PFAS

Summary

Links Between Per- and Polyfluoroalkyl Substances and Diabetes/Obesity

The Details

About Per- and Polyfluoroalkyl Substances

Reviews of the Evidence

Type 1 Diabetes

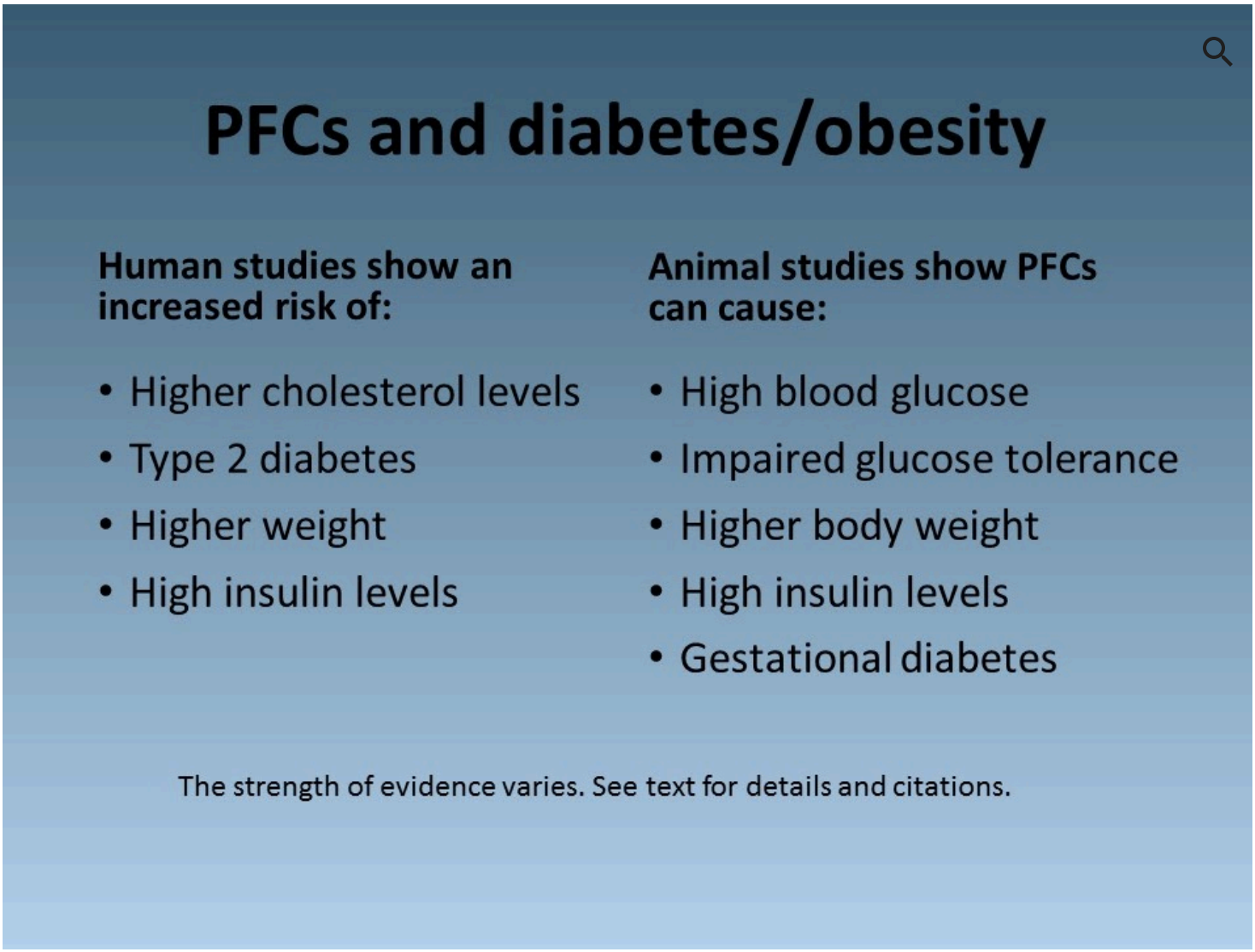
Type 2 Diabetes, Body Weight, and Metabolic Syndrome

Laboratory Studies: Diabetes/Obesity

Gestational Diabetes

Diabetes Management and Complications

References



Summary

Links Between Per- and Polyfluoroalkyl Substances and Diabetes/Obesity

Over 600 peer-reviewed studies published since 2006 in scientific journals have examined the relationship between per- and polyfluoroalkyl substances (PFAS) or perfluorinated compounds (PFCs) and diabetes or obesity.

The human epidemiological studies have on PFAS and diabetes/obesity have been mixed, with some finding found that people with higher exposures to PFAS have a higher risk of diabetes or obesity, while others do not. It is pretty clear and well-accepted that exposure to some PFAS are linked to higher cholesterol levels, however (Andersen et al. 2021).

Laboratory studies on animals or cells show that PFAS exposures can cause biological effects related to diabetes/obesity, and have helped to identify the key periods of susceptibility and the mechanisms.

The Details

About Per- and Polyfluoroalkyl Substances

Reviews of the Evidence

A review of the human evidence on PFAS and cardiovascular disease risk factors supports a strong relationship between PFAS exposure and an increased risk of high blood pressure and high cholesterol levels, but not with excess weight or glucose intolerance (Schlezinger and Gokce, 2024).

A meta-analysis of the findings from 12 studies of PFAS in children and adolescents found that exposure to PFAS was linked to higher levels of total and LDL cholesterol levels, and with lower insulin resistance (Zheng et al. 2024).

A meta-analysis of human studies found that PFAS levels were linked to higher LDL and total cholesterol levels (Song et al. 2024).

A meta-analysis of data from 29 studies found that PFOA and PFOS were significantly associated with total and LDL cholesterol levels in adults (Liu et. al. 2023).

A review found consistent evidence for associations between PFAS and high cholesterol levels and effects on lipid metabolism, but that evidence is still lacking for cardiovascular disease and type 2 diabetes (Schillemans et al. 2023).

A systematic review and meta-analysis found that prenatal exposure to some PFAS is linked to higher BMI/waist circumference in children, and exposure during childhood to lower BMI (Frigerio et al. 2023).

Another review found no evidence of an association between prenatal PFAS exposure and obesity in children, but postnatal exposure was linked to lower BMI (Frangione et al. 2023).

A meta-analysis of human studies found that exposure to PFAS (and phthalates, PCBs, and PBDEs) increase the risk of gestational diabetes, and experimental studies highlight potential mechanisms (Yao et al. 2023).

A systematic review and meta-analysis of 22 studies found that associations between PFAS exposure and type 2 diabetes were consistent in cohort studies, while the associations were almost non-significant in case-control and cross-sectional studies, and concluded that PFAS exposure may increase the risk of type 2 diabetes. There was a non-linear association between PFOA exposure and type 2 diabetes risk (Gui et al. 2022).

An artificial intelligence tool was used to explore available published literature, and found that PFAS exposure could negatively influence all components of metabolic syndrome, either individually or simultaneously as a mixture (Kaiser et al. 2022).

Authors ased a literature review and other public data to develop an "adverse outcome pathway" to analyze the mechanisms by which PFOS can induce fatty liver disease (Kim et al. 2023).

A review of PFAS and the gut finds that, "Exp re to PFAS could cause inflammation in the gut, destruction of the gut epithelium and tight junction structure, reduction of the mucus layer, and induction of the toxicity of immune cells" (Li

epithelium and tight junction structure, reduction of the mucus layer, and induction of the toxicity of immune cells." (Li et al. 2022), which could be relevant for diabetes development.

A review finds that "Several studies have demonstrated associations between serum PFAS concentrations and glycemic indicators of type 2 diabetes including glucose, insulin, and HOMA-IR [insulin resistance] in adolescent and adult cohorts. In addition, some studies have shown positive associations with incident type 2 diabetes and multiple PFAS." (Roth and Petriello, 2022).

A systematic review of 58 (!) articles found that PFAS exposure is associated with higher levels of LDL, HDL, and total cholesterol, especially for PFOA and PFNA with LDL cholesterol, and PFOA and PFOS with total cholesterol. Associations between PFAS and triglycerides tended to be negative, especially for perfluoroundecanoic acid (PFUnDA) (Ho et al. 2022).

A review finds that "Epidemiological studies have revealed associations between exposure to specific PFAS and a variety of health effects, including altered immune and thyroid function, liver disease, lipid and insulin dysregulation, kidney disease, adverse reproductive and developmental outcomes, and cancer. Concordance with experimental animal data exists for many of these effects." (Fenton et al. 2020).

A review of 22 human studies on PFAS and obesity and 32 human studies on PFAS and diabetes found that approximately 2/3 of studies reported positive associations between PFAS exposure and the prevalence of obesity and/or type 2 diabetes (Qi et al. 2020).

Similarly, a review identified 11 studies on gestational diabetes, 3 studies on type 1 diabetes, 7 studies on type 2 diabetes, 6 studies on prediabetes or unspecified diabetes, and 15 studies on insulin resistance or glucose tolerance. They found that 24 reported positive associations, 9 negative associations, 2 non-linear associations, and 2 inverse associations, and 8 reported no associations between PFAS and diabetes-related outcomes, and that more research is needed to make any conclusions overall (Margolis and Sant, 2021).

A review finds that PFAS are "aggravating the occurrence" of obesity-associated diabetes, cardiovascular disease, and liver disease (Liu et al. 2021).

A review finds that PFAS exposure may affect the growth of infants and children, increase cholesterol levels, and affect the immune system, among other effects (Anderko and Pennea, 2020). In general, exposure to PFAS in the womb may affect the placenta, and lead to lifelong health effects in the offspring (Blake and Fenton, 2020).

A review of prenatal and early life exposure to PFAS found that for birth size, most studies found that prenatal PFAS exposure may impair fetal growth. And, while prenatal PFAS is mostly linked to a lower BMI in the first 2 years of life, it is linked to higher BMI in childhood and adolescence, although not all studies agree (Lee et al. 2021),

In a combined analysis of the human and animal evidence, "developmental exposure to PFOA adversely affects human

health based on sufficient evidence of decreased fetal growth in both human and non-human mammalian species" (Lam et al. 2014). That is, there is evidence that PFOA exposure in the womb reduces the growth of the fetus. Whether there are other related effects later in life is not yet clear. A review of the human evidence on developmental exposure to PFAS finds that "epidemiological findings are consistent and suggest possible associations with fetal and postnatal growth and immune function" (Liew et al. 2018).

A review of PFAS and metabolic syndrome does not find a link between them, although there aren't many studies on the topic (Zare Jeddi et al. 2021).

Video on PFAS and Diabetes/Obesity

This video, Exposure to common chemicals may lead to obesity, diabetes, features Dr. Abby Fleisch speaking on PFAS and diabetes/obesity (from from Healio Endocrine Today, 2019).

Type 1 Diabetes

Early Life Exposures

Prenatal exposure to five (of 25 analyzed) PFAS (especially PFHxS and PFHpS) were associated with an increased risk of developing type 1 diabetes-related autoimmunity in children in Finland (McGlinchey et al. 2020). An earlier study, however, found that there was no association between early life (umbilical cord blood) exposure to 14 PFAS and the development of type 1 diabetes (Salo et al. 2018). Why the difference? I don't know. The 2020 study used the EDIA and DIABIMMUNE cohorts, primarily the EDIA cohort. The 2nd study used the FINDIA and DIABIMMUNE cohorts. Both studies included PFHxS and PFHpS. The 2020 study involved a much more detailed analysis, with an identification of potential mechanisms (involving bile acids, the gut, lipids, and a whole host of things), genetic analyses, consistent findings from animal studies (see "Laboratory Studies" below), and cluster analysis. The authors of the 2020 study did not cite or discuss the findings of the 2018 study, making the cause of the different findings hard to determine.

A study from Sweden found that prenatal exposure to various chemicals, including PFAS (as well as BPS and a mycotoxin), may contribute to the development of autoimmune diseases, including type 1 diabetes (Karthikeyan et al. 2024).

PFAS levels were linked to detrimental changes in breastmilk, which were in turn associated with slower infant growth and more intestinal inflammation in the infants (Lamichhane et al. 2021). These authors also found that PFAS levels were linked to lower quality breastmilk especially in mothers of offspring who went on to develop autoimmune diseases, including type 1 diabetes (Hyötyläinen et al. 2024).

Childhood Exposures

A small, cross-sectional study from Italy found that PFOS levels were higher in children and adolescents with new-onset type 1 diabetes than in controls without diabetes. PFOA levels were not associated (Predieri et al. 2015). A longitudinal study from Denmark found that PFOA levels in childhood were associated with lower beta cell function in adolescence (Domazet et al. 2016).

In children with type 1 diabetes, levels of PFHxS (and BPF, PCB-138, and a phthalate) were linked to thyroid hormone levels (and levels of some phthalate metabolites and PCB-153 were associated with higher long-term blood glucose levels (HbA1c) (Dufour et al. 2023).

High Exposure Levels

In an area with high PFAS exposure levels (see Mid-Ohio Valley Studies section below), a study of community members looked for autoimmune diseases, including type 1 diabetes. They did find an association between the autoimmune disease ulcerative colitis, but not type 1 diabetes (Steenland et al. 2013). A furthers study also found no increased risk of

type 1 diabetes with PFAS exposure-- in fact there was a decreased risk (Conway et al. 2016). PFAS are potentially immunotoxic, which could favor the development of autoimmune diseases (or suppress the immune system) (Corsini et al. 2014). (There is discussion about whether PFAS suppress or enhance the immune system (or both) -- both can be hazardous to health -- and both are immunotoxic (DeWitt et al. 2019).)

