitoring studies worldwide (Fromme *et al.*, 2009; Roth *et al.*, 2020). PFAS have been linked to a wide range of adverse health effects, including hormonal and

immunological disturbances, elevated cholesterol and liver enzymes, and an increased risk of certain cancers (ATSDR, 2021; EFSA CONTAM PANEL *et al.*, 2020; National Academies, 2022). Commonly measured PFAS are perfluorooctanesulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorohexanesulfonic acid (PFHxS), perfluorononanoic acid (PFNA) and perfluorodecanoic acid (PFDA). Since 2006 regulations for individual PFAS have been set by the United Nations Environmental Programme (UNEP) "The Stockholm Convention". Nonetheless, many hotspot areas, in which humans are highly exposed to PFAS through

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contaminated drinking water, soil or food, have been reported (Frisbee et al., 2009; Lasters et al., 2022; Pitter et al., 2020; Xu et al., 2021).

PFAS are almost completely absorbed in the gut, protein bound in serum, and concentrated in the liver and kidneys (Olsen et al., 2003; Pérez et al., 2013). PFAS are not metabolized (EFSA 2020, ATSDR, 2021) and are mainly eliminated in urine and feces (ATSDR, 2021; EFSA CONTAM PANEL et al., 2020). However, an extensive reabsorption takes place both in renal tubules (K. Harada et al., 2005) and in the gut (Ducatman et al., 2021; Fletcher et al., 2022; Ruggiero et al., 2021). Given the enterohepatic re-absorption of PFAS, the excretion is very limited leading to long half-life, e.g. the half-life of PFOS is known to be in the range of 2.7–5.0 years (Li et al., 2022).

Cholestyramine and colesevelam are Anion Exchange Inhibitors (AER), which form insoluble complexes with bile acid in the gut, thereby inhibiting reabsorption and increasing fecal loss of cholesterol (Scaldaferri et al., 2013). It has been suggested that AERs could also reduce the biliary reabsorption of PFAS. Rats treated with cholestyramine for 21 days had significantly decreased levels of PFOS, with plasma concentration being reduced by 87 % compared to untreated rats (Johnson et al., 1984). Human case studies reported that treatment with cholestyramine reduced serum PFOS (Genuis et al., 2010) (Genuis et al., 2013). Among 56,175 Americans, highly exposed to PFAS from drinking water (Ducatman et al., 2021), 36 participants reported treatment with cholestyramine and they had serum PFOS in the lower 5 % of the distribution. Similar results were found by Andersen et al. (Andersen et al., 2021), where AER-users ($n = 22$) in the NHANES cohort ($n = 14,609$, sampled 2003–2016) had 15.1 % lower serum PFOS concentrations than the rest of the cohort. Given the long half-lives, emerging hot-spots and negative health effects of PFAS, these previous results indicate the potential to treat certain highly exposed groups with AERs to minimize the body burden of PFAS. However, the authors are not aware of any previous experimental, human controlled trials. The purpose of this study was to assess whether treatment with an AER could reduce serum levels of PFOS in a population highly exposed to PFOS.

2. Methods

2.1. Study design

This study was conducted in a single hospital center as a randomized

controlled trial, using 1:1 randomization with two intervention groups. Open label treatment intervention with a crossover design was performed, with initial allocation to either active treatment or observation followed by a washout period of two-weeks before commencement of the second opposite. Each period of treatment or observation were 12-weeks. The study design is shown in Fig. 1.

2.2. Study setting

Study participants were recruited amongst members of a local Cow Grazing Association in Korsoer, Denmark. In 2021, it was discovered that this group had consumed meat from cattle accidentally contaminated with PFOS and PFHxS from a nearby firefighting school. Immediately after the discovery, the members were advised to stop eating the meat. PFAS blood tests three months later revealed that the majority of members (118 out of 187) had serum levels of PFOS and PFHxS above the estimated 97.5th percentile of previously reported levels in a Danish background population, corresponding to PFOS > 21.2 ng/mL and PFHxS > 1.9 ng/mL (Grandjean et al., 2020). For this reason, these individuals were considered highly exposed.

