Environmental Sciences Europe

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Perfluorooctane sulfonic acid exposure and diabetes: a cross-sectional analysis of American adults and in vitro experiments

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Abstract

Background Perfluorooctane sulfonic acid (PFOS) exposure has a negative impact on the environment and biological health. However, the relationship between PFOS exposure and diabetes in adults is not clear.

Objective In this study, we included two distinct components: (1) in the cross-sectional analysis, we used data from the National Health and Nutrition Inspection Survey (NHANES) from 2015 to 2018 and eventually included 2539 subjects. The association between PFOS exposure and the risk of diabetes in adults was assessed by a logistic regression model, and further subgroup analysis was carried out according to sex, hypertension status and high cholesterol status. We adjusted for all covariates and found that the positive association between higher PFOS exposure and diabetes remained stable. (2) In vitro experiments were conducted as follows, rat insulinoma β cells (INS-1) were used as experimental materials; cell proliferation activity was detected using the MTT assay; quantitative real-time PCR was used to detect the mRNA expression of insulin; and Western blotting was used to detect insulin protein expression levels.

Results Compared with Q1, the OR of the highest exposure level group (Q4) of PFOS was 1.342(95% CI 0.940, 1.916). We conducted a logistic regression analysis based on sex, hypertension, and high cholesterol stratification. Stratified by sex, we found that the exposure level of PFOS was significantly positively associated with diabetes (*P* for trend < 0.05). Subgroup analysis showed that the positive association between PFOS exposure and diabetes was more significant in nonhypertensive individuals (*P* for trend < 0.01) and those with normal cholesterol levels (*P* for trend < 0.001). To further determine the causal relationship between PFOS exposure and diabetes, we used rat insulinoma β cells (INS-1) as experimental materials to study the effect of PFOS exposure on insulin secretion. We found that PFOS exposure significantly affected insulin secretion and insulin mRNA and protein expression.

Conclusions In summary, PFOS exposure is positively associated with the risk of diabetes. However, further studies are needed to confirm our results.

Keywords PFOS, Diabetes, NHANES, Logistic regression

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Background

According to the latest report from the Guardian, a new study found that toilet paper in multiple parts of the world contains toxic substances (per- and polyfluoroalkyl substances, PFAS). That study included a survey of 21 major toilet paper brands in North America, Western Europe, Africa, Central America, and South America [1]. In recent years, PFAS have been extensively used in manufacturing compounds, resulting in their widespread entry into the global environment. PFAS are considered a new class of persistent organic pollutants due to their difficulty in degradation and bioaccumulation [2, 3]. PFAS compounds are eventually partially converted into perfluorooctane carboxylic acid (PFOA) and perfluorooctane sulfonic acid (PFOS), but especially PFOS, which accumulates hundreds of times more dioxins in organisms [4, 5, 7].

PFOS, as a persistent new type of environmental pollutant, has been found to have toxic effects on biological reproduction, development, nerves, immunity, genetics, and other aspects [6]. In addition to obvious organ toxicity, the role of PFOS in the occurrence of metabolic related diseases (such as diabetes and hypertension) is increasingly concerning [8, 9]. The results of animal experiments indicate that exposure to PFOS during pregnancy significantly affects the blood sugar levels of experimental animals. Insulin is a hormone that is produced by pancreatic β cell secretion. It is stimulated by various exogenous or endogenous substances and is the only hormone in the body that can lower blood sugar [26].

In a previous study, our team found that PFOS induced glucose-stimulated insulin secretion damage in INS-1 cells [25]. On the basis of previous studies, this study explored the relationship between PFOS exposure and diabetes.

In this study, we aimed to assess the relationship between exposure to PFOS and diabetes. Since October 2013, EPA required under the SNUR rules that items such as textiles, carpets, furniture, electronic products, and household appliances that may contain certain PFAS chemicals cannot be imported into the United States without EPA review, using data from the U.S. National Health and Nutrition Examination Survey (NHANES) for 2015–2018, a large-scale population-based epidemiological study on the concentration of perfluorooctane sulfonates in serum, with sufficient power. To further determine the relationship between PFOS exposure level and diabetes, we used rat insulinoma β cells (INS-1) as experimental materials to investigate the effect of PFOS exposure on insulin secretion.