Laboratory Studies

A laboratory study on non-obese diabetic mice (NOD mice), a model of type 1 diabetes, found that exposure during development to perfluoroundecanoic acid, PFUnDA increased the development of insulitis, which occurs before diabetes development in these mice. It also increased cell death in the islets. However, it did not lead to accelerated diabetes development overall (Bodin et al. 2016). A mixture of persistent organic pollutants (that included PFAS) led to early signs of autoimmunity development in NOD mice (Berntsen et al. 2018). The metabolic changes found in both of these studies were consistent with the metabolic changes seen in the human study from Finland, described above (McGlinchey et al. 2020). Developmental exposure to this POP mixture led to several additional metabolic changes in NOD mice-- changes that are linked to an increased risk of type 1 diabetes in humans (Sinioja et al. 2022).

Further research by the same authors also found that developmental exposure to PFUnDA in NOD mice led to some interesting effects that were dose-dependent, non-monotonic, and that are linked to early changes in type 1 diabetes development in humans (Hyötyläinen et al. 2021).

PFOS alternatives affect the gut microbiota and pancreas of mice (Zhao et al. 2023).

The Immune System and Autoimmunity

A report on immunotoxicity of PFOA and PFOS by the National Toxicology Program (NTP) finds that, "PFOA is presumed to be an immune hazard to humans based on a high level of evidence that PFOA suppressed the antibody response from animal studies and a moderate level of evidence from studies in humans. Although the strongest evidence for an effect of PFOA on the immune system is for suppression of the antibody response, there is additional, although weaker, evidence that is primarily from epidemiological studies that PFOA reduced infectious disease resistance, increased hypersensitivity-related outcomes, and increased autoimmune disease incidence" (NTP 2016). The report also finds that PFOS "is presumed to be an immune hazard to humans." It is pretty clear that PFAS can affect the immune system (reviewed by DeWitt et al. 2012). However, so far, the evidence that PFAS increase the risk of autoimmune diseases is "weak" (Ehrlich et al. 2023), but hopefully as more evidence is uncovered we will know more.

A community health study from New Hampshire found that PFAS exposure was linked to autoimmune disorders in both women and children (Panikkar et al. 2019).

Interestingly, PFAS exposures are associated with autoimmune-like characteristics in North Carolina alligators (from the Cape Fear river, polluted with PFAS, as compared to alligators in an unpolluted river) (Guillette et al. 2022).

In Finland, higher PFAS exposure during prenatal and early life may accelerate the progression to celiac disease in genetically predisposed children in the Type 1 Diabetes Prediction and Prevention (DIPP) study (Sinisalu et al. 2020). New York girls with higher levels of PFOS and PFOA had a higher risk of celiac disease, an autoimmune disease common in people with type 1 diabetes (Gaylord et al. 2020). These findings raise further questions of how environmental chemicals may affect autoimmunity in genetically susceptible people, as well as how PFAS may affect the gut...

The Gut and Other Environmental Factors Linked to Type 1 Diabetes

When exposed to intestinal cells in a laboratory, a mixture of PFOS and other chemical surfactants caused leakage through the tight junctions (although PFOS seemed to protect from this effect) (Glynn et al. 2017). In mice, PFOS exposure caused changes in the gut microbiome and glucose metabolism, oxidative stress, inflammation, and more (Zhang et al. 2020). Another mouse study found that PFOS damages the gut microbiota and gut barrier function (Wang et al. 2020). In zebrafish, PFOS causes intestinal inflammation, and affects the immune system beyond the gut (Diaz et al. 2021). In mice, PFOA triggers epigenetic changes and alters the expression of genes essential for maintaining the physical barrier of small intestine (Rashid et al. 2020). PFOA also damaged the intestinal barrier and caused gut inflammation in mice (Shi et al. 2020). However, a human study found that higher PFAS exposure was linked to lower gut inflammation, and not related to gut permeability (Xu et al. 2019). In rats, PFOS caused increased body weight and intestinal inflammation (Liang et al. 2021). PFAS substitutes affect the gut as well. One PFAS substitute caused gut inflammation, changes in gut microbiota, and disturbed the gut barrier in mice (Pan et al. 2019), and another substitute, OBS, caused changes to the gut microbiota composition in zebrafish (Wang et al. 2020). In mice, developmental exposure to OBS affected the intestinal barrier function and intestinal inflammation of both exposed dams and offspring (Wang et al. 2021). In mother mice, exposure to PFOA or GenX disrupted the intestinal barrier (Xu et al. 2022). In adult zebrafish, exposure to PFOS and its alternatives F-53B and OBS induced immunotoxicity and changes in gut microbiota, with interactions between the immune system and gut microbiota (Huang et al. 2021). A PFOA alternative, HFPO-TA, caused imbalanced gut microbiota and other effects on the gut in mice (Hu et al. 2022). Changes to the gut microbiota, gut permeability, and gut inflammation are all linked to type 1 diabetes as well as other types of diabetes (see the Diet and the Gut page).

Prenatal exposure to PFAS is also associated with an increased risk of infectious disease in early life (Dalsager et al. 2016; Dalsager et al. 2021; Goudarzi et al. 2017); infections are linked to type 1 diabetes (see the Viruses and Bacteria page).

PFOS levels were associated with lower vitamin D levels in the U.S. population, especially in whites and the elderly, while PFHxS levels were associated with higher vitamin D levels (Etzel et al. 2018). Human and animal evidence suggests that PFOA also interferes with vita D signaling (Di Nisio et al. 2020). Low vitamin D levels are linked to type 1 (and type 2) diabetes (see the Vitamin D Deficiency page).

Type 2 Diabetes, Body Weight, and Metabolic Syndrome

Lower- Level Exposures in Humans

Longitudinal Studies in Adults

The strongest evidence for the ability for environmental exposures to contribute to the development of diabetes comes from longitudinal studies. These are studies that take place over a period of time, where the exposure is measured before the disease develops.

Background exposures to PFOS and PFOA in the late 1990s were associated with higher type 2 diabetes risk during the following years in a prospective case-control study of women from the U.S.-based Nurses' Health Study II (Sun et al. 2018). In the U.S. Study of Women's Health Across the Nation, higher exposure levels to numerous PFAS as well as PFAS mixtures was associated with a higher risk of type 2 diabetes (Park et al. 2022). This study also found that higher levels of some PFAS were associated with greater body size and body fat, and higher rates of change over time (Ding et al. 2021a), and some with altered levels of leptin (Ding et al. 2021b). It also found that PFAS levels were associated with higher total and LDL cholesterol during menopause (Kang et al. 2023; Chatzi and Baumert, 2023).

A long-term study of French women estimated exposure to PFAS based on French food contamination data and dietary consumption data. It found an association between type 2 diabetes and PFOA and PFOS in women without obesity (Mancini et al. 2018).

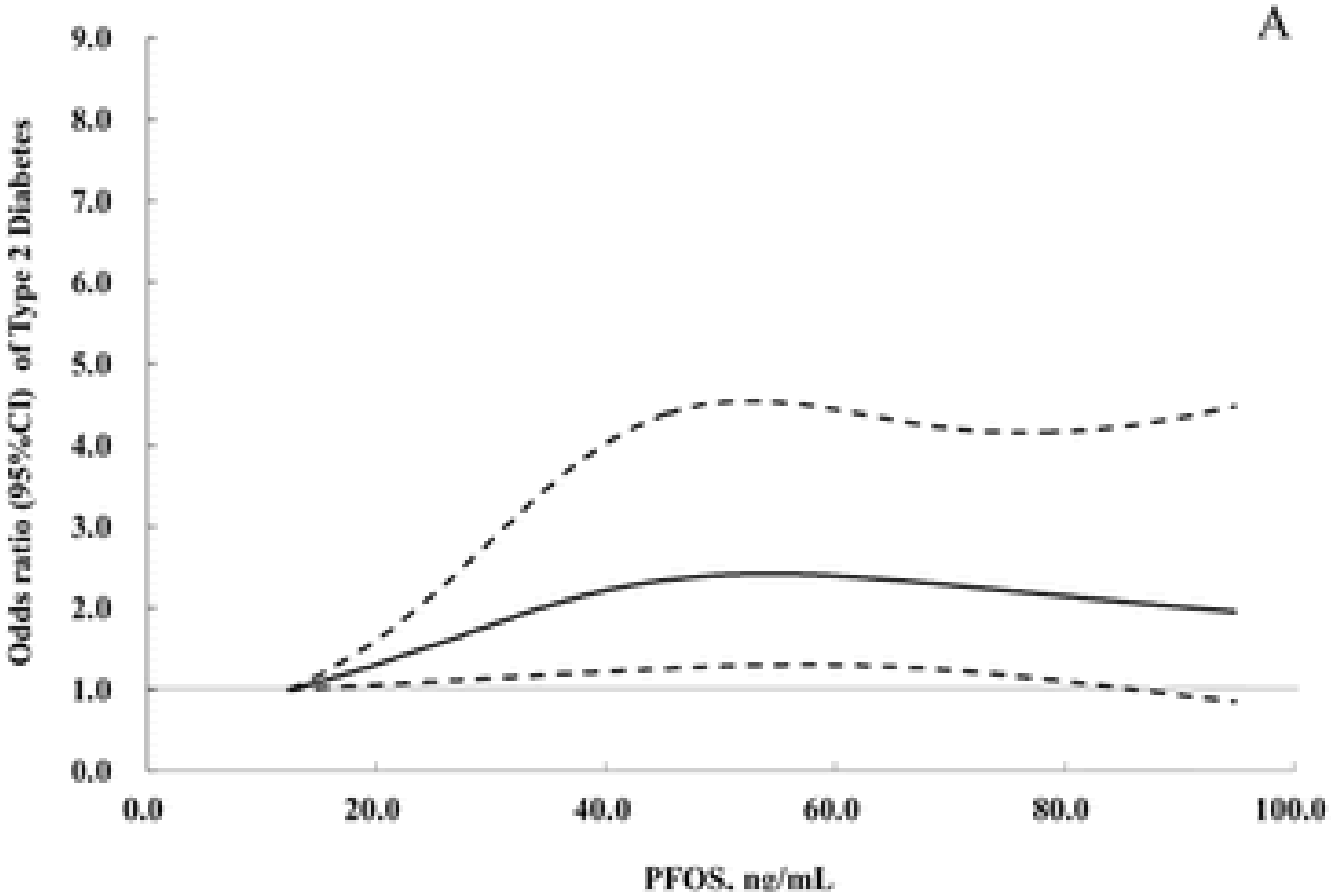
Adults with overweight/obesity with low level exposures (from Boston, MA and Baton Rouge, LA) with higher PFAS levels had greater weight regain after a diet, especially women (Liu et al. 2018). Also in this group, PFAS levels were associated with certain types of cholesterol, which are associated with cardiovascular disease (Liu et al. 2020).

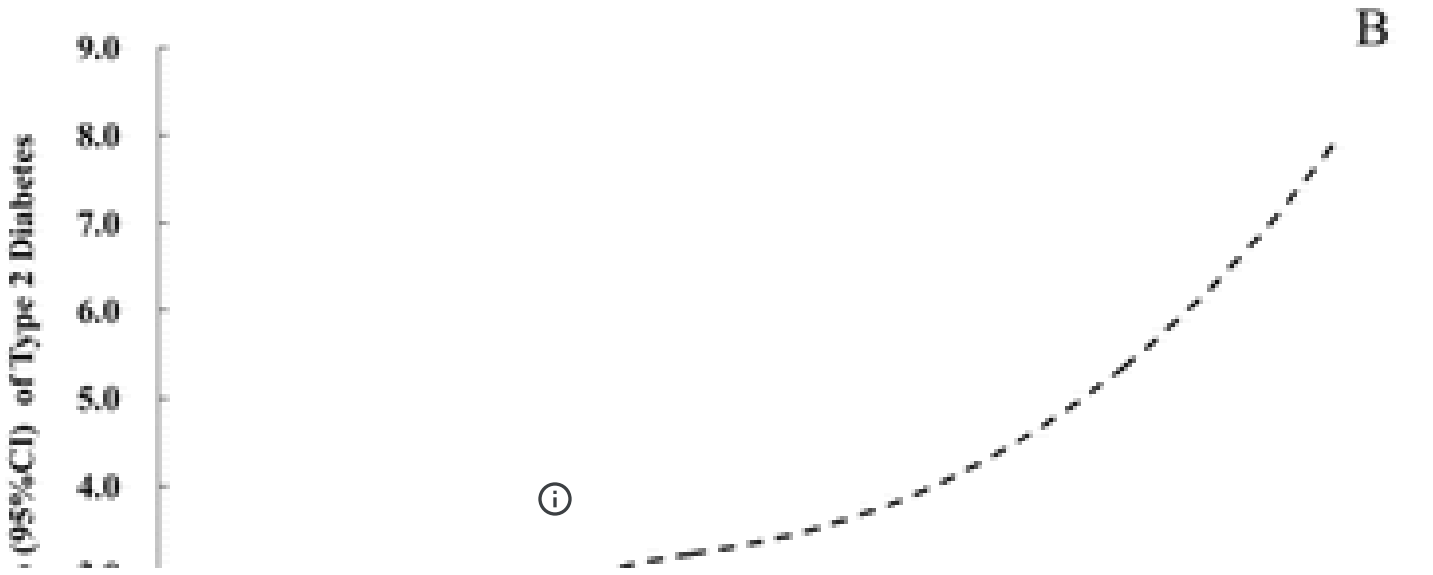
In the U.S. Diabetes Prevention Program, PFOS and PFOA were associated with insulin resistance, beta cell function, and HbA1c. Yet after 4.6 years of follow-up, these chemicals did not appear to affect the incidence of diabetes or changes in these markers (Cardenas et al. 2017). However, further research of this group shows that some PFAS levels were associated with the long-term development of type 2 diabetes-- but only in people who did not participate in the diet/exercise program. (Some PFAS were associated with microvascular disease development, even in people who did lifestyle changes) (Cardenas et al. 2019a). Also in this group, adults at high risk for diabetes with higher PFAS levels had higher increases in weight and hip girth over time, but a lifestyle intervention reduced these associations (Cardenas et al. 2019b). These studies illustrate that diet and exercise may mitigate the obesogenic and diabetogenic effects of environmental chemicals. To hear Dr. Abby Fleisch discuss these studies, see the video link above.