Members who met the following inclusion criteria were invited to participate in the study: Age ≥ 18 years and known serum PFOS level above 21 ng/mL within one year prior to screening. Written informed consent was obtained from all participants, prior to conduction of the study. Exclusion criteria were: contraindication for use of the study medication (e.g. total intestinal or biliary tract obstruction, hypertriglyceridemia or fat malabsorption as well as treatment-refractory constipation) or medical treatment listed with a risk of interaction with the study drug (oral anticoagulants, thyroid hormones, oral contraceptives, thiazides (incl. combination preparations), doxepin (tricyclic antidepressant), nicotinic acid, tetracycline, benzyl penicillin, phenobarbital, digoxin). Pregnant or breastfeeding women, those planning to become pregnant within six months from baseline and those using unsafe contraception were also excluded. Women of childbearing age performed a pregnancy test (urine hCG).

2.3. Randomization

Each participant was randomly assigned into intervention group A or B using REDCap. Block-randomization in blocks of 16 was used.

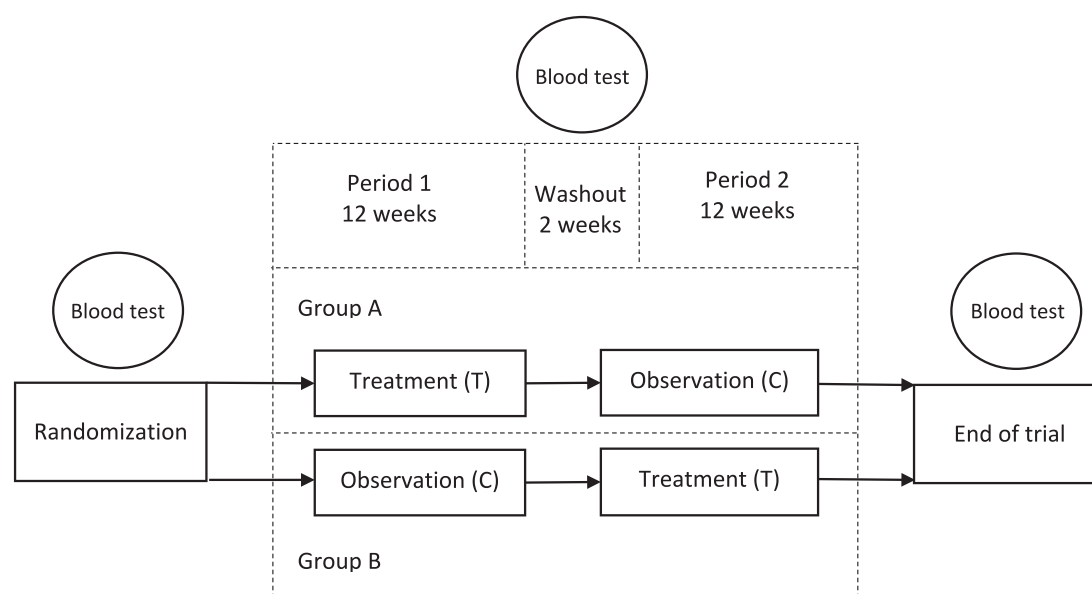


Fig. 1. Study design. **Legend:** Treatment (T) with Anion Exchange Inhibitor. Observation (control period (C)) with no treatment. Participants allocated to group A followed the intervention sequence T/C and group B followed the intervention sequence C/T. Blood tests consisted of analysis of perfluoroalkyl substances as well as clinical blood samples.

2.4. Intervention

As illustrated in Fig. 1, intervention group A received 12 weeks of treatment (T) with AER in “Period 1”, followed by 12 weeks of observation without treatment (C) in “Period 2”. Conversely, intervention group B began “Period 1” with 12 weeks of observation without treatment (C) followed by 12 weeks of treatment with AER in “Period 2”.