Materials and methods

Cross-sectional analysis

Study population

The population data used in this study were extracted from the National Health and Nutrition Examination Survey (NHANES) in the United States. Details of the survey design and methods can be found on the NHANES website. In this study, we merged the population from the NHANES database from 2015 to 2016 and 2017 to 2018 for four consecutive years.

From 2015 to 2018, there were a total of 19225 participants in the NHANES database. We excluded people under the age of 18 and were left with 15827 participants. We further excluded people with missing basic information and were left with 12317 participants. We screened 2788 participants with PFOS concentration data and excluded people with missing information on hypertension and high cholesterol, leaving 2610 participants. After further excluding the population lacking diabetes information, 2539 people were finally included in the study. The detailed screening process is shown in Fig. 1.

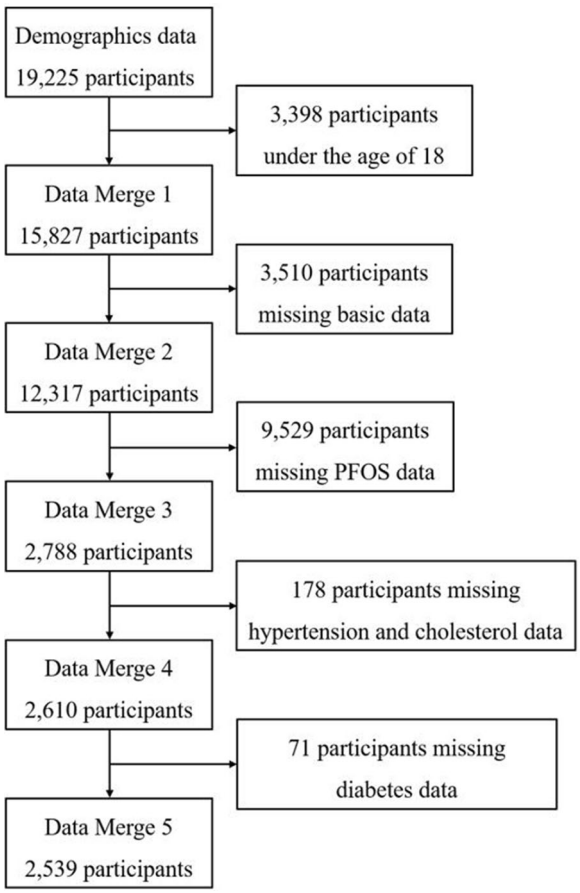

Fig. 1 Flowchart of data merge

Serum PFOS concentration detection

All serum samples from the population were subjected to CDC unified analysis and quality control. The concentration of PFOS was detected using solid-phase extraction and high-performance liquid chromatography turbo ionization tandem mass spectrometry [10]. The limit of detection (LOD) is 0.1 ng/mL, and when the concentration is below LOD, LOD/$\sqrt{2}$ is used instead. We performed a logarithmic conversion (log10) on the serum PFOS concentration as the concentration data showed a significantly skewed distribution. Sm-PFOS is a branched isomer of PFOS, and n-PFOS is a linear isomer of PFOS. We summed the concentrations of branched and linear isomers of PFOS to obtain the "total" concentrations: ∑PFOS = n-PFOS + Sm-PFOS [11].

Evaluation of covariates

The selection of covariates is based on the factors found in the literature that are significantly related to the occurrence of diabetes [12, 13]. The covariates include demographic data such as age, race, sex, education level, and household income level. Personal data included body mass index (BMI). Age was divided into three groups (18–39, 40–64, and ≥ 65 years), household income level was divided into two groups based on the income poverty ratio [14] (< 1.3 households were low-income families, and ≥ 1.3 households were medium- to high-income families), and BMI was divided into three groups (< 18.5, 18.5–24.9, ≥ 24.9 kg/m^2). Health factors include hypertension and high cholesterol.

In vitro experiments

Cell culture and preparation of PFOS solution

INS-1 cells were cultured in RPMI-1640 medium containing 10% fetal bovine serum (BI, USA), 100 U/ml penicillin, 100 μg/ml streptomycin (BI, USA), 5.6 mmol/L glucose (Sigma, USA), 1 mmol/L sodium pyruvate (Sigma, USA), and 50 μmol/L 2-mercaptoethanol (Sigma, USA). Routine culture was performed in a carbon dioxide incubator (Heraeus, Germany) at 37.0 ℃ with a volume fraction of 5%.