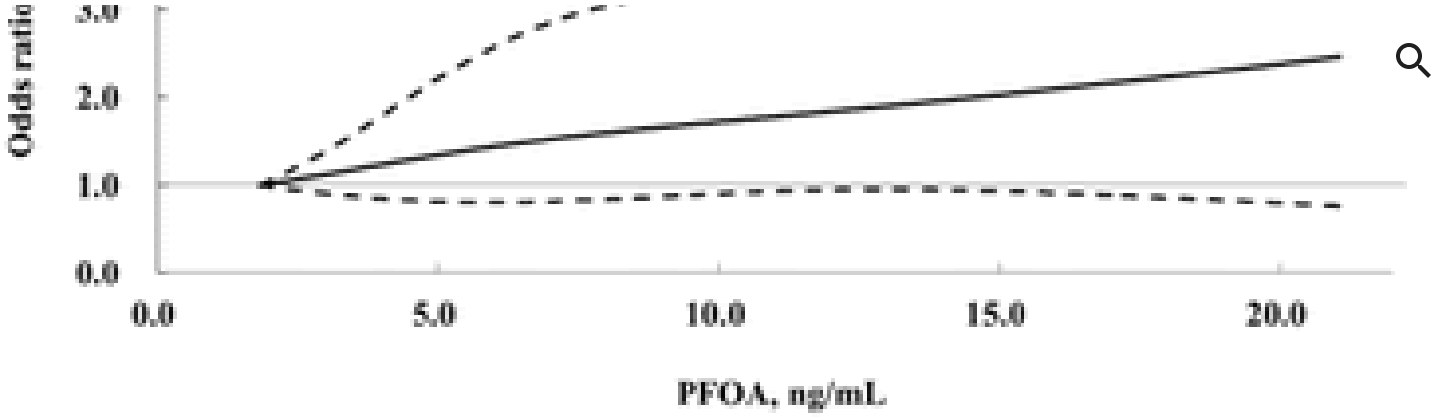
Risk of Diabetes vs PFAS Exposure Levels

Dose–response relationships of PFOS (top) and PFOA (bottom) concentrations with type 2 diabetes risk in the Nurses' Health Study II. The solid lines represents odds ratios (ORs), in this case the risk of diabetes, which is increased when the OR is above 1. The dotted lines are 95% confidence intervals.

Source: Sun et al. 2018, EHP.






Odds ratio
3.0
2.0
1.0
0.0
0.0
5.0
10.0
15.0
20.0
PFOA, ng/mL

In Sweden, people with higher PFAS levels had a slightly lower risk of type 2 diabetes, although mostly the relationships were not statistically significant. Among those without diabetes, long-term PFAS exposure was associated with lower insulin resistance (Donat-Vargas et al. 2019a). Also, PFAS levels were associated with lower triglyceride levels, but no link between PFAS and cholesterol levels or high blood pressure (Donat-Vargas et al. 2019b). Another Swedish study, of older adults, found PFAS levels were linked to cholesterol and triglyceride levels over a 10 year period (Dunder et al. 2022). In Norway, a longitudinal study found no associations between type 2 diabetes and PFAS levels. The PFAS levels did change over the years, with PFOA and PFOS levels declining, but other PFAS were increasing (Charles et al. 2020).

Also in Sweden, a more detailed analysis found two groups of PFAS-related metabolites that correlated positively with PFAS levels, but that had opposite directions on type 2 diabetes risk-- one increased and one decreased risk. The findings perhaps help explain the conflicting associations found in literature between PFAS and type 2 diabetes (Schillemans et al. 2020). These authors also found potential effects of long-chain PFAS on triglyceride levels (Schillemans et al. 2022).

In elderly Swedes, levels of 42 contaminants were measured, and then diabetes incidence followed for 15 years. Nine contaminants (PFOS, cadmium, lead, mercury, nickel, trans-nonachlor, the phthalate MiBP, PCB-126, and PCB-169) improved the model predicting incident diabetes in the first 5 years of follow-up (Lind et al. 2022). In middle aged and older Swedes, PFOA was associated with a lower risk of diabetes in women, but in a non-monotonic manner, such that low levels of exposure were linked to an increased risk (Dunder et al. 2023).

Spanish seniors with obesity/metabolic syndrome (but not diabetes) who had higher estimated dietary intake levels of PFOS had higher fasting and long-term glucose levels (HbA1c) at baseline, and increased BMI and insulin resistance after a year (Khoury et al. 2024).

In Korean adults, PFOS and PFOA levels at baseline were higher in those who developed diabetes at follow-up. PFOA was associated with a higher risk of developing diabetes (Chung et al. 2022).

A long-term study from Korea found that there were differences in PFHxS and PFDoDA levels between participants with and without diabetes, and while PFAS were not associated with BMI, they were associated with higher total cholesterol, LDL ("bad") cholesterol, and triglycerides and with lower HDL ("good") cholesterol (Seo et al. 2018).

In U.S. adults with pre-diabetes in the Diabetes Prevention Program, at baseline, those with higher PFOA, PFHxS, and PFNA levels had higher total cholesterol levels. Over 15 years of follow-up, the baseline levels of PFOA, PFOS, PFHxS and PFNA, were associated with the development of high cholesterol and high triglycerides, but only in the placebo group and not the lifestyle intervention group. In other words, the findings suggest harmful effects of some PFAS in prediabetic adults. However, these detrimental effects of PFAS were lessened by a healthy lifestyle (Lin et al. 2019).

Interestingly, one year after bariatric weight loss surgery, people have lower PFAS levels than before surgery (in

contrast to higher levels of other POPs). This might be explained by a reduced food intake and alterations in the absorption of nutrients (Jansen et al. 2019).

In Europeans, higher levels of plasma PFOA and PFHxS were associated with increased weight gain after dieting. The amount of weight regained was similar to or larger than the average amount regained in people using various types of diets (Grandjean et al. 2023). See related article in *Environmental Health News*, PFAS has more effect than type of diet on weight gain: Study.

In China, levels of PFPeA, PFOA, and 9Cl-PF3ONS were associated with a higher incidence of non-alcoholic fatty liver disease (NAFLD), while PFNA, PFHxS, and PFOS were associated with a lower incidence (Wu et al. 2024).

Longitudinal Studies in Children

Higher PFOA and PFHxS levels were associated with higher glucose levels in Hispanic children from urban Los Angeles who had overweight/obesity (Alderete et al. 2019). In European children, higher PFOA levels were associated with higher systolic blood pressure (Warembourg et al. 2019).

Exposure levels of some PFAS during childhood was associated with changes in body composition into early adolescence in Boston children-- some PFAS with less lean mass, some with less total fat mass, some with more visceral fat mass (Janis et al. 2021).

In young adults from Southern California, higher exposure to PFOA was associated with higher 30-minute glucose levels and glucose area under the curve during a glucose tolerance test (Chen et al. 2020). Southern California girls with higher PFHxS levels had higher post-meal glucose levels and lower beta-cell function compared to girls with lower levels. These associations appeared during puberty and grew stronger post-puberty. There were no associations in boys, nor any associations between diabetes-related measurements and the other three PFAS measured (Goodrich et al. 2021). In U.S. adolescents and young adults, PFAS mixtures were associated with altered metabolism of fats and proteins, as well as thyroid hormone levels, which play a role in diabetes and obesity (Goodrich et al. 2023).

In the Faroe Islands, PFAS concentrations (PFDA, PFNA, and PFOS) at ages five and nine were associated with higher total, HDL, and LDL cholesterol levels at age nine. Girls had stronger positive associations between PFASs and total/LDL cholesterol levels, and boys had stronger positive associations with HDL (Blomberg et al. 2021).

In U.S. adolescents, PFAS burden scores were different in the HOME Study (Cincinatti) vs NHANES (nationwide). In the HOME study, this score was associated with higher total/HDL/LDL cholesterol levels, insulin levels, and insulin resistance. In NHANES, the score was associated with higher diastolic blood pressure (Liu et al. 2024).

In the U.S., PFAS levels during childhood may be associated with altered growth in early adolescence, with higher exposure linked to generally lower levels of height, BMI, and fat mass (Kuiper et al. 2024).

In U.S. teens with obesity who underwent bariatric surgery, for the first 6 months following the surgery, PFAS concentrations remained level, followed by a decline from 6 to 36 months (Baumert et al. 2024).

More Information on PFAS

Factsheet on PFASs from the National Institute of Environmental Health Sciences (NIEHS)

PFAS Resources from The Endocrine Disruption Exchange

PFAS Project hosted by Northeastern University

Article: Evaluation and Management Strategies for Per- and Polyfluoroalkyl Substances (PFASs) in Drinking Water Aquifers: Perspectives from Impacted U.S. Northeast Communities (Guelfo et al. 2018) and commentary, Guiding Communities Affected by PFASs: Tools for Tackling Contaminated Drinking Water (Seltenrich 2019).

Exposures During Development

Evidence is growing that exposure to pollution during critical developmental periods, such as *in utero* or during childhood, may have effects later in life.

A meta-analysis of 10 studies found that early life exposure to PFOA was associated with a higher risk of being overweight in childhood, and a higher BMI in childhood (Liu et al. 2018). A collection of European studies found that prenatal, rather than postnatal, PFAS exposure might contribute to unfavorable cholesterol levels and body weight in childhood (Papadopoulou et al. 2021).

In eight U.S. long-term studies, gestational exposure to higher levels of PFAS were associated with slightly higher childhood BMI and risk of overweight or obesity (Liu et al. 2023).

In mothers/children from 6 European countries, prenatal exposures to environmental chemical mixtures, including PFAS, were associated with increased metabolic syndrome risk in childhood (Güil-Oumrait et al. 2024; Mustieles et al. 2024).

In Denmark, *in utero* exposure to PFOA was associated with higher weight, overweight/obesity, higher waist circumference, and higher insulin levels in female offspring at age 20 (with similar results in males but fewer data points). Other PFAS, including PFOS and PFNA did not show any associations (Halldorsson et al. 2012). An additional Danish study (the Odense Child Cohort) found that maternal levels of PFNA and PFDA were associated with higher BMI at 3 and 18 months of age in female children. In both boys and girls, prenatal PFNA and PFDA were associated with higher body fat percentage at age 3 months, and prenatal PFDA was associated with higher total cholesterol at 18 months (Jensen et al. 2020).

In British girls, exposure to PFOS in the womb is associated with lower birth weight, but then higher weight at age 20 months (Maisonet et al. 2012). Further study of the British girls at age 9 found that prenatal PFOA and PFOS levels were associated with percent body fat in different ways, depending on the mother's level of education. PFHxS and PFNA were not associated (Hartman et al. 2017). One also found associations between PFAS and levels of adiponectin, a hormone that plays a role in glucose levels (Minatoya et al. 2017). Another did not find statistically significant associations between prenatal PFAS levels and adiponectin or leptin, another energy-related hormone, although the levels of both hormones were higher in infants with higher PFOA levels (Buck et al. 2018). In the UK, *in utero* PFAS exposures were linked to metabolic changes in fetuses that resembled those observed with later exposures, and are linked with the susceptibility, initiation, progression, and exacerbation of a number of metabolic diseases (Hyötyläinen et al. 2024). In the UK, a mixture of 31 chemicals, including PFAS, PCBs, and organochlorine pesticides, was associated with lower postnatal body size (up to 19 months of age) (Marks et al. 2021).

In Sweden and Norway, higher maternal PFOA and PFOS levels were associated with higher child overweight/obesity at 5 years of age (Lauritzen et al. 2018). A Swedish study using advanced mathematical methods showed how prenatal PFOA levels are linked to lower birthweight but then higher weight during/after infant growth spurts and in childhood (Tanner et al. 2019). Yet another Swedish study found no consistent links between maternal PFAS levels and child overweight at age 4 (Martinsson et al. 2020).

In Denmark, however, PFOA or PFOS levels in mothers during pregnancy were not associated with body mass index, waist circumference, or risk of overweight in their children at 7 years of age (if anything, the more highly exposed children were thinner than the others, although the difference was not statistically significant) (Andersen et al. 2013). These same authors had also found that maternal PFAS levels were associated with lower body weight in the first year of life (Andersen et al. 2010). Another Danish study found that pregnancy PFOA concentrations were associated with lower birth size and BMI, and increased childhood height. Pregnancy PFOS concentrations were also associated with lower birth BMI, but in childhood pregnancy plasma PFOS concentration interacted with child sex on BMI and fat percentage at 6 years with negative associations in girls and positive in boys (Sevelsted et al. 2022).

In Europe, childhood levels of PFOS was associated with higher waist circumference at ages 15 and 21. PFOA levels in childhood were associated with lower beta cell function in adolescence (Domazet et al. 2016).

A large European study found no association between prenatal or childhood PFAS exposure levels and childhood BMI (Vrijheid et al. 2020).

In Sweden, prenatal exposure to a mixture of EDCs (phthalates, other plasticizers, phenols, PAHs, pesticides, PFAS, organochlorine pesticides, and PCBs) was associated with lower BMI and overweight among girls, and there were non-significant associations among boys at age 5 1/2 (Svensson et al. 2023).

In the Netherlands, Higher PFAS levels in early life were associated with accelerated gain in percent fat mass during the first 6 months of life; PFAS in breastmilk did not reduce the benefits of breastfeeding (van Beijsterveldt et al. 2024).