Participants received the study medication for all 12 weeks of treatment at the beginning of the treatment period. Participants in randomization group A received the study medication immediately after randomization, whilst group B commenced the treatment after the observation and wash-out periods. The treatment followed the standard dose recommended by the Danish Medicines Agency. All participants received a fixed dose of the study medication, without the option of up- or down-titration. Originally, the trial was designed for treatment with colesevelam (Cholestagel®), but due to a supply shortage, colesevelam was substituted with cholestyramine (Cholestyramine®) in a protocol amendment. Thus, the first four participants were treated with three tablets of colesevelam, at a dose of 625 mg twice daily with a total daily dose of 3,750 mg. The subsequent participants were treated three times daily with one pouch of Cholestyramine as powder to oral suspension, at a dose of 4 g with a total daily dose of 12 g. After 2–4 weeks of treatment, the participants received a phone call to register any possible adverse effects and to ensure compliance with the study protocol. At end of the treatment period, participants returned unused study medication to an accountability check and had the opportunity to report any adverse event during the study period. Participants with less than 80 % use of study medication were classified as non-compliant.

2.5. Clinical data

Clinical data and blood samples were collected at three clinical visits: first screening/ randomization (baseline), at the time of cross-over and at the end of trial. The baseline visit included a medical interview on medical history and lifestyle, a physical examination and routine clinical biochemistry.

Study data was collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted by the Capital Region in Denmark. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources (Harris et al., 2009, 2019).

2.6. Endpoints

Our primary endpoint was the mean change in serum PFOS after 12 weeks of treatment with AER, compared to the 12 weeks of observation. The secondary endpoint was the percentage change in PFOS in the control period following treatment, as an indication of the level of post-treatment redistribution. As only half of the study population was randomly assigned to treatment first followed by observation, the secondary outcome was only assessed in 50 % of participants. PFHxS, PFOA, PFDA and PFNA were analyzed as explorative endpoints. Adverse events were also registered for the full duration of the trial.

2.7. PFAS measurement

Serum from each point of measurement (Fig. 1) was stored at -80°C and analyzed for PFOS (sum of isomers), PFHxS, PFOA, PFNA and PFDA at the end of the study in one batch. PFAS concentrations were determined at the Department of Public Health, Clinical Pharmacology, Pharmacy and Environmental Medicine, University of Southern Denmark, by use of isotope dilution, online solid phase extraction, high-

pressure liquid chromatography and triple quadrupole mass spectrometry (LC-MS/MS) (Jensen et al., 2015). Calibrators, serum and solvent blanks, as well as quality control samples were included with the series of samples analyzed. Quality control samples included serum samples from previous quality assessment programs and in-house made quality control samples. All quality control samples were well within the acceptance ranges. Imprecision was $< 6\%$ for all the analytes and the limit of quantitation was 0.03 ng/mL . Accuracy and reliability of the data for the PFAS analysis was ensured by regular participation of the laboratory in the G-EQUAS quality assessment scheme, organized by the German Society of Occupational Medicine. The staff at the analyzing laboratory had no knowledge of the randomization sequence of the participants in the study.

2.8. Statistical analysis

As this was the first randomized controlled study to test the effect of AER on the excretion of PFAS, limited information about the expected effect size was available. Based on the available literature, sample size was determined by power calculation applying different estimations. Authors expected a median PFOS of 70 ng/mL , with a positively skewed distribution and a half-life of PFOS of 3.4 years (decrease of 20 % of serum concentration/year) with a SD of 1.21 years (decrease of 19 % to 22 %/ year) (Li et al., 2018). Participants were expected to excrete PFOS at least twice as fast with treatment. Normally, the maximum effect of AERs on low-density lipoprotein (LDL) is expected after 30 days of treatment. Consequently, a treatment period of 12 weeks was determined to increase the PFOS elimination from 5 % to 10 %. Enrolling 24 participants in each of the two intervention groups gave an estimated power of 0.8 (two-sided alpha level of 0.05) to detect an average of a 7 % decrease of serum PFOS levels during treatment period. To account for missing data and/or drop-out, this study aimed to enroll a total 60 participants.