Logarithmic growth phase cells with good growth status were added to the culture medium to make a uniform cell suspension and plated into a 96-well plate at a density of 5000 cells per well. Each group had 6 wells, and the PFOS-exposed cell concentrations were 0, 12.5, 25, 50, 100, and 200 μmol/L (1 μmol/L = 500.13 ng/mL). Cell activity was measured using an MTT assay kit (Kaiji, Nanjing, China). Three samples were set for each group of cells, the error bar is the result of repeated holes in the same group of experiments, all of which were cultured and stimulated for 48 h in a carbon dioxide incubator at 37.0 ℃ with a volume fraction of 5%. The cells were collected for subsequent RNA and total protein extraction.

PFOS powder was weighed and dissolved in DMSO. The PFOS solution was disinfected and filtered through a 0.22-μm filter. Based on the results of the MTT test, we chose the doses that had no significant effect on cell viability as the exposure doses for subsequent experiments.

Cell viability

Cell viability was assessed with the MTT assay. After 48 h of exposure, the exposure medium was removed from the wells and replaced with 20 μl of thiazole blue solution (0.5 mg/ml). The cells were incubated at 37 °C for 4 h. After incubation, the solution was removed, 100 μl DMSO solution was added to each cell, and the plate was shaken for 10 min. The absorbance was measured at 492 nm with a microplate reader (Thermo, USA).

Insulin ELISA detection

INS-1 cells with good logarithmic growth status were inoculated onto a 24-well culture plate (500 μl/well), and after 24 h, the cells were exposed to different doses of PFOS (0, 12.5, 25, 50 μmol/L) for 48 h. The old culture medium was discarded, and after PBS cleaning, the cells were exposed to Krebs–Ringer bicarbonate HEPES (KRBH) buffer containing 0.5% BSA and 3.0 mM glucose. After 1 h, the old culture medium was discarded, and KRBH buffer containing 16.7 mM glucose was added. The cells were incubated in the incubator for 1 h. After incubation, the supernatant was collected to measure insulin secretion levels. Simultaneous determination of protein concentration for standardization of insulin level data.

Real-time fluorescence quantitative PCR (RT-qPCR)

Total RNA was extracted and reverse transcribed to synthesize cDNA. The reaction mixture was prepared using a qPCR kit, and real-time fluorescence quantitative polymerase chain reaction (RT-qPCR) was used to detect insulin mRNA expression levels. β-Actin was chosen as the housekeeping gene, and the relative mRNA expression levels were calculated by the $2^{-\Delta\Delta CT}$ method. Primer information is shown in Table 1.

Western blot

Total protein was extracted, and the total protein concentration was detected by a BCA protein assay kit. SDS–PAGE was used, and the proteins were then transferred to PVDF membranes. TBST containing 5% skimmed milk powder was sealed for 1 h, incubated overnight with specific primary antibody diluent (1:1000) at 4 ℃, incubated with secondary antibody diluent (1:2000) the next day for 1 h, washed with TBST three times after

Table 1 Primer's sequences

Gene	GenBank no.	Forward primers (5′–3′)	Reverse primers (5′–3′)	Amplification product size
Insulin	NM_019130.2	TCTTCTACACAC CCATGTCCC	GGTGCAGCACT GATCCAC	149 bp
β-actin	NM_031144.3	GACTACCTCATG AAGATCCTGACC	TCTCTTTAATGT CACGCACGATT	85 bp

completion, exposed with a chemiluminescence imaging system (Bio-Rad, USA), and the gray value was measured with ImageJ software to calculate the relative expression amount of target protein/internal reference protein.

Statistical analyses

This study used SPSS 26.0, Excel and R version 4.1.2 software for all statistical analyses. NHANES data are nationally representative due to a complex sampling design and the use of sample weights. We weighted the data according to the sample weight calculation method recommended by NHANES. In this study, the 4-year data from 2015 to 2018 are combined, and the 4-year weight is equal to 1 prime 2 of the 2-year weight. If a continuous variable conformed to the normal distribution, it was represented by mean ± standard deviation (Mean ± SD) and compared by t test; the error bar in the figure shows the standard deviation. If the skewed distribution is represented by the median (quartile), it was compared by the Mann–Whitney U test; the number of use cases (percentage, %) of a categorical variable was assessed by the Chi-square test.