In Spain, prenatal PFAS levels were not generally associated with a higher BMI and other measures of metabolism through age 7 (Manzano-Salgado et al. 2017). However, this study also found interactions with nutrients. For example, there were obesogenic effects of PFOS that decreased in women with higher levels of an antioxidant (Cano-Sancho et al. 2023). For an article describing this study, see Invited Perspective: Can Eating a Healthy Diet during Pregnancy Attenuate the Obesogenic Effects of Persistent Organic Pollutants? (Jaacks et al. 2023).

In Boston, Massachusetts, PFAS levels in mothers were not associated with metabolic changes in children, although children with higher PFAS levels had lower insulin resistance (Fleisch et al. 2017). However, another study of the same cohort by the same authors found that maternal PFAS levels were associated with small increases in weight-related measurements in girls in mid-childhood (Mora et al. 2017). And, these authors also found that levels of various PFAS were associated with changes in various cholesterol measurements, and not all the changes were detrimental (Mora et al. 2018). A study from upstate New York also found PFOA and PFOS levels at birth were associated with a lower BMI up to age 3 (Yeung et al. 2019). In New Hampshire, infant girls born to mothers with higher pregnancy concentrations of PFOS had greater BMI growth during the first year of life (Romano et al. 2022).

In Colorado, in male infants, maternal perfluorooctanoate and perfluorononanoate levels were positively associated

with weight gain in infancy, and in female infants, maternal PFOS and PFHxS were associated with lower weight-for-age. In both sexes, 2-(N-methyl-perfluorooctane sulfonamido) acetate was associated with greater odds of rapid growth in infancy (Starling et al. 2019). In Colorado, PFAS levels in mothers was linked to epigenetic changes in umbilical cord blood, in genes linked to metabolism, inflammation, immune function, and growth (Starling et al. 2020). These authors also found that prenatal PFAS levels are associated with increased fat mass and body mass index in childhood (Starling et al. 2023).

In Cincinnati Ohio, higher PFOA levels in the womb were associated with a lower BMI up to age 2 (Shoaff et al. 2018). This HOME study also found that gestational PFOA and PFHxS concentrations were associated with the risk of obesity in 12 year olds, while no pattern was seen for postnatal PFAS concentrations (Liu et al. 2020). Also in Cincinnati, fetal exposure to PFOA was associated with higher insulin resistance in adolescence, and higher waist circumference and insulin levels. Fetal PFHxS levels were also problematic (Li et al. 2021). This study also found that childhood physical activity affected the associations of prenatal PFOA concentrations with children's cardiometabolic risk at age 12: higher PFOA levels was associated with worse cardiometabolic risk scores among children with lower physical activity, but not among those with higher physical activity. Diet, however, did not modify the associations, nor did diet or physical activity modify associations with other PFAS (Braun et al. 2022).

In the U.S., among women without obesity, greater PFUnDA was associated with their children having higher waist circumference, fat mass, and % body fat. Among women without obesity, the associations of PFAS and their children's weight varied significantly by race/ethnicity. However, among the children of women with obesity, greater PFOS, PFNA, and PFDA concentrations were associated with lower weight-related measures (Bloom et al. 2021). In both pregnant women and children in the U.S., PFAS exposure levels were associated with various metabolites, such as fatty acid metabolites, that can play a role in obesity (Prince et al. 2023).

In Greenland and the Ukraine, neither PFOA nor PFOS levels in mothers during pregnancy were associated with their children being overweight at ages 5-9. However, the children did have higher waist-to-height ratios (Høyer et al. 2015).

In the Faroe Islands, maternal PFOS and PFOA (but not PFHxS, PFNA or PFDA) levels after childbirth were associated with higher BMI in the offspring at 18 months and 5 years of age (Karlsen et al. 2017). Another Faroe Island study found associations between PFAS levels in mothers and children and levels of leptin, adiponectin and resistin up to age 5, but not at older ages (Shelly et al. 2019). And another found that lifelong exposure levels (from gestation, through childhood and early adulthood) were associated with decreased insulin sensitivity and increased pancreatic beta-cell function in young adults (Valvi et al. 2021). An additional Faroe Island study found that prenatal and childhood PFAS levels were associated with changes to leptin and other adipokines at age 9, which are in turn linked to obesity (Shih et al. 2021). Prenatal and adult PFOS exposures were also associated with increased insulin resistance and increased beta-cell function; PFOA associations were similar but not as strong. There were interactions with genetic background (Valvi et al. 2023).

In China, umbilical cord levels of PFAS were associated with various measures of growth at birth and at 19 months. Associations varied by specific PFAS and by sex (Cao et al. 2018). Another Chinese study also found that maternal levels of various PFAS were associated with various measurements of infant growth that varied by chemical and by sex (Zhang et al. 2021). In Shanghai, prenatal exposure to perfluorobutanesulfonic acid (PFBS), a replacement chemical for PFOS, was associated with increased various weight-related measures in 5 year old girls (Chen et al. 2019). In Hangzhou, China, levels of various PFAS in mothers' breast milk were associated with lower length or weight gain rate in infants (Jin et al. 2020). In Shanghai, prenatal levels of PFAS were linked to disrupted cholesterol and triglyceride levels in newborns (Tian et al. 2020). In China, prenatal PFAS mixtures were generally associated with lower body weight measures in boys, and higher in girls (Zhang et al. 2022). PFAS levels were associated with higher adiponectin and lower leptin levels in cord blood, especially in males (Ding et al. 2022).

In China, higher *in utero* PFAS exposure (PFOS, PFNA, and PFDA) was associated with persistently higher BMI in children to age 4 (Zeng et al. 2023), and another study also found that maternal PFAS exposure was associated with increased body weight in the first two years of life, with PFTrDA having the strongest association (Song et al. 2023). Also in China, prenatal levels of five PFAS (PFBA, PFHpA, PFHxS, PFHpS, and PFDoDA) and a PFAS mixture were associated with a higher BMI trajectory in males, and PFUnDA and PFDoDA were associated with increased BMI from birth to age 10 (Dai et al. 2023). In China, prenatal PFAS levels were associated with increased body weight in childhood, especially among girls, and especially PFNA (Sun et al. 2024). In China, prenatal exposure to a PFAS mixture was associated with increased weight during infancy, especially in females, while prenatal PFOA exposure was associated with decreased weight in males (Li et al. 2024).

In Japan, prenatal exposure to PFOA and PFOS initially were associated with lower BMI during infancy, but this effect dissipated over time and reversed in direction during later childhood. The effects were stronger in girls (Horikoshi et al. 2021).

In Singapore, fetal exposure to PFAS was linked to higher abdominal fat at birth but not in childhood (Chen et al. 2023).

Birth Weight

In Japan, PFOS levels were associated with reduced fatty acid levels in pregnant women. These polyunsaturated fatty acids are essential for fetal growth. The female babies also had a lower birth weight if exposed to higher levels of PFOS (these associations were not found with PFOA or in male babies) (Kishi et al. 2015). In Taiwan, PFAS levels were associated with lower birth weight in girls. Levels were not associated with weight through age 11 in either sex, but were associated with lower height (Wang et al. 2016). In Canada, maternal PFOA levels were associated with a lower birth weight (Ashley-Martin et al. 2017). A large, population-wide study from Italy found that living in an area contaminated with PFAS significantly increased the odds of small for gestational age birth (Manea et al. 2020).

Other studies have also found associations between PFAS and birth weight as well, usually lower birth weight (Apelberg et al. 2007; Bjerregaard-Olesen et al. 2019; de Cock et al. 2016; Fei et al. 2007; Lenters et al. 2016; Marks et al. 2019; Minatoya et al. 2017; Rokoff et al. 2018; Shoaff et al. 2018; Starling et al. 2017; Wang et al. 2019; Washino et al. 2009; Woods et al. 2017), including a meta-analysis (Cao et al. 2021).

The Madrid Statement

In 2015, fourteen experts published the Madrid Statement on Poly- and Perfluoroalkyl Substances (PFASs), subsequently signed by 206 scientists and professionals from 40 countries (Blum et al. 2015; Birnbaum and Grandjean 2015).

The Statement documents the scientific consensus about the environmental persistence, bioaccumulation, and potential toxicity of these substances.

Cross-Sectional Studies in Adults

Cross-sectional studies are studies that measure exposure and disease at one point in time. These provide weaker evidence than longitudinal studies, since the disease may potentially affect the exposure, and not vice versa.

North America

In the U.S., PFAS were linked to non-alcoholic fatty liver disease (NAFLD), especially in women (Limei et al. 2023). Also in U.S. adults, higher PFAS exposure was associated with higher fatty liver disease risk and worse liver function, especially among those with heavy alcohol intake, obesity, or high-fat diets (Zhang et al. 2023). Although another U.S. study found that PFAS levels were linked to a lower risk of NAFLD (Momo et al. 2024). All 3 of these studies used the same dataset (NHANES) and it looks like the authors listed a few reasons for the discrepencies: different time periods, different sample sizes, different NAFLD definitions, etc.

A cross-sectional study of Canadian adults found associations between some PFAS and cholesterol levels, but not glucose levels or metabolic syndrome (Fisher et al. 2013). Another found associations between PFAS and cholesterol/triglyceride levels as well (Cakmak et al. 2022).

A cross-sectional study of U.S. Americans also found associations between some PFAS and cholesterol levels, but not insulin resistance or body size (Nelson et al. 2010). (It seems like associations between PFAS and higher cholesterol levels are pretty consistent across studies, especially in studies of more highly exposed people, but also among less exposed, e.g., Eriksen et al. 2013). Despite using in part some of the same dataset as Nelson et al., (NHANES), Lin et al. (2009) found links between PFAS and various measures of blood glucose in Americans. For example, they found that in adolescents, higher PFNA levels were associated with higher blood sugar levels and cholesterol levels. In adults, higher PFNA levels were associated with higher beta cell function, and higher PFOS levels were associated with higher insulin levels, higher beta cell function, and insulin resistance. Another study using NHANES data found that different types (isomers) of PFOA were variously associated with higher blood glucose levels (and others with lower HbA1c), higher beta cell function, higher HDL and total cholesterol. Various types of PFOS were associated with higher beta cell function, lower HDL, and lower triglycerides. Both PFOS and PFOA were indicators of metabolic syndrome (Liu et al. 2018). And, also with NHANES data, PFOA (but not other PFAS) levels were associated with diabetes in men (not women) and with total cholesterol in adults (He et al. 2018). Another analysis of NHANES data, looking at multiple years, found that PFNA was associated with increased risk of metabolic syndrome and well as several individual components, while the highest levels of PFHxS were associated with elevated triglycerides. Other PFAS were associated with decreased risk of at least one outcome (Christensen et al. 2018). Both obesity and gender affect the relationship between PFAS and cholesterol levels in NHANES: in males with obesity, there were positive associations between total and LDL cholesterol with PFOA and PFNA. In females with obesity, total cholesterol levels increased in tandem with levels of PFDA, PFNA, and Me-PFOSAA, and there was a positive association of LDL cholesterol with PFOS, PFDA, and PFNA (Jain and Ducatman, 2018).

Also in NHANES, total cholesterol levels were positively associated with PFAS levels (Dong et al. 2019). A further NHANES study found that looking at multiple PFAS at one time can better characterize exposures and how they are linked to cholesterol levels (Fan et al. 2020). In older adults in NHANES, higher PFOA and PFNA levels were associated with an increased risk of fatty liver disease (Wu et al. 2023). In NHANES (adults and adolescents), Higher PFAS levels were associated with a lower risk of metabolic syndrome, although the correlations varied across the different components of metabolic syndrome (Zheng et al. 2023). In NHANES, various PFAS and PFAS mixtures were linked to various health outcomes, such as PFOS to blood pressure, PFAS to cholesterol levels, etc. (Boafo et al. 2023). In NHANES, the links between various PFAS and various metabolic health outcome differ by sex, BMI, and type of PFAS (Wu et al. 2024). For example, PFAS levels were linked to higher fasting glucose and lower insulin levels overall. PFNA was associated with higher fasting glucose. PFOA/PFUA/PFHxS were associated with lower insulin levels/lower insulin resistance, while PFNA showed the opposite (Tian et al. 2024). In NHANES, PFOA was associated with an increased risk of fatty liver disease, as was PFHxS in older women (Zhang et al. 2024).

Compared to the average US population, firefighters from Arizona had higher levels of PFHxS in their bodies, lower levels of PFNA and PFUA, and the same levels of 9 other PFAS. Those with higher PFDeA levels had lower total cholesterol levels, but in general, PFAS concentrations were not associated with most cardiovascular risk measures (Khalil et al. 2020). In Californian women firefighters and office workers, PFAS were linked to bile acids and hormones that control cholesterol and glucose metabolism and inflammation (Bessonneau et al. 2021). In Australian firefighters, higher levels of all PFAS studied were significantly associated with higher levels of total and LDL cholesterol (Nilsson et al. 2022).

In the GenX study in North Carolina, PFNA and PFOS were associated with higher levels of total and non-HDL cholesterol, with associations larger in older adults (Rosen et al. 2022).

In the U.S. Diabetes Prevention Program, PFAS levels were associated with various metabolites linked to type 2 diabetes (Mitro et al. 2020).

A study of Inuit people in Nunavik in Northern Canada, used an icebreaker to access participants: "All survey and clinical tests were performed on board the Amundsen, a Canadian Coast Guard Icebreaker, so participants had to be able to reach the icebreaker." It found that higher PFAS levels (especially long-chain) were associated with higher total, LDL, and HDL cholesterol levels, and prediabetes. There was no association between PFAS and triglycerides, diabetes, or high blood pressure (Aker et al. 2023).