Descriptive statistics were used to summarize participants' characteristics. Statistical analysis adopted an intention-to-treat principle, for all participants who received at least one dose of study medication. Crossover studies consider carryover effect, period effect and sequence effect (Lim and In, 2021). As there is no comparison with another treatment, and AERs are not absorbed from the gastrointestinal tract, carryover was not taken into account. Comparisons between the relative differences in mean serum concentrations in the treatment (T) and observation (C) periods for the sequences (T/C and C/T) were undertaken to account for sequence effect. To test for period effect, relative changes in mean serum concentration of PFOS were compared in the treatment (T) and the observation (C) period. Statistical analyses were conducted using Student's t-tests. The analysis was initially conducted on an individual level, comparing outcome level before and after each period. Results are shown as the mean of the pool effect for each period. Data is shown without adjustments. Explorative analysis on the effect of treatment was conducted based on category in terms of sex (male or female) and age (above or below median age).

Additional explorative analyses of period and sequence effects were completed for PFHxS, PFOA, PFNA and PFDA, using the same methodology as for PFOS.

Only complete case data was included in analyses in terms of effect without use of imputation. All statistical analyses were conducted using R Statistical Software (v4.1.2; R Core Team 2021) using an alpha level of 0.05. A statistician independent of the trial management and unaware of the group assignments performed the statistical analysis.

3. Results

3.1. Study participants

From November 2021 to June 2022, 46 participants were recruited to this study. Following randomization, one participant (intervention

group A) was excluded at baseline due to the diagnosis of an illness requiring treatment. The CONSORT diagram is shown in Fig. 2.

The study participants had a mean age of 50 years (SD 13) and 51 % were male. The median serum concentration of PFOS was 191 ng/ mL (IQR 129–229), PFHxS 8.8 ng/ mL (5.7–11.9), PFOA 0.92 ng/ mL (0.72–1.05), PFNA 0.49 ng/ mL (0.41–0.64), and PFDA 0.17 ng/ mL (0.13–0.21). No samples for PFAS analysis were below detection level. At baseline, 25 participants (56 %) had a chronic disease requiring prescribed medication. Out of those 11 received treatment with statins to treat dyslipidemia. Total cholesterol mean was 4.9 mmol/ L (SD 1.1) and LDL 2.7 mmol/ L (SD 1.0). Additional baseline characteristics of the participants are shown in Table 1. No participant received medical treatment with effect on gastrointestinal transition time.

3.2. Test for sequence effect

In order to pool effect of treatment in a crossover, sequence effect was tested for. A numeric, larger treatment effect was seen in intervention group A and a larger decrease in serum PFOS during control period was seen in intervention group B. However, no statistically significant sequence effect was identified comparing differences in relative decrease of serum PFOS after treatment and control period between the groups (respectively $p = 0.17$ and 0.43). Therefore, effect of treatment or observation for the following is presented as pooled analysis (Lim and In, 2021). Baseline characteristic in the randomization strata is shown in supplementary Table 1S.

3.3. Change of PFOS levels on treatment

The mean decrease of serum PFOS during treatment was 115 ng/mL (95 % CI: 89–140), corresponding to a decrease of 63 % (95 % CI: 57–70). During observation mean decrease was 4.3 ng/ mL (95 % CI: 0.51–8.1) corresponding to a decrease of 3.3 % (95 % CI: 1.0–5.6). Thus, the relative reduction between treatment and observation periods was 60 % (95 % CI: 53–67) or 111 ng/mL (95 % CI: 85–136), corresponding to a highly significant effect of treatment ($p < 0.0001$). Adjustments for age or sex had no effect on treatment response ($p = 0.11$ and $p = 0.19$), respectively. At the end of study, six participants reached serum levels of PFOS < 21 ng/ mL (corresponding to Danish background levels).