The serum PFOS concentration was divided into four groups according to the quartile (Q1: $< P_{25}$, Q2: P_{25}-P_{50}, Q3: P_{50}-P_{75}, Q4: $\geq P_{75}$). Using the Q1 group as the reference group, a weighted logistic regression model was used to analyze the association between PFOS exposure levels and diabetes. The results are reported as odds ratio (OR), 95% CI (confidence interval, 95% CI), and *P* values. There are no covariates adjusted in Model 1. Sex, country of birth, race and BMI were adjusted in Model 2, and all covariates were adjusted in Model 3. To investigate whether there are differences in associations between different sexes, hypertension and high cholesterol, we stratified the results by sex (male and female), hypertension and high cholesterol. A *P* value < 0.05 indicated a statistically significant difference.

Result

Baseline characteristics of the study population

There were 2539 people included in this study. Compared with the nondiabetic population, the educational level of the included subjects with diabetes was lower ($P < 0.001$), and the included subjects with diabetes had higher levels of hypertension, high cholesterol, n-PFOS, Sm-PFOS and ∑PFOS ($P < 0.001$) (Table 2).

Association between PFOS exposure and diabetes

In Model 1, no variable was adjusted. Higher PFOS exposure was associated with a higher risk of diabetes, and the trend test was statistically significant (*P* for trend < 0.001). Compared with Q1, the OR of the group with the highest exposure level of PFOS (Q4) was 2.317 (95% CI 1.680, 3.196). In Model 2, we adjusted for sex, country of birth, race and BMI and found that there was still a positive association between higher PFOS exposure levels and diabetes, and the trend test was statistically significant (*P* for trend < 0.001). Compared with Q1, the OR of the highest PFOS exposure level group (Q4) was 2.452 (95% CI 1.770, 3.396). In Model 3, we adjusted for all covariates and found that the positive association between higher PFOS exposure and diabetes was still stable. Compared with Q1, the OR of the highest exposure level group (Q4) of PFOS was 1.342 (95% CI 0.940, 1.916) (Table 3).

Subgroup analysis

To investigate the association between PFOS exposure levels and diabetes, we conducted a logistic regression analysis based on sex, hypertension, and high cholesterol stratification. When stratified by sex (sample size: male, $n = 1357$; female, $n = 1182$) and adjusted for age, race, ratio of family income to poverty, education, hypertension, and high cholesterol level, we found that the exposure level of PFOS was significantly positively associated with diabetes (*P* for trend < 0.05). When stratified by hypertension (sample size: hypertension, $n = 856$; nonhypertension, $n = 1683$) and adjusted for sex, age, race, ratio of family income to poverty, education, and high cholesterol level, there was a statistically significant positive association between PFOS exposure and diabetes in nonhypertension people (*P* for trend < 0.01). When stratified by high cholesterol (sample size: high cholesterol level, $n = 802$; non-high cholesterol level, $n = 1737$) and adjusted for sex, age, race, ratio of family income to poverty, and education, there was a statistically significant positive association between PFOS exposure level and diabetes in people with normal cholesterol levels (*P* for trend < 0.001) (Fig. 2).