Europe

A cross-sectional study of elderly Swedes found that the PFAS perfluorononanoic acid (PFNA) and PFOA were significantly related to diabetes in a non-linear manner. PFOA was also related to insulin secretion, but none of the PFAS were associated with insulin resistanc ıe exposures encountered in this study were typical of the general population (Lind et al. 2014). These authors also found that various PFAS were associated with various measures of

population (Lind et al. 2014). These authors also found that various PFAS were associated with various measures of metabolism, suggesting that each PFAS may have different effects (Salihovic et al. 2018). In Swedish middle-aged adults, PFOS and PFHxS levels did not show any consistent associations with body composition or weight, but PFOA, and especially PFNA and PFDA were linked to lower measures of fat in women (Lind et al. 2022). Also in Swedish middle-aged adults, PFAS levels were associated with cholesterol levels using detailed measurements that aren't normally included in routine clinical testing (Haug et al. 2023), and with altered levels of proteins linked to inflammation, metabolism and cardiovascular disease (Dunder et al. 2023).

In Finland, PFAS levels were linked to non-alcoholic fatty liver disease (NAFLD) and disrupted glucose metabolism, especially in women (Sen et al. 2021). In reproductive aged Norwegian women, fish consumption was the strongest predictor of PFAS (and mercury) levels. Higher fish consumption and PFOS concentrations were both associated with higher total and LDL cholesterol levels (Bjorke-Monsen et al. 2021).

In older Danish adults, exposure to numerous PFAS was linked to obesity, insulin resistance, and changes to the gut microbiome (Sen et al. 2024).

In Europeans, cholesterol levels were associated with various PFAS, especially in women (Papadopoulou et al. 2022).

In French people with fatty liver disease, PFAS levels were associated with more severe disease (David et al. 2023).

In highly exposed adults from Italy, exposure to a mixture of PFAS mixture was associated with higher cholesterol levels, regardless of the three different methods used to analyze the data. All three methods showed a major contribution of PFOS and PFNA, although the main exposure was due to PFOA (Batzella et al. 2022).

In people living on an island off Croatia, PFOS, PFOA, and PFNA levels were associated with an increased risk of metabolic syndrome, with only PFNA reaching statistical significance. PFNA levels were also associated with an increased risk of overweight or obesity (Chen et al. 2019).

In adults from Czechia, there were positive associations between PFOA and blood glucose, systolic and diastolic blood pressure, total cholesterol and LDL cholesterol; and between PFOS and blood glucose, BMI, waist circumference, systolic blood pressure, total and HDL cholesterol (Maranhao Neto et al. 2022). In Czech firefighters (and other men), a mixture of PFAS and polycyclic aromatic hydrocarbons (PAHs) was associated with higher total and LDL cholesterol levels (Pálešová et al. 2023). In Czech adults, there were associations between PFAS and cholesterol levels, but not with metabolic syndrome (Puklová et al. 2024).

Asia/Australia

Working-aged Taiwanese adults with higher PFOS levels had a higher risk of impaired glucose homeostasis and diabetes. However, those with PFOA, PFNA, PFUA had a lower risk (Su et al. 2016). Middle-aged Taiwanese adults with higher PFOA and PFOS levels had higher LDL cholesterol levels (Lin et al. 2019). Also in Taiwan, PFAS levels were not

associated with metabolic syndrome overall, but there were various associations between cholesterol levels and various PFAS that depended on sex and on medications taken (Lin et al. 2020).

In a nationwide study from China, there were associations between exposure to numerous PFAS and and increased risk of prediabetes and diabetes, some non-linear. People who ate seafood had PFAS levels nearly double those who did not, however, seafood also reduced the increased risk of diabetes/prediabetes from PFAS (Qu et al. 2024).

In Chinese adult men, PFAS levels were associated with various markers of metabolism (Wang et al. 2017). Another study of Chinese adult men found that PFAS levels were associated with metabolic syndrome (Yang et al. 2018). Also in China, PFAS those with higher levels (especially PFOA) had a higher risk of being overweight or having an increased waist circumference-- especially women (Tian et al. 2019). In Chinese adult men and women without diabetes, levels of various PFAS were associated with slightly higher fasting glucose and long-term average glucose levels (HbA1c) (Duan et al. 2019). In China, PFAS levels were associated with higher blood pressure and hypertension, especially in women, and especially newer PFAS alternative chemicals (Mi et al. 2020). In Chinese adults, PFAS levels were associated with metabolic syndrome, including some non-linear associations (Ye et al. 2020). In the C8 Health Project in China, greater serum levels of various PFAS (including 2 PFOS alternatives) were associated with higher risk of metabolic syndrome. There was also a positive association between the overall mixture of PFAS and the odds of metabolic syndrome in women (Yu et al. 2021). This C8 study also found that both older and newer PFAS were linked to worse cholesterol and triglyceride levels in adults (Cong et al. 2021). This C8 project also found that higher PFAS isomer levels (which are a slightly different type of PFAS) were associated with higher fasting blood glucose, fasting insulin, and insulin resistance, as well as a higher risk of type 2 diabetes, especially in women (Zeeshan et al. 2021). This project also found that both legacy (PFOA, PFOS) and alternative (Cl-PFESAs and PFBA) PFASs were associated with higher blood glucose markers; 6:2Cl-PFESA was the primary contributor (Zhang et al. 2021).

In East China, levels of most PFASs were associated with a lower risk of type 2 diabetes, but in people without diabetes, higher PFOA levels were associated with higher fasting glucose levels. Higher levels of PFNA, PFUnDA, and Cl-PFESA were associated with higher total cholesterol and these plus PFOS with higher LDL cholesterol (Han et al. 2021). Another Chinese study found that exposure to PFHxS and PFHpA had an inverted U-shaped dose-response relationship with type 2 diabetes risk, with the highest risk at middle exposure levels. Most other PFAS were associated with a lower risk of type 2, especially at higher exposure levels (Duan et al. 2021). Also in China, PFOA and PFOS levels were associated with higher total and LDL cholesterol levels (Cheng et al. 2022).

In China, the PFAS alternatives called Cl-PFESAs were linked to worse cholesterol and triglyceride levels (Mi et al. 2021). In fact both older (legacy) and newer (emerging) PFAS were associated with poor cholesterol levels (Wu et al. 2023). Of numerous chemicals (POPs, PBDEs, PCBs, phthalates, PFAS), PFAS were associated with higher total and LDL cholesterol levels in Chinese men (Chen et al. 2023).

In Korea, higher PFAS levels were associated with an increased risk of prediabetes, especially PFOS (Kang and Kim,

2024). A trial of elderly adults from Korea found that while PFAS levels were associated with insulin resistance, supplementation with vitamin C reversed these effects (Kim et al. 2016). In Korean adults, exposure to individual and combined PFAS was associated with higher liver enzymes, which are linked to cholesterol/triglyceride levels and liver disease (Kim et al. 2023). Also in Korea, mixtures of chemicals are also associated with an increased the risk of non-alcoholic fatty liver disease (NAFLD), especially in women. PFAS were some of the most important chemicals contributing to the risk (Park et al. 2024).

In Japan, interactions between maternal PFOS levels and some genes may affect maternal fatty acid levels in pregnant women (Kobayashi et al. 2021).

In Australia, adults with higher PFAS levels had higher total cholesterol levels (Lazarevic et al. 2023).

Cross-Sectional Studies in Children

In teenagers from across Europe, PFOA, PFNA, PFOS, and the PFAS mixture were associated with a lower BMI, and PFHxS was associated with a higher BMI (Schillemans et al. 2022). In US. adolescents, higher PFAS levels were associated with lower insulin resistance and blood glucose (Yan et al. 2023).

A cross-sectional study of Danish children found that in overweight children, higher PFAS levels were associated with higher insulin levels, higher beta cell activity, higher insulin resistance, and higher triglycerides. There was no association between these and PFAS in normal-weight children (Timmermann et al. 2014). Another Danish study found that children with higher levels of PFOA, PFDA and PFHxS had lower levels of leptin, while those with higher levels of PFOA had higher levels of adiponectin. In boys, higher levels of PFHxS were associated with lower levels of adiponectin (Domazet et al. 2020). In Danish teens, there were no consistent associations between PFAS exposure and body fat, although PFOS was associated with lower abdominal fat and total body fat (Thomsen et al. 2021).

In Norwegian adolescents, there was a possible link between several PFAS and problematic cholesterol levels, high blood pressure, and obesity (Averina et al. 2021).

In U.S. children, higher levels of PFHxS, PFOS, and PFAS mixtures were associated with lower height-for-age in boys. PFHxS was also associated with decreased weight-for-age and BMI in boys. In girls, PFHxS was associated with lower height-for-age (Scinicariello et al. 2020). PFOS levels were associated with lower weight/BMI in U.S. teens, and PFNA with lower weight in boys (Wang et al. 2023). However, U.S. teenagers with higher PFOA levels had a higher risk of overweight/obesity (Geiger et al. 2020).

In U.S. children with obesity, PFAS levels were associated with various metabolic measurements, including cholesterol levels, but not blood glucose levels (Khalil et al. 2018). Also in U.S. children, levels of PFOA and PFNA were associated with total cholesterol levels (Jain and Ducatman 2018). In U.S. adolescents, higher PFOS levels in boys were associated with higher diastolic blood pressure (Ma et al. 2019). Higher PFAS exposure levels were associated with more severe disease in U.S. children with non-alcoholic fatty liver disease (NAFLD) (Jin et al. 2019).

A study of two year old Korean children found that those with higher levels of various PFAS were shorter, and those with higher levels of PFNA weighed less than those with lower exposures (Lee et al 2018). Also in Korean children, PFUnDA levels were associated with higher total and LDL cholesterol levels (Kang et al. 2018).

In Taiwanese children, different lipid (e.g., cholesterol, triglycerides) patterns were discovered in children exposed to different levels of specific PFASs, such as PFTrDA, PFOS, and PFDA. These changes in lipid levels may be involved in liver lipid metabolism and metabolic disorders (Lee et al. 2021).

In Chinese infants, PFAS levels in umbilical blood were associated with triacylgycerol levels and other metabolic markers at birth (Sinisalu et al. 2021).

In children from Cincinnati, Ohio, PFAS levels were associated with metabolic features and pathways related to energy production (Kingsley et al. 2019). Which brings us to other studies of this region:

Higher-Level Exposures in Humans

Mid-Ohio Valley

An area of the Mid-Ohio Valley has been contaminated by high levels of PFOA. Research suggests an increased risk of mortality due to type 2 diabetes in workers occupationally exposed to PFOA, as compared to other DuPont workers (Steenland and Woskie, 2012). Previous research suggest an association between diabetes and PFOA exposure in workers as well (Lundin et al. 2009). Workers in the Mid-Ohio Valley were exposed to PFOA in a chemical plant that produced Teflon. Emissions from this plant polluted the drinking water of the nearby community. Recent studies of these community members have looked for diabetes risk, as well as other health issues. These studies are known as the C8 Health Project (C8 is another term for PFOA) (see Frisbee et al. 2009 for a description of study design). The medication ezetimibe, which inhibits cholesterol absorption, does not affect serum PFAS concentrations in people in the C8 study (Ma and Ducatman, 2022).

A cross-sectional study of the exposed Mid-Ohio Valley community members did not find an association between PFOA and type 2 diabetes or fasting glucose levels (MacNeil et al. 2009), nor did a long-term study of this population (Karnes et al. 2014). A more detailed study found that those with diabetes (especially type 1) had *lower* levels of PFAS than those without diabetes (Conway et al. 2016). Early-life PFOA levels were not associated with obesity or overweight in adulthood (Barry et al. 2014). However they did find associations between PFOA levels and high cholesterol (Winquist and Steenland 2014). For an article describing these findings, see PFOA and High Cholesterol: Basis for the Finding of a Probable Link, published in *Environmental Health Perspectives* (Betts 2014).

A long-term study from Cincinnati looked at associations in the offspring of women living downstream from a PFAS manufacturing plant. They found that higher maternal PFOA levels were associated with higher weight and waist circumference in their children, as well as greater BMI gains from ages 2-8 (Braun et al. 2016). A follow up study found that gestational PFOA exposure was associated with higher BMI by age 12, while PFOS and PFHxS exposure is associated with lower BMI in the first 12 years of life (Braun et al. 2020). Another long-term study from the Cincinnati area found PFAS levels were not associated with BMI, but were associated with altered kidney and thyroid function (Blake et al. 2018). In Cincinnati girls, PFOA levels were associated with lower BMI (Fassler et al. 2019; Pinney et al. 2019). They also found that in adolescence, females in the higher PFAS exposure group had higher blood pressure, visceral fat, and cardiometabolic risk, while males had lower (Fleury et al. 2024).

In Kentucky, PFAS levels as well as cholesterol levels significantly decreased following a 6-month lipid-lowering lifestyle-based intervention (Morgan et al. 2023).

The World Trade Center

Large amounts of various chemical contaminants, including PFAS, were released at the time of the World Trade Center

disaster in 2011. In children and adolescents who were exposed to the contaminants, those with higher levels of PFOAs had increased triglycerides, total. cholesterol, and LDL cholesterol. Perfluorohexanesulfonic acid levels, however, were associated with lower insulin resistance (Koshy et al. 2017).

A study of New York City women who were pregnant at that time found that several PFAS were associated with higher lipid levels in umbilical cord blood, especially triglycerides and both PFOA and PFHxS (Spratlen et al. 2019).

Other Areas

In Ronneby, Sweden, an area contaminated with PFAS fire-fighting foam, a large study of adults who had ever lived in Ronneby during 1985-2013 found an increased risk of type 2 diabetes after high PFAS exposure through drinking water. "In particular, a higher risk of early onset diabetes was found, indicating increased susceptibility to PFAS-related health effects at younger ages." (Xu et al. 2023). Also in Ronneby, PFAS levels were associated with higher LDL and total cholesterol levels (Li et al. 2020).