Table 1
Baseline characteristics of the 45 participants.

Characteristics	Participants (n = 45)
Age, years (SD)	50 (13)
Male sex, n (%)	23 (51)
PFOS, ng/ml (IQR)	191(129–229)
PFHxS, ng/ml (IQR)	8.8 (5.7–11.9)
PFOA, ng/ml (IQR)	0.92 (0.72–1.05)
PFNA, ng/ml (IQR)	0.49 (0.41–0.64)
PFDA, ng/ml (IQR)	0.17 (0.13–0.21)
BMI, kg/m ² , (SD)	29 (5.0)
Blood pressure, systolic /diastolic, mmHg, (SD)	136/88 (21/ 13)
Any chronic disease in medical history, n (%) *	25 (56)
Cardiovascular disease, n (%)**	11 (24)
Dyslipidemia, n (%)	11 (24)
Diabetes type 2, n (%)	5 (9)
Haemoglobin, mmol/ L, (SD)	9.1 (0.9)
Creatinine, μ mol/ L, (SD)	72 (11)
eGFR, ml/ min/ 1.73 m ² , (SD)	87 (6)
Total cholesterol, mmol/ L, (SD)	4.9 (1.1)
LDL, mmol/ L, (SD)	2.7 (1.0)
HDL, mmol/ L, (SD)	1.4 (0.5)
Triglyceride, mmol/L, (SD)	1.6 (0.9)
25-Hydroxy-Vitamin D3, nmol/L, (SD)	60 (24)

Legend: *No participants received medical treatment with effect on gastrointestinal transition time. ** Hypertension, stroke or ischemic heart disease. PFOS = Perfluorooctanesulfonic acid, PFHxS = Perfluorohexanesulfonic acid, PFOA = Perfluorooctanoic acid, PFNA = Perfluorononanoic acid, PFDA = Perfluorodecanoic acid. Estimated glomerular filtration rate (eGFR) is based on CKD-EPI creatinine equation including: Sex and age, but not race. Numeric variables are presented with mean and standard deviation (SD), PFAS's values with median and interquartile range (IQR), and categorical variables with amount and percentage of study population (%).

3.4. Post-treatment redistribution of PFOS

In the intervention group A, with the sequence treatment followed by observation, serum PFOS was further reduced by 2.5 ng/mL (95 % CI: –0.3 to 5.2) during the observational period indicating limited redistribution.

3.5. Change of other PFAS

Additionally, changes in other PFAS levels were analyzed, with decreases between 19 and 48 % with treatment, as shown in Fig. 3. During