Table 2 Characteristics of the study population

Characteristics	Diabetic (%/P_{25},P_{75})	Nondiabetic (%/P_{25},P_{75})	x^2/Z	*P* value
Sex				
Male	194(53.0)	1163(53.5)	0.033	0.855
Female	172(47.0)	1010(46.5)		
Country of birth				
America	245(66.9)	1537(70.7)	2.152	0.155
Others	121(33.1)	636(29.3)		
Race				
Mexican American	69(18.9)	331(15.2)	19.818	0.001
Other Hispanic	57(15.6)	219(10.1)		
Non-Hispanic White	99(27.0)	785(36.1)		
Non-Hispanic Black	85(23.2)	467(21.5)		
Non-Hispanic Asians	38(10.4)	259(11.9)		
Others	18(4.9)	112(5.2)		
Age				
18–39	28(7.6)	790(36.4)		
40–64	172(47.0)	976(44.9)	178.808	< 0.001
> 65	166(45.4)	407(18.7)		
Ratio of family income to poverty				
Low-income families	136(37.2)	666(30.6)	6.142	0.013
Medium- to high-income families	230(62.8)	1507(69.4)		
BMI				
< 18.5	66(18.0)	419(19.3)		
18.5–24.9	100(27.3)	635(29.2)	1.244	0.545
≥ 24.9	200(54.6)	1119(51.5)		
Education				
Below high school	102(27.9)	415(19.1)		
High school graduate	153(41.8)	794(36.5)	28.734	< 0.001
College graduate or above	111(30.3)	964(44.4)		
Hypertension				
Yes	263(71.9)	593(27.3)	278.420	< 0.001
No	103(28.1)	1580(72.7)		
High cholesterol level				
Yes	220(60.1)	582(26.8)	160.989	< 0.001
No	146(39.9)	1591(73.2)		
n-PFOS (ng/mL)	4.1(2.2,7.7)	3.1(1.8,5.6)	− 4.461	< 0.001
Sm-PFOS (ng/mL)	1.9(1.0,3.4)	1.3(0.7,2.4)	− 6.236	< 0.001
∑PFOS (ng/mL)	6.3(3.2,11.2)	4.6(2.6,8.1)	− 5.441	< 0.001

Table 3 Association between PFOS exposure and diabetes

∑PFOS	Model 1		Model 2		Model 3	
***n* = 2539**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Q1	Reference		Reference		Reference	
Q2	1.115 (0.780,1.595)	0.550	1.118 (0.791,1.599)	0.543	1.042 (0.710,1.531)	0.832
Q3	1.554 (1.110,2.117)	0.010	1.574 (1.121,2.211)	0.009	1.117 (0.772,1.617)	0.556
Q4	2.317 (1.680,3.196)	< 0.001	2.452 (1.770,3.396)	< 0.001	1.342 (0.940,1.916)	0.105
P for trend		< 0.001		< 0.001		0.064