In people living near a PFAS plant in Shandong, China, those with higher levels of PFO5DoDA (this study looked at less-common PFAS) had higher total cholesterol, LDL cholesterol, and triglyceride levels (Yao et al. 2020). In a highly exposed population in Laizhou Bay, a chemical production area in northern China, higher PFOA exposure was associated with higher total and LDL cholesterol levels, and other PFAS with higher HDL cholesterol levels. There were some associations between PFAS mixtures and thyroid hormone levels as well (Liu et al. 2023). In elderly Chinese people living near chemical plants, PFAS levels were strongly associated with various metabolites, mainly having to do with fatty acids and metabolism (Yang et al. 2024). In people occupationally exposed in Jinan, China, PFAS mixtures were associated with higher cholesterol and LDL cholesterol levels in those over 40 (Liu et al. 2024).

In Italy, there was not a consistent association between PFAS and metabolic syndrome, and conflicting findings were observed for individual components of the syndrome (Zare Jeddi et al. 2021). In Italy, people with higher levels of PFOA, PFOS, and PFHxS had higher total, HDL, and LDL cholesterol levels. Those with higher PFOA and PFHxS levels had higher triglycerides. The largest rate of increase per unit of PFAS occurred at the lower range of PFAS levels (Canova et al. 2020). The same authors also found that PFAS concentrations were associated with increased systolic and diastolic blood pressure (Pitter et al. 2020). And they found that in Italian children, there was a consistent association between PFAS and cholesterol levels which was stronger for PFOS and PFNA, and especially in children compared to adolescents. Also, higher PFAS levels were associated with lower BMI (Canova et al. 2021).

Laboratory Studies: Diabetes/Obesity

Adult male rats exposed to PFNA experienced high blood sugar by increasing the release of glucose from the liver (Fang et al. 2012). PFOA-treated mice had increased blood glucose and insulin levels, increased insulin resistance, and higher levels of leptin and adiponectin (Du et al. 2018).

PFOA exposure reduced the production of glycogen in the liver of mice, and actually increased insulin sensitivity and glucose tolerance. While these effects may appear to be beneficial, the mechanism by which they occurred may have harmful effects in the long run-- several protein levels were also affected, and these proteins are potentially involved in diabetes and liver disease (Yan et al. 2015). Other authors also found that PFOA affects liver and beta cells in animals, and impaired liver function. Specifically, PFOA caused higher insulin and LDL cholesterol levels, and reduced glucagon, glucose, and HDL cholesterol levels (Wu et al. 2017). These authors also found that PFOA exposure also decreased fasting blood glucose, raised insulin levels, increased liver enzymes, and changed lipid levels in mice (Wu et al. 2018). Other authors found that PFOA causes higher blood glucose levels in mice, lower glycogen levels in the liver, and also-- this is new-- promoting energy consumption, especially carbohydrate consumption (Zheng et al. 2017). Long-term and low-dose exposure to PFOA and GenX disrupts lipid metabolism in mice (Attema et al. 2022; Shi et al. 2024). Both high and low levels of exposure to PFOA increase triglyceride levels in mice blood and liver, especially in the liver (Gao et al. 2022). And it's not just triglycerides; PFOA affected levels of 350 lipids in mice livers (Stoffels et al. 2023). In mice, PFOA causes liver damage; the effects vary depending on whether or not the mice have obesity (González-Alvarez and Keating, 2023).

At low levels, PFOS affects both metabolism and the immune system of zebrafish. The data imply that the currently applicable tolerable levels of PFOS in commercial goods should be re-evaluated (Martínez et al. 2019).

Mice fed high doses of PFAS show reduced body weight and lower fat mass, via reduced food intake (Shabalina et al. 2015). (While high doses of some chemicals can cause lower weight, it may be that lower doses have opposite effects). In other mice, PFOA exposure at levels that humans encounter did not affect cholesterol or triglyceride levels, but did affect them at very high doses (Pouwer et al. 2019). Other studies, however, found that PFOA exposure at levels that humans encounter, and with an average American diet, do affect cholesterol levels (Schlezinger et al. 2020).

PFOS was found to reduce some of the unhealthy effects of a high fat diet in mice (Huck et al. 2018).

PFOS causes changes in the liver and the intestine in zebrafish, an animal model used to study the effects of toxic chemical exposures (Cui et al. 2016). PFAS also affect the deposition of triglycerides in the liver of mice (Das et al. 2017; Hui et al. 2017). In frogs, PFOA caused lipid accumulation in the liver, and higher total cholesterol and triglyceride levels (Zhang et al. 2018a). In rats, exposure to PFOA induced liver damage and affected glucose markers in rats (Zhang et al. 2023).

In adult mice, PFOS exposure caused metabolic disturbances, particularly in lipid and glucose metabolism, and perturbed gut metabolism, inducing changes associated with inflammation and metabolism (Lai et al. 2018). PFOS also increases fat cell development, and fat accumulation in mice (Xu et al. 2016). And PFOS causes insulin resistance in mice as well (Dong et al. 2022; Wang et al. 2023).

In mice fed a calorie-restricted diet, PFOS did not significantly alter weight loss or white fat tissue mass, but PFOS did increase triglyceride accumulation in the liver. PFOS also interfered with the glucose lowering effects of the diabetes drug metformin in liver cells and made metformin less effective in fat cells (Salter et al. 2021).

Curiously, while high level exposure to PFOA stimulates lipid accumulation in fat cells, it also lowers weight in mice, perhaps due to decreases food intake and increased heat production (Reckziegel et al. 2024).

In mice, exposure to both PFO4DA and PFO5DoDA increased body weight and caused high blood glucose levels (Chen et al. 2021). In mice fed a standard American (i.e., unhealthy) diet, PFOA caused higher triglyceride levels (Schlezinger et al. 2021).

PFHxS caused obesity, metabolic syndrome, liver damage, and affected the gut microbiota in mice fed a high-fat diet (He et al. 2022).

In mice, two new PFAS, GenX and Nafion byproduct 2 (NBP2) were assessed. GenX accumulated less in the liver than NBP2 yet altered lipids more (Kirkwood-Donelson et al. 2024).

PFDA worsened the effects of a high-fat diet in mice, causing body weight gain, impaired glucose metabolism, inflammation, and liver fat accumulation (Wang et al. 2023).

A "molecular dynamics" model, which evaluated all the biological effects and pathways linked to PFAS, found that four genes were at the center of this network, including genes linked to diabetes and obesity (Liu et al. 2019). A "systems toxicology" approach tried to explain why human studies find that PFAS are linked to higher cholesterol levels in humans, but not necessarily in animals (Westerhout et al. 2024).

A mixture of PFAS at levels found in the environment (in earthworms at a ski area!) led to higher body weight, plus oxidative stress and other detrimental effects in the liver of mice (Khan et al. 2023). In caged birds, environmentally relevant levels of PFAS affected body fat in the same way that leads to obesity in mammals (Lopez-Antia et al. 2023).

Sodium ρ-perfluorous nonenoxybenzene sulfonate (OBS), a newly discovered kind of perfluoroalkyl and polyfluoroalkyl compound [btw, there are more than 7000 PFAS...], is a surfactant for increasing oil production and an environmental contaminant. In mice, OBS accumulated in the gut and liver, causing gut barrier dysfunction and liver dysfunction (Wang et al. 2019). Maternal exposure to OBS affected the liver and triglyceride levels of both dams and offspring mice (Wang et al. 2022).

The perfluorinated compound TFMS affected the liver and gut microbiota of mice (Zhou et al. 2020), as did PFOA (Wang et al. 2020). PFOS also affects gut microbiota and increases intestinal permeability and inflammation in mice (Diaz et al. 2021). In mice, both PFOS and GenX affected gut microbiota, and affected the GI tract, liver, and metabolism (Rashid et al. 2023). The PFOS alternative F-53B altered the gut microbiota and damaged the liver in mice (Li et al. 2024).

Both PFOA and HQ-115 (a new type of PFAS) affected lipid metabolism in the liver of mice (Sands et al. 2024). The PFOA substitute HFPO-TA affected glucose tolerance and glucose/lipid metabolism in rats (Zhang et al. 2024).

Interestingly, probiotic bacteria alleviated the energy metabolism disorders caused by PFBS, a replacement for PFOS, in zebrafish (Liu et al. 2021a). Another study from these authors specifically found that in zebrafish, PFBS disturbed lipid metabolism, increased blood glucose levels (by 2.5-fold relative to the controls), and decreased glucagon levels in the liver of females, while probiotics counteracted these effects (Liu et al. 2021b). They also found that in zebrafish, PFBS exposure decreased nutrient reserves, affected gut microbiota and the gut lining, and affected the liver, which were all alleviated by the probiotics (Hu et al. 2021). These authors also found that PFBS increased triglyceride levels in aged zebrafish, and fecal transplantation from young zebrafish inhibited the toxicity of PFBS and restored triglyceride levels to normal (Hu et al. 2022). Exposing aged zebrafish to PFBS also caused high glucose levels, high glucagon levels, impaired insulin secretion, depleted glycogen stores. These effects were mitigated by fecal transplantation from young zebrafish (Liu et al. 2022). PFBS causes fatty changes in the liver of mice at low levels as well (Chen et al. 2022). The effects of PFBS on the gut microbiota and liver function in mice are worse with a restricted diet (Liu et al. 2023).

Fucoidan, found in seaweed, is a potential nutraceutical product against PFOA-associated obesity (Liu et al. 2022).

The soluble fibers inulin and pectin protected mice against PFOS-induced liver metabolic disturbances, fat accumulation in the liver, transcriptional changes, gut microbiota changes, and even the accumulation of PFOS in the body (Deng et al. 2022). Also see related Invited Perspective: PFOS–Pick Fiber, Oust Sulfonate (Golonka and Vijay-Kumar, 2022).

A compound found in green tea counteracted the obesogenic effects of PFDA in mice (Xu et al. 2023).

Other studies also examine mechanisms by which PFAS affect diabetes-related processes (e.g., Zhang et al. 2021).

In Vitro Studies of Cells

Pancreatic Cells

PFOA can kill pancreatic cells via inflammation and oxidative stress (Mahmoud et al. 2021). PFOA can affect beta cells by decreasing cell viability and increasing cell death (Suh et al. 2017). High doses of PFOA killed beta cells, while low doses inhibited insulin secretion (He et al. 2022).

Acute exposure to PFOS stimulates insulin secretion from beta cells in the laboratory (Zhang et al. 2020) and also in mice, via a mechanism that is likely relevant for humans (Qin et al. 2020). Another study, though, found that PFOS impaired glucose stimulated insulin secretion in beta cells (Duan et al. 2021). Chronic exposure of beta cells to PFOS reduced insulin secretion and caused beta cell death. It appears that acute exposure to PFOS can stimulate insulin secretion, and chronic exposure can reduce it (Elumalai et al. 2023). Another study found that PFOS reduced insulin secretion from beta cells, and the flavonoids procyanidins reduced the effect (Xu et al. 2023).

In pre-pancreatic stem cells, a number of PFASs may alter the development of the pancreas, including PFOA and PFOS as well as their substitutes Liu et al. 2020). PFOA detrimentally affects mouse pancreatic acinar cells which are part of the exocrine pancreas, involved in digestion (Hocevar et al. 2020).

PFOA caused epigenetic changes in pancreatic cells (Abudayyak et al. 2023).

PFAS can affect alpha cells and/or glucagon secretion (Al-Abdulla et al. 2023; Dos Santos et al. 2022).

Stem Cells/Fat Cells

PFOA increases the differentiation of fat cells, which then accumulate triglycerides (Yamamoto et al. 2015).

At low doses, PFOS and PFOA are toxic to stem cells, and affect their differentiation into fat cells (Gao et al. 2020; Liu et al. 2018). In bone marrow stem cells, PFOS repressed bone building and enhanced fat cell development (Liu et al. 2019). A number of PFAS besides PFOA and PFOS (including PFBS, PFHxS, PFBA and PFHxA) also have obesity-related effects in stem cells (Liu et al. 2020). In fact, all ten PFAS investigated in one study were able to induce cell differentiation into fat cells (Modaresi et al. 2021).

PFOS and PFOA decreased bone cell differentiation and enhanced fat cell differentiation of human mesenchymal stem cells, and some replacement chemicals had similar or even stronger effects (Qin et al. 2022). The replacement OBS, for example, appears to be an obesogen although less potent than PFOS, but it can decrease bone density just like PFOS (Qin et al. 2023).

PFDA, a PFAS chemical used in food packaging, increased triglyceride accumulation and inflammation in liver and fat cells (Wang et al. 2022).

Immune Cells

Laboratory studies show that PFAS may have effects on the immune system that are consistent with autoimmune diseases. Human cells exposed to PFOS had these effects at exposures at the high end of human exposure range (Midgett et al. 2015).

Liver Cells

PFOS essentially causes insulin resistance in liver cells; scientists are working to identify the exact mechanisms involved (Li et al. 2024; Qiu et al. 2016). PFOA reduced glycogen synthesis and glucose uptake and had other effects in liver cells linked to insulin resistance (De Toni et al. 2021). PFOS causes fat accumulation in liver cells (Ling et al. 2022).

In zebrafish liver cells, PFOA affected gene expression of genes relating to tight junctions, immune system, endocrine system, and metabolism-related pathways (Wu et al. 2022).

In human liver cells, PFOS, PFOA, and PFNA triglyceride levels, but had no effect on cholesterol levels (Louisse et al. 2020).

The newer PFAS 6:2 Cl-PFESA increased lipid accumulation in liver cells, and the authors identified a marker that could be used as a toxicity maker for risk assessment (Li et al. 2023).