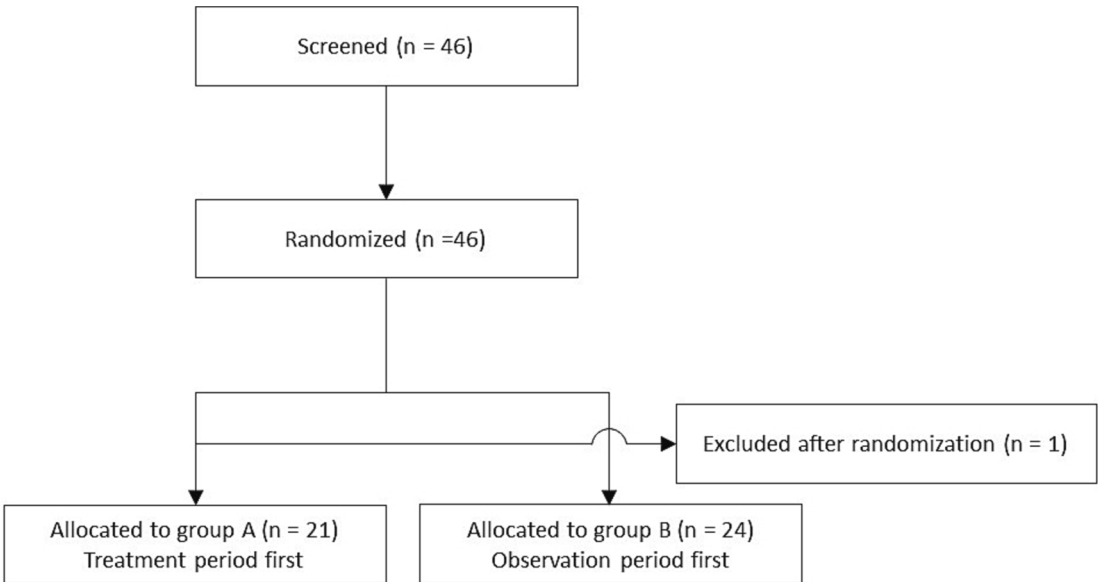


Fig. 2. CONSORT diagram of the study population.

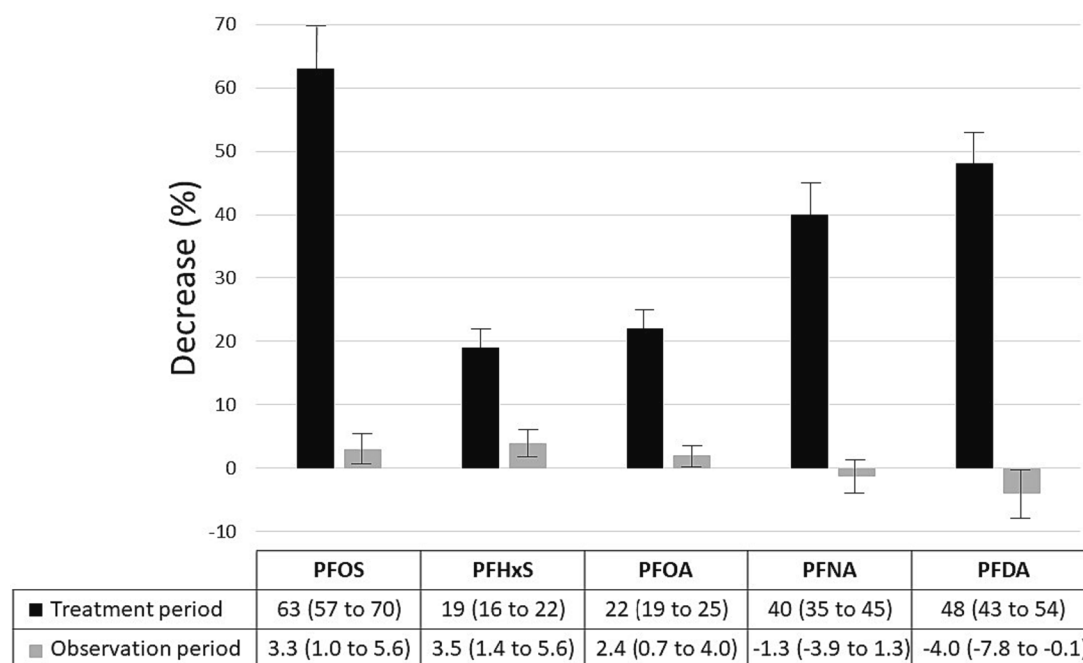


Fig. 3. Relative elimination of PFAS in 12 weeks treatment or observation period. **Legend, Fig. 3:** Percentage of change before vs. after either treatment or observation for 12 weeks. Mean percentage decrease in PFAS's and 95 % confidence limits error bars. PFOS = Perfluorooctanesulfonic acid, PFHxS = Perfluorohexanesulfonic acid, PFOA = Perfluorooctanoic acid, PFNA = Perfluorononanoic acid, PFDA = Perfluorodecanoic acid.

the observation period, mean reductions in serum levels for PFHxS was 3.5 % and 2.4 % for PFOA. However, serum levels increased by 1.3 % for PFNA and 4.0 % for PFDA.