Quartiles (Q) of ∑PFOS (ng/ml): Q1: < 2.7; Q2: 2.7–4.8; Q3: 4.8–8.5; Q4: ≥ 8.5

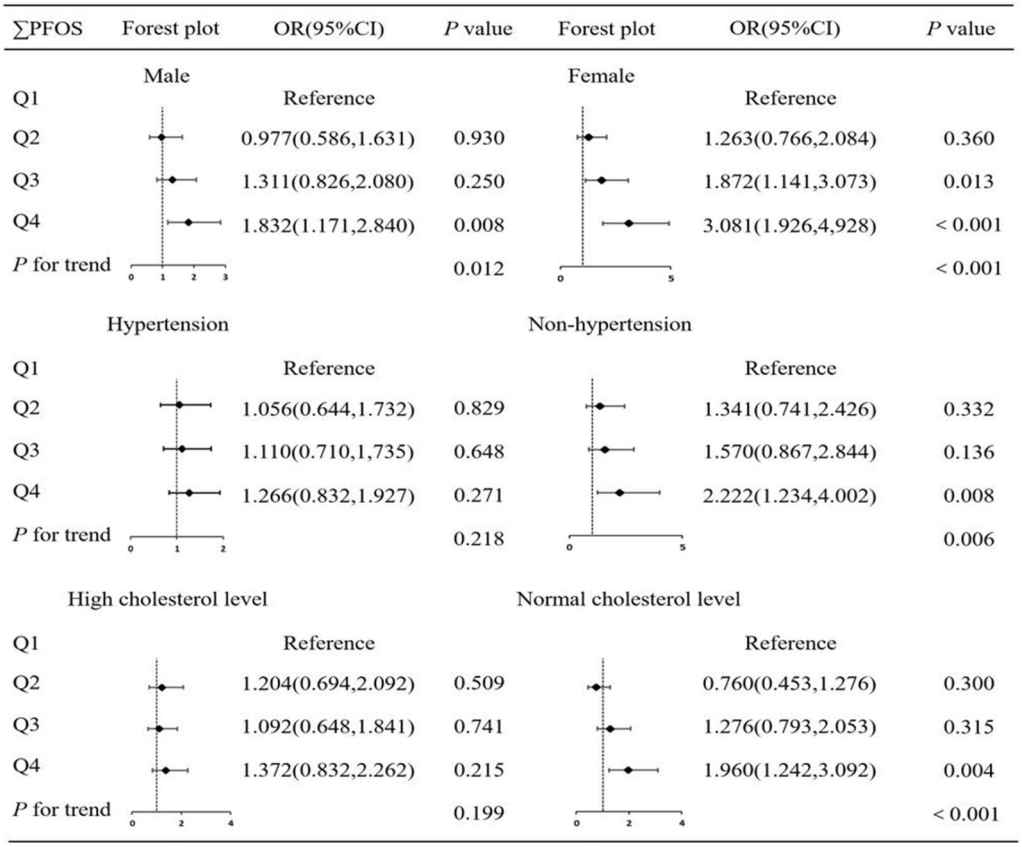

Fig. 2 Subgroup analysis of the estimated changes

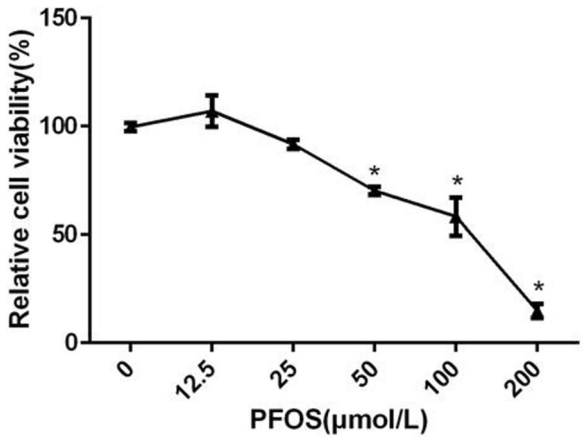

Fig. 3 The effect of exposure to different doses of PFOS on the activity of INS-1 cells * $P < 0.05$ vs. control

The effect of exposure to different doses of PFOS on INS-1 cell activity

As shown in Fig. 3, under the treatment of different doses of PFOS, the activity of INS-1 cells showed a trend of first increasing and then decreasing. Compared with the control group, the cell activity significantly decreased after 48 h of exposure to 50, 100 and 200 μmol/L PFOS ($P < 0.05$).

In this study, based on the MTT detection results, we selected exposure doses that did not significantly affect cell viability for subsequent experiments. In subsequent exposure experiments, we selected 12.5, 25, and 50 μmol/L PFOS as exposure doses.

The effect of different doses of PFOS exposure on insulin secretion levels in INS-1 cells under glucose stimulation conditions.

As shown in Fig. 4, compared with the control group, the insulin secretion levels of INS-1 cells showed a decreasing trend under glucose stimulation conditions after 48 h of PFOS exposure. The exposure doses of PFOS were 12.5, 25, and 50 μmol/L, and the relative insulin secretion levels decreased by 31.59%, 36.64%, and 43.69%, respectively ($P < 0.01$).

Relative mRNA expression levels of insulin

The relative expression of insulin mRNA in INS-1 cells showed a decreasing trend. Compared with the control group, after 48 h of exposure to 50 μmol/L PFOS, the

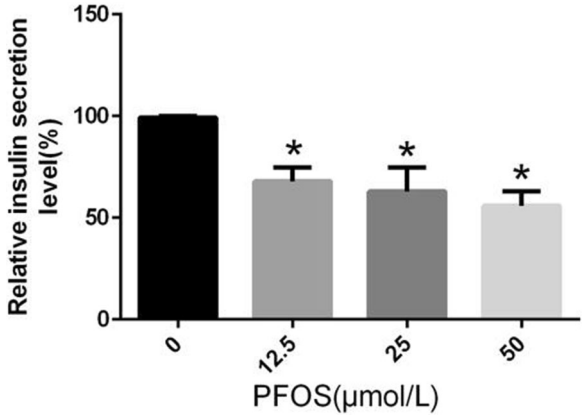

Fig. 4 Insulin secretion levels in INS-1 cells after PFOS exposure. * $P < 0.01$ vs. control

relative expression of insulin mRNA in INS-1 cells was significantly reduced ($P < 0.05$) (Fig. 5).