Exposures During Development

Pregnant/mother rats were exposed to PFOS, to see the effects on the offspring (exposed in the womb and while nursing). The offspring had low body weight from birth to weaning, and had impaired glucose tolerance, and higher insulin levels, resembling pre-diabetes (Lv et al. 2013). When pregnant mice were exposed to low doses of PFOA, their offspring had metabolic effects that differed by sex (van Esterik et al. 2016).

Mice exposed to low doses of PFOA in the womb had reduced body weight at birth followed by excess body weight at mid-life, as well as higher insulin levels at mid-life. There was no effect of PFOA on these parameters from exposure during adulthood, showing that developmental exposures may be most critical (Hines et al. 2009). Another mouse study found that gestational exposure to PFOA resulted in obesity, liver inflammation, disorders of lipid metabolism, and disruption of gut barrier integrity in male offspring, and that these effects were reduced by chlorogenic acid supplementation (Shao et al. 2020).

When mother mice were exposed to PFOS during pregnancy, they had higher insulin resistance than untreated controls, suggesting a gestational-diabetes-like pattern. Early in life, their male offspring had higher insulin levels, although the female offspring had normal levels. Later in life, as adults, both groups of offspring had higher fasting glucose and insulin levels than controls. The pups fed a high-fat diet showed even greater effects than those fed a normal diet (Wan et al. 2014). *In utero* PFOS exposure altered epigenetics, predisposing mice to later life glucose metabolism problems (Ho et al. 2023). In mice, maternal exposure to PFOS increased triglyceride and total cholesterol levels and affected gut microbiota in offspring (Yi et al. 2024). In zebrafish embryos, PFOS exposure increased triglycerides, LDL and total cholesterol, and decreased HDL cholesterol and glucose levels (Mahapatra et al. 2023).

In offspring mice exposed to PFOA or GenX (a PFOA replacement) in the womb, both males and females were affected, but males had more diabetes/obesity related effects like weight gain and insulin resistance, and females had more liver damage. GenX caused damage at lower doses than PFOA (Cope et al. 2022). Developmental exposure to GenX, like PFOA, caused changes to the gut mucosa and liver, including decreasing liver glycogen storage in mice (Zhang et al. 2023).

In rats, PFOS exposure during prenatal life caused low birth weight followed by catch-up growth in female offspring, and lead to high blood pressure in both males and females (Dangudubiyyam et al. 2020). In rats, developmental exposure to PFHxS led to lower birth weight and higher body weight in offspring as adults as well (Ramskov Tetzlaff et al. 2020).

In mice, PFOS exposure in the womb appears to affect oxidative stress more in the fetus than the pregnant mother, and this could affect fetal development (Lee et al. 2015).

Studies in zebrafish show that PFOS exposure during development also affects the development of the pancreas in ways that may predispose to diabetes (Sant et al. 2018; Sant et al. 2017; Sant et al. 2021). Also in fish, PFOA exposure during

development affects glucose levels in offspring, possibly in future generations as well (Lee et al. 2017). Developmental exposure of zebrafish to PFOS at levels found in humans caused increased length and weight, among other effects (Christou et al. 2021). PFOS and PFOA affected lipid metabolism in zebrafish embryos, and DHA supplements did not correct the problems (Yang et al. 2022). A new type of PFAS, Nafion by-product 2, disrupted cholesterol and triglyceride levels, and more, in zebrafish embryos (Gui et al. 2023). Also in zebrafish embryos, exposure to PFHxS disrupted metabolic processes, including sugar metabolism (Xu et al. 2023).

In roundworms, early life exposure to low concentrations of PFOA and PFOS induced obesity, which was not due to an increased feeding rate (Lin et al. 2022).

Developmental exposure to the PFOA replacement chemical GenX caused a variety of diabetes-related health issues in offspring (Conley et al. 2020).

PFHxS caused fatty liver, metabolic syndrome, and insulin resistance in zebrafish embryos (Ulhaq et al. 2024).

Developmental exposure to the short-chain PFAS PFMOAA caused hypoglycemia and lower glycogen levels, lower thyroid hormone levels, higher cholesterol levels, and more (Conley et al. 2024).

Exposure to OBS, a type of PFAS, increased total and LDL cholesterol levels in mice mothers and male offspring, and lowered HDL cholesterol levels in male offspring (Wang et al. 2021).

In rats, maternal PFBS exposure led to some changes in metabolic gene expression, but not in glucose or cholesterol/triglyceride levels (Meng et al. 2023).

Developmental exposure to low levels of PFAS had effects on zebrafish linked to fatty liver disease (Gadi et al. 2023).

Developmental exposure to the PFOA substitute HFPO-TA caused metabolic effects in chickens, including fatty liver and high insulin levels (Zhong et al. 2024).

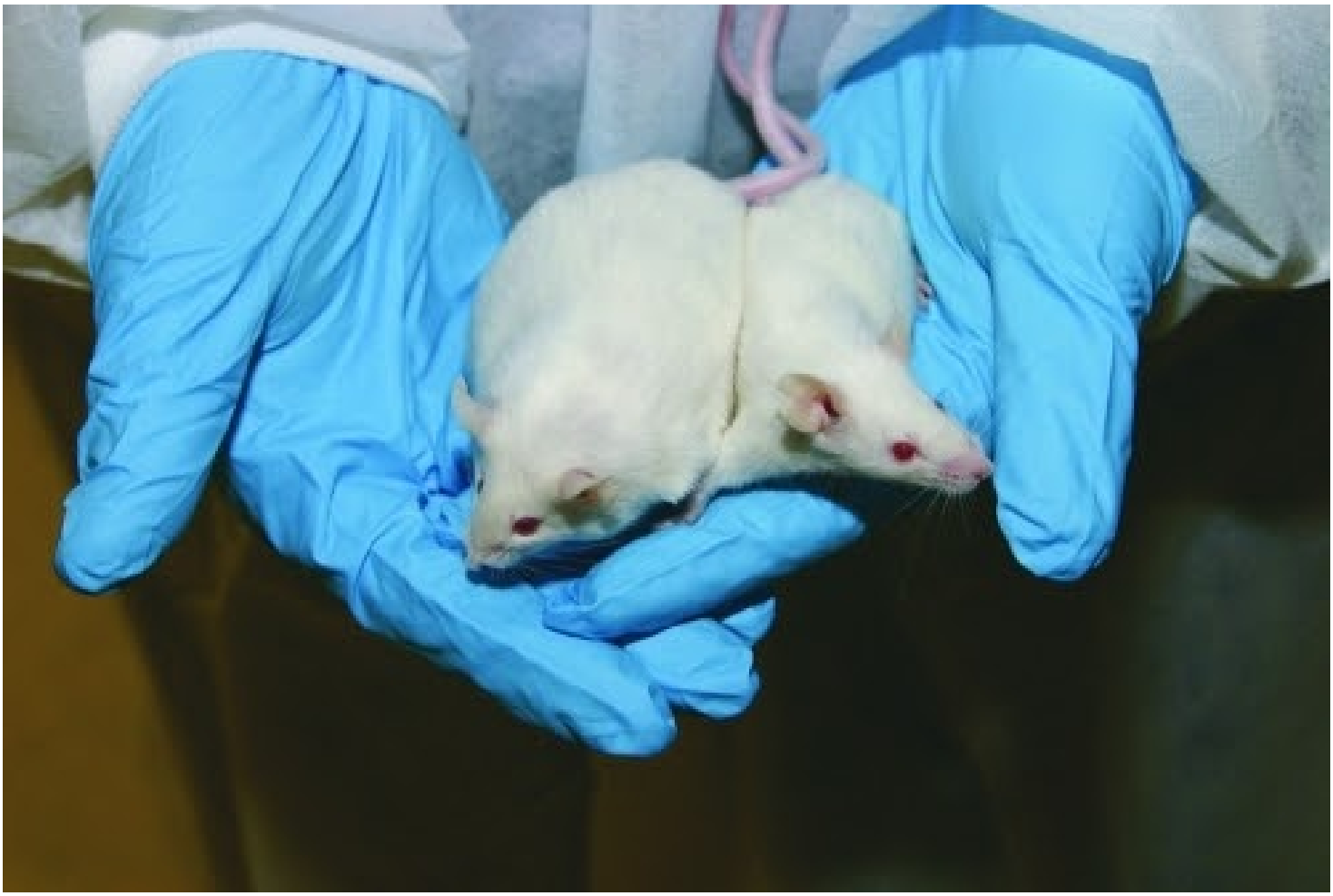
Alpha lipoic acid (ALA) is a supplement used to treat obesity and diabetes. Researchers wondered if it could mitigate the effects of PFOS exposure. In zebrafish, developmental exposure to ALA and PFOS individually and together had similar effects, however, and ALA exacerbated some effects of PFOS (Tompach et al. 2024).

Exposing fathers can lead to effects as well

Exposure to a mixture of old and new PFAS in adult male mice caused altered gene expression in the liver and fat of offspring, changes linked to cholesterol and fatty liver (Maxwell et al. 2024).

Prenatal Exposure to PFOA Causes Obesity in Mice

Mice exposed prenatally to PFOA were more likely than controls to develop obesity when they reached adulthood.



Source: Christopher G. Reuther, EHP via Holtcamp 2012, EHP; Hines et al. 2009.

Transgenerational Effects

In C. elegans, exposure to PFOA for four generations led to higher fat content in most generations (Li et al. 2019). Short-chain PFAS also had transgenerational effects related to obesity, for 4 generations (Li et al. 2021).

Chemicals in Combination

The effects of PFAS may be greater in combination with other chemicals. In fish, separate exposure to PFOS or tributyltin in early life elevated fatty tissue areas at low doses, but not at the highest doses. Combined exposure significantly promoted fat accumulation in newly hatched larvae, even when the doses of TBT and PFOS were both at the levels that did not show obesogenic effects (Qui et al. 2018).

Sterilizing wastewater with sodium hypochlorite can react with pharmaceuticals to generate disinfection by-products and can cause the final effluent to be even more harmful to aquatic organisms. One study, for example, found that the metabolism of Daphnia magna is sensitive to changes in the final effluent that are caused by sterilization. With the addition of PFOS, the metabolic profile is further altered (Wagner et al. 2019).

Exposure during development to a mixture of PFAS, triclosan, and phthalates (based on the levels of these compounds found in pregnant Swedish women) affected metabolic rate, increased the number of fat cells and fatty tissue young zebrafish fed a calorie-rich diet (Mentor et al. 2019).

Different types of PFAS together may also have cumulative effects. Developmental exposure to PFOA, PFOS, PFHxS and their mixture increased liver triglycerides in mice, and the mixture had very distinct effects when compared to each single compound, suggesting some cumulative effects (Marques et al. 2021). These authors further determined how exposure to this mixture leads to fatty liver (Kaye et al. 2024). A mixture of PFAS at levels found in the environment affected the metabolism (e.g., lowered energy expenditure and glucose levels) of zebrafish larvae (Liu et al. 2023).

PFAS Alternatives

The PFOS replacement chemical, 6:2 chlorinated polyfluorinated ether sulfonate (6:2 Cl-PFESA), increased liver lipid accumulation, triglycerides and LDL cholesterol, and decreased HDL and total cholesterol in mice (Zhang et al. 2018b). It appears that this replacement chemical is more toxic to the liver than the one it replaces... which is a similar problem with the PFOA replacement chemical hexafluoropropylene oxide trimer acid (HFPO-TA), which may be more of an obesogen than PFOA (Li et al. 2019).

Another PFOS replacement chemical, PFBS, promotes the differentiation of pre-fat cells into fat cells and increased triglyceride levels (Qi et al. 2018). Developmental exposure to PFBS also disrupts the development of the pancreas and energy homeostasis in zebrafish (Sant et al. 2018), and, as noted above, is associated with higher weight-related measures in girls (Chen et al. 2019). Probiotics helped mitigate some effects of PFBS in zebrafish, but made others worse (Chen et al. 2020).

A PFOS replacement chemical used in China, F-53B, adversely impacts zebrafish livers, with the disruption dependent on sex and developmental stage (Shi et al. 2019). F-53B appears to be worse than PFOS in fact (Tu et al. 2019).

PFAS replacement chemicals perfluoroether carboxylic acids (PFECA) (including GenX and PFO3TDA) may be just as toxic as PFOA. The effects include metabolic disruption (Gebreab et al. 2020).

Hexafluoropropylene oxide dimer acid (HFPO-DA, also called GenX) is a substitute for PFOA. In mice, HFPO-DA exposure caused inflammation in the colon, dysfunction of gut barrier in the colon, and the imbalance of gut microbiota and changes in gut microbiota diversity (Xie et al. 2021).

Hexafluoropropylene oxide trimer acid (HFPO-TA), an alternative to PFOA, decreased total cholesterol and triglyceride activities, disturbed lipid metabolism, and induced inflammation, among other things, in zebrafish embryos (Sun et al. 2022). Different authors found that PFOA, HFPO-TA, and GenX all increased total cholesterol in zebrafish, and PFOA and HFPO-TA also increased triglyceride levels (Sun et al. 2023).

Wonderful. But not surprising. This is a common problem with replacement chemicals; they end up having the same problems as the chemicals they replace.

Gestational Diabetes

A meta-analysis of data from 25 studies found that PFOA, PFHxS, PFBS, and PFHpA were associated with an increased risk of gestational diabetes (Pang et al. 2024). A review of PFAS and gestational diabetes finds that in general, exposure to PFAS were associated with higher glucose and insulin levels in pregnancy. Disrupted thyroid levels are linked to PFAS as well, and these authors argue that the thyroid effects may be linked to the increased risk of gestational diabetes (Birru et al. 2021). However, another review found no link to gestational diabetes (but did find links to preterm birth, preeclampsia, and miscarriage) (Gao et al. 2021). A meta-analysis of data from eight studies found that PFOA exposure was associated with an increased risk of gestational diabetes, but exposure to other PFAS, including PFOS, PFHxS, and PFNA, was not (Wang et al. 2021).