3.6. Adverse events

Adverse effects of the study medication were registered for five participants, who reported mild gastrointestinal symptoms and headache. One participant did not complete the study due to gastrointestinal symptoms related to study drug. No serious adverse effects were recorded. In addition, eleven participants did not comply with protocol, with nine participants having a compliance of less than 80 % use of the study medication and two participants missing blood test for one of three measures of PFAS. No participants donated blood during the study period.

4. Discussion

In this first randomized controlled study of its kind, a significant reduction of 60 % in serum PFOS was identified after treatment with an anion exchange resin for 12 weeks among 45 highly exposed adults. The reduction in serum levels were, for PFHxS 15 %; for PFOA 20 %; for PFNA 39 % and for PFDA 44 %. During the observation 12-week period the corresponding reduction in PFOS was 3 %. These highly statistically significant findings are groundbreaking suggesting that PFAS elimination can be significantly enhanced with AER treatment, offering reassurance to highly exposed individuals.

No post-treatment re-distribution, i.e. mobilization from other compartments, was found, as PFAS did not increase in participants in the observation period after the initial treatment response. However, this result was only based on 21 participants due to the crossover design and hence, the study may not possess sufficient power to accurately measure this outcome. Therefore, extent of redistribution should be investigated further in additional studies and it would be beneficial with multiple measurements over time to increase the accuracy.

To the author's knowledge, no clinical controlled human studies of this nature have previously been conducted. However, the findings are

in accordance with an animal study in which rats, exposed to PFOS and treated with cholestyramine for 21 days, had a 9-fold increase in PFOS elimination in feces (Johnson et al., 1984). In addition, the findings are supported by human case series (Genuis et al., 2010, 2013) and population studies in which participants treated with bile acid sequestrants had PFAS concentrations in the lowest range (Andersen et al., 2021; Ducatman et al., 2021).

PFAS are absorbed from the gut (Ericson et al., 2008; Kimura et al., 2017), bind to serum proteins and accumulate mainly in the liver, kidney and blood (Sheng et al., 2016). They are not metabolized and renal clearance is low due to active renal reabsorption (Andersen et al., 2008; Li et al., 2022). Biliary excretion is also low due to enterohepatic circulation and it has been estimated that a large proportion of excreted PFAS is reabsorbed from the gastrointestinal tract through this method (K. H. Harada et al., 2007). Both cholestyramine ('Cholestyramine', 2012) and colesevelam (H. Bays and Jones, 2007) are bile acids sequestrants, acting as bile acid resins or anion exchange resins. The AERs are large, highly positively charged anion exchange resins that bind to negatively charged anions such as bile acids (salts) by exchanging chloride ions, forming insoluble complexes that are excreted in feces. They have been used in the treatment of hypercholesterolemia by inhibiting the enterohepatic reabsorption, thus enhancing fecal excretion of cholesterol (Roth et al., 2020). The same mechanism applies for PFOS. This study is the first of its kind and previously approved drugs, with few and mild side effects (constipation, abdominal pain, diarrhea, dyspepsia, flatulence and nausea), were used (Genuis et al., 2010; Scaldaferrri et al., 2013). However, some limitations need to be addressed. First, the participants were very motivated for treatment, due to their known high exposure to PFAS. In other settings, among less motivated samples, the gastrointestinal side effects of AER may be less well tolerated. Therefore, treatment should primarily be offered to highly exposed individuals for shorter time periods, though the optimal time-frame of treatment needs to be determined in future studies. Still, studies have found that the use of AER have long term beneficial effects on both cardiovascular disease and diabetes risk factors (Hansen et al., 2017). Second, the initial plan was to use colesevelam, which was administered as twice-daily tablets. However, due to a shortage of supply of

colesevelam a switch to the powder cholestyramine was necessary. The study participants reported cholestyramine to have a non-palatable taste, leading to well-known compliance issues (Bays et al., 2011). As cholestyramine is administered three times daily, three participants reported they forgot to take the trial medication during the day and a total of nine participants were non-compliant. Gastrointestinal adverse effects were the main reason for cessation of treatment, as well as reduced compliance during the trial. Lastly, other factors which could have contributed to the reduction in serum PFAS e.g. self-treatment and diet was not accounted for. Moreover, participants were only treated for 12 weeks and therefore, this study cannot determine whether longer treatment periods would further enhance elimination of PFAS.

PFAS are widely used, persists in the environment and are present in all human populations, which is of public health concern, due to their possible adverse health effects (EFSA CONTAM PANEL et al., 2020). An increasing number of hotspot areas in which humans are exposed to PFAS through contaminated water, soil or food have been reported worldwide (“Forever pollution”, 2023). Currently no treatment is available for highly exposed individuals. Our findings suggest that PFAS elimination can be enhanced by administration of the approved AER drugs, which have tolerable side effects for motivated participants, with the potential to provide reassurance to those affected by hotspots. In addition, although cholestyramine is well tolerated, colesevelam may be a better tolerated alternative due to its capsule form. Future studies should also further elaborate on both dose and duration of treatment with AER. It is also important to state, that although serum PFOS significantly decreased over a 12-weeks period, it is not elucidated whether this is accompanied by a corresponding decline in adverse health outcomes. This question requires further research in larger long-term studies. Conversely, it is not possible with this current study to assess whether a sufficient decrease in PFAS levels could have been achieved with a treatment period shorter than 12 week. This question could be addressed with consecutive samples to estimate correct elimination rate of PFAS with AER treatment. PFAS are detected in umbilical cord blood, amniotic fluid and breast milk, indicating that the vulnerable fetus and infant is exposed to these substances. Moreover, EFSA identified reduced antibody response towards routine childhood vaccinations as the critical effect of PFAS on children (EFSA CONTAM PANEL et al., 2020). Therefore, our findings may be of particular interest for highly exposed women of reproductive age, with the potential to reduce or prevent PFAS exposure of the next generation. However, few participants in this study were of reproductive age and more studies in this population group are urgently needed, including treatment with varying length and dose.

5. Conclusion

Our findings from this first randomized controlled clinical trial indicate that PFAS elimination can be enhanced by administration of an anion exchange resin for 12-weeks, possibly by preventing reabsorption in the enterohepatic circulation. Whether the marked reduction in serum PFOS is accompanied by a decrease in adverse health effects associated with high PFAS exposure requires further investigation. Our findings are of major public health interest and may offer possible treatment for highly exposed individuals. Of particular interest are women of reproductive age in order to reduce PFAS exposure of the next generation. However, further studies elucidating both the duration and dose of treatment are urgently needed.

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Ethical approval

The study was approved by the independent regional ethical committee in region Zealand, Denmark (project no.: SJ-942) and Danish Medicine Agency as well as the European Union Drug Regulating Authorities Clinical Trials Database (EMN-2021-06997). Collection of clinical data was notified to the Danish Data Protection Agency (REG-112-2021). The trial was performed in accordance with the Principles of Helsinki and was monitored and reviewed by the Copenhagen Good Clinical Practice guidelines to ensure that the study comply with ethical principles and the Danish legislation. All participants gave informed consent prior to participation and no participants were related to either the study personnel or the authors.

CRediT authorship contribution statement

Janne Julie Møller: Investigation, Writing – review & editing, Visualization. **Ann Christine Lyngberg:** Conceptualization, Methodology, Resources, Data curation, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Paula Edeusa Christina Hammer:** Writing – review & editing. **Esben Meulengracht Flachs:** Formal analysis, Software. **Ole Steen Mortensen:** Writing – review & editing. **Tina Kold Jensen:** Resources, Writing – review & editing. **Gesche Jürgens:** Methodology, Writing – review & editing. **Axel Andersson:** Writing – review & editing, Verification. **Anne Merete Boas Soja:** Writing – review & editing, Verification. **Morten Lindhardt:** Conceptualization, Methodology, Resources, Software, Investigation, Visualization, Writing – review & editing, Supervision, Project administration, Funding acquisition, Verification.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2024.108497>.

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