Preconception levels of PFOA were associated with gestational diabetes in a prospective U.S. study of women with background levels of PFAS exposure. Six other PFAS were also associated with an increased risk, although not statistically significant (Zhang et al. 2015). In Canadian women, first-trimester levels of most PFAS were not associated with gestational diabetes. However, this study found a higher risk of impaired glucose tolerance during pregnancy in women with moderate (second-quartile) levels of perfluorohexane sulfonate (PFHxS) (Shapiro et al. 2016). The Canadian women with higher PFOS levels also had higher gestational weight gain (Ashley-Martin et al. 2016). A study of pregnant women from Spain found that PFOS and PFHxS levels were associated with impaired glucose tolerance and gestational diabetes (Matilla-Santander et al. 2017). In Danish women with a high risk of gestational diabetes, PFHxS levels were associated with increased fasting glucose, fasting insulin, and insulin resistance. PFNA levels were associated with higher fasting insulin and beta cell function. Other PFAS were not associated, and there were no associations in pregnant women who were otherwise at low risk of gestational diabetes (Jensen et al. 2018). In California, PFDA, PFNA, and PFOA exposure in both early and mid-pregnancy were associated with a higher risk of gestational diabetes (Peterson et al. 2023).

Colorado pregnant women with higher PFOA, PFNA, PFDeA, and PFHxS levels had lower blood glucose levels (Starling et al. 2017), although a different U.S. study found women with a family history of type 2 diabetes who had higher levels of PFOA, PFNA, PFHpA, and PFDoDA had a higher risk of gestational diabetes (Rahman et al. 2019). A Boston study found that pregnant women with higher levels of PFOS had higher glucose levels, with evidence that associations varied by age and racial/ethnic group, but there was not an association with gestational diabetes (Preston et al. 2020). This study also found that PFAS levels during pregnancy were associated with greater gestational weight gain, weight retention, and weight gain years after pregnancy (Mitro et al. 2020). On the other hand, a study from Rochester, NY found that PFAS, especially PFOA and PFHxS, were associated with lower gestational weight gain and postpartum weight retention (Kinkade et al. 2023).

In pregnant Californian women with overw : or obesity, PFAS levels were associated with lower fasting glucose and insulin levels, and lower insulin resistance (Mehta et al. 2020). However in a diverse group of women in San Francisco,

PFOS levels (as well as other chemicals) were linked to a higher risk of gestational diabetes (Trowbridge et al. 2023). For an article about this study, see Liang and Walker, 2023).

In pregnant Illinois women, many PFAS were linked to lower insulin and insulin resistance and higher cholesterol, although the associations varied by chemical and by mixtures (Cinzori et al. 2024).

In Norway, pregnant women with higher levels of PFAS had higher levels of HDL cholesterol (the "good" cholesterol) and total cholesterol (not so good) (Starling et al. 2014).

In Chinese pregnant women, exposure to PFAS was associated with higher blood glucose levels in pregnancy and an increased risk of gestational diabetes, especially in normal weight women. PFOS, PFNA and PFHpA may be the main contributors (Yu et al. 2021). Also in China, PFOA levels were associated with higher insulin levels, higher insulin resistance, and higher blood glucose levels, while PFOA tended to be associated with lower glucose levels (Wang H et al. 2018). Another study from China found that while maternal PFAS exposure was not associated with risk of gestational diabetes, there were significant positive associations between exposure to specific types of PFAS and increasing blood glucose (Wang Y et al. 2018). Another found that short-chain types of certain PFAS were associated with both gestational diabetes risk and impaired glucose tolerance in pregnant women (Liu et al. 2019). Various PFAS were associated with higher glucose levels in pregnant women, also probably in China (Uppal et al. 2018). Higher maternal PFBS and PFDoA levels in early pregnancy were associated with a substantially higher gestational diabetes risk in China (Xu et al. 2020). Another Chinese study found that PFAS levels were linked to higher 1 hour post-meal blood sugar levels, but not fasting blood sugar levels (Ren et al. 2020). PFAS levels were variously associated with cholesterol and triglyceride levels in pregnant Chinese women (Yang et al. 2020).

Also in China, exposure to PFOA, PFUnDA, PFDoA, PFOS, and 6:2Cl-PFESA was associated with a higher risk of gestational diabetes, as well as with higher fasting and post-meal glucose levels, and long-term average blood glucose (HbA1c). PFOA as the most important. However, some PFAS, including PFHxS, were associated with lower levels of some of these measurements (Xu et al. 2022). Another Chinese study found that higher exposure levels to numerous PFAS (PFOA, PFNA, PFHxS, and 6:2 Cl-PFESA) were associated with a higher risk of gestational diabetes, however (Zhang et al. 2022). Also in China, PFAS exposure was associated with an increased risk of gestational diabetes, especially PFOA, and especially in normal-weight women (Zang et al. 2023).

Scientists in China looked for 325 chemicals in pregnant women and found 33 chemicals in over 70% of them. The mixture was associated with a higher risk of gestational diabetes, and PFHxS was one of the chemicals most strongly linked to this risk (Huang et al. 2023).

In Chinese women conceiving through assisted reproduction, exposure to 10 of 19 PFAS measured, especially newer PFAS alternatives, were associated with a hi ' risk of gestational diabetes or higher post-meal glucose levels (Mao et al. 2024).

In Hong Kong, maternal exposure to a PFAS mixture was associated with higher long-term blood glucose levels (HbA1c), and there were associations between PFAS exposure and the risk of gestational diabetes. These women had higher levels of PFOS in their bodies than Chinese or U.S. women (Yang et al. 2024).

Now here's something really interesting: in the Faroe Islands, there were correlations between maternal and umbilical cord levels of PFAS, indicating significant transfer of these compounds from the mother to the fetus. Importantly, they also found that there was significantly higher transfer in mothers with gestational diabetes (Eryasa et al. 2019).

Three years following pregnancy, levels of various PFAS measured during pregnancy concentrations were associated with greater weight and waist circumference, and higher systolic blood pressure in Boston women (Mitro et al. 2020). In Ohio, higher levels of PFOA, PFOS, and PFNA were associated with a small increase in gestational weight gain and rate of weight gain during pregnancy (Romano et al. 2020). In New Hampshire, PFOS, PFOA, and PFNA were associated with higher postpartum weight retention, especially among those with a higher pre-pregnancy BMI (Wang et al. 2023).

In a U.S. study of pregnant women, over 98% of the study population had detectable concentrations of four PFAS, and concentrations varied by race/ethnicity. Total cholesterol was positively associated with PFDA, PFNA, and PFOS, and triglycerides with PFDA, PFNA, PFOS, and PFOA, but PFAS were not associated with fasting insulin (Gardener et al. 2020). Also in healthy U.S. pregnant women, higher PFNA levels were linked to higher blood pressure, and higher PFAS to lower cholesterol/triglyceride levels (Varshavsky et al. 2021). PFAS in pregnant African American women were generally linked to higher vitamin D levels, however (Chang et al. 2021). Also in pregnant African American women (in Atlanta), PFAS mixtures were linked to maternal metabolic changes (including systemic inflammation and oxidative stress) more than single PFAS chemicals (Liang et al. 2023).

In Italy, cholesterol levels varied according to PFAS levels, although the differences were mainly in the third trimester (Dalla Zuanna et al. 2020). In Sweden, in a region with high PFAS exposure levels, there was no association between PFAS and gestational diabetes (Ebel et al. 2023).

In Canada, PFUnA exposure was associated with an lower risk of gestational diabetes (Soomro et al. 2024).

Laboratory Studies

Mice exposed to a low-dose mixture of EDCs (the pesticide atrazine, BPA, PFOA, and dioxin) while pregnant later had hyperglycemia with a persistent elevation in blood glucose two hours after glucose administration in a glucose tolerance test, while these effects were not observed in mixture-exposed non-pregnant females (six months after exposure). These findings provide biological plausibility for the associations seen between chemical exposures during pregnancy and subsequent maternal diabetes and shows that pregnancy itself can play a role in the effects of chemical exposures (Merrill et al. 2021).

Pregnant rats exposed to PFOS developed changes in the expression of genes related to insulin resistance and other

Pregnant rats exposed to PFOS developed changes in the expression of genes related to insulin resistance and other metabolic effects, and linked to fasting blood glucose levels (Yu et al. 2023). Meanwhile, F-53B, a PFOS replacement, caused gut barrier damage and gut microbiota changes linked to impaired glucose tolerance in pregnant mice (Feng et al. 2024). Pregnant rats exposed to PFBS, and alternative to PFOS, had changes to glucose metabolism, including lower glucose levels after a glucose tolerance test (Yu et al. 2024).

Diabetes Management and Complications

Interestingly, the medicinal plant *Tagetes erecta* L., used for the management of diabetes, accumulate PFOA, PFOS, and PFBS, and is a potential source of exposure (Mudumbi et al. 2019).

Blood Glucose Levels

U.S. adults 65 and older with type 2 diabetes who had higher levels of PFNA and PFHxS (both sexes) had higher blood glucose levels (HbA1c), and the same for PFDeA in men (Brosset and Ngueta, 2022).

Cardiovascular Disease

A review finds that PFAS are linked to cardiovascular disease and higher total cholesterol levels (Lind and Lind 2020).

Some cross-sectional human studies show associations between PFAS and heart disease/cardiovascular disease in the U.S. (e.g., Huang et al. 2018).

In China, PFAS are associated with high blood pressure (Bao et al. 2017). In the U.S. National Health and Nutrition Examination Survey (NHANES), there was a non-linear association between high blood pressure and PFAS (Liao et al. 2020), although among participants in the U.S. Diabetes Prevention Program, PFAS levels were generally not associated with blood pressure levels over time (Lin et al. 2020).

One longitudinal study from Sweden found no associations for seven of eight PFAS measured and heart disease (Mattsson et al. 2015), while another long-term Swedish study found higher PFAS levels associated with increased heart disease risk factors (Lind et al. 2018). Also in Sweden, PFAS are associated with other signs of cardiovascular disease (Lind et al. 2017).

A C8 Project study determined that PFAS do not increase risk of stroke among people with or without diabetes (Hutcheson et al. 2019).

U.S. adults with prediabetes who had higher plasma concentrations of some PFAS had higher risk of coronary and thoracic aorta calcification, which are linked to cardiovascular disease (Osorio-Yáñez et al. 2021).

Kidney Disease

In U.S. adults with prediabetes in the Diabetes Prevention Program Trial, those with higher plasma PFAS concentrations at baseline had lower kidney function throughout 14 years of follow-up (Lin et al. 2021).

PFAS are associated with worse kidney function (Jain and Ducatman, 2018), including in the typical U.S. population (Zhao et al. 2019), and in some high-exposu pulations, PFAS are associated with worse kidney function and chronic kidney disease Wang et al. 2019). PFAS in combination with some heavy metals are also associated with worse kidney

function in U.S. adults (Jain 2019). Higher PFAS levels are associated with reduced kidney function in healthy U.S. adolescents as well (Kataria et al. 2015).

In people with high exposure levels, PFAS are associated with better kidney function in people with chronic kidney disease and diabetes, with a stronger relation observed when anemia is present (Conway et al. 2018), and in those with diabetes, a lower risk of heart disease as well (Honda-Kohmo et al. 2019).

The relationship between PFAS and kidney problems be non-linear, as kidney disease advances, it may cause more excretion of PFAS (Jain and Ducatman 2019).

A laboratory study found that exposure to PFOA or PFOS aggravated diabetic kidney injury in cells (Gong et al. 2019).

For those who are undergoing dialysis, the membrane used in the procedure is linked to PFAS levels. Those who used hydrophobic polysulfone (PS) dialysis membranes had lower PFOS and PFOA levels and lower blood glucose levels than those who used other dialysis membranes (Liu et al. 2018). So it seems some dialysis membranes can actually remove PFAS from the blood (Ferrari et al. 2019). Further studies also find lower PFAS levels in people undergoing dialysis (Huang et al. 2023).

Liver Disease

A long-term Swedish study found that "normal" PFAS levels are associated with changes to liver function (Salihovic et al. 2018). PFAS levels in China are associated with fatty liver disease as well (Yang et al. 2023).

A laboratory study exposed rats with (type 1) diabetes to PFAS and found that the exposure caused the accumulation of triglycerides and total cholesterol in the liver, not a good thing (Fang et al. 2015). Chicken embryos exposed to PFOS, especially at the lowest doses, affect genes that control fatty acid metabolism in the liver, also not a good thing (Jacobsen et al. 2018). PFAS exposures are linked to nonalcoholic fatty liver disease (NAFLD) (Armstrong and Guo, 2019), both with biomarkers in humans (Bassler et al. 2019), and to fatty liver-related problems in mothers and offspring exposed during development in mice (Liang et al. 2019).

Both PFAS and diet affected liver steatosis development in mice (Pfohl et al. 2021). At high doses, numerous PFAS and PFAS mixtures caused triglyceride accumulation in liver cells and affected genes related to fatty liver and cholesterol (Sadrabadi et al. 2023).

Some things may be able to counteract these effects. For example, lactic acid bacteria help alleviate PFOA liver toxicity caused by PFOA by adjusting the gut microbiota (Shi et al. 2021).

Mortality

Italian men who worked in a chemical plant producing PFAS had not only very high exposure levels, but also an

increased risk of death, and those with the highest levels of PFOA had a higher rate of death by various specific diseases, including diabetes (Girardi and Merler, 2019).

Additional Complications

Higher PFDA levels increased the association between a family history of diabetes and arthritis (Yang et al. 2024).

References

Diabetes and the Environment