Relative expression of insulin protein

The relative expression of insulin protein in INS-1 cells showed a decreasing trend. After exposure to 25 and 50 μmol/L PFOS for 48 h, the relative expression of insulin protein in INS-1 cells decreased by 34.99% and 78.52% ($P < 0.05$) (Fig. 6).

Discussion

The impairment of islet β-cell function was the main cause of type-2 diabetes, and the impairment of islet β-cell function was mainly caused by insufficient insulin secretion or insulin resistance, which could not effectively reduce blood sugar. Type-2 diabetes accounts for approximately about 90–95% of diabetes cases and is one of the most complex metabolic diseases [15]. PFOS

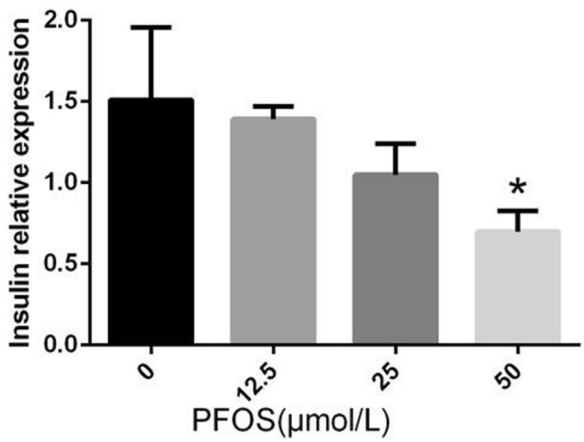

Fig. 5 Relative mRNA expression levels of insulin in INS-1 cells after PFOS exposure * $P < 0.05$ vs. control

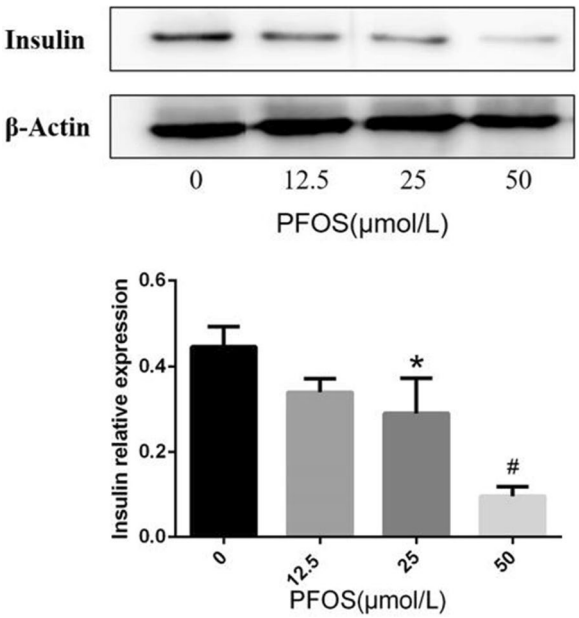

Fig. 6 Relative expression level of Insulin protein in INS-1 cells after PFOS exposure * $P < 0.05$ vs. control

has been proven to have immunotoxicity and reduce the immune function of the body [16]. Because PFOS is stable and has high biological aggregation, it will have a great impact on the immune metabolic function of the body.

This study explored the relationship between serum PFOS exposure level and the risk of diabetes in adults based on NHANES data from 2015 to 2018. The results showed that higher serum PFOS exposure was associated with a higher risk of diabetes. Through further experimental research, we confirmed the causal relationship between PFOS exposure and diabetes.

In this study, older age, higher education level, higher income, history of hypertension and high cholesterol, and increased serum PFOS concentration were significantly associated with an increased risk of diabetes. The study in Chinese pregnant women found that the median concentration of serum PFOS was 2.78 ng/mL, which was lower than that of 4.8 ng/mL in this study. A study conducted in Sweden over 70 years old reported serum PFOS levels [17], and the median serum PFOS concentration in this population was 13.2 ng/mL. Studies conducted in the Korean population reported similar results. The median serum PFOS concentration in the general population was 10.51 ng/mL, which was higher than the median serum PFOS concentration in the population investigated in this study. By consulting the literature and comparing the concentration of serum PFOS in different countries and regions of the

world, it was found that the concentration of PFOS in China was the highest (52.7 ng/mL) and that in India was the lowest (1.85 ng/mL).

This study found that there was a positive association between serum PFOS and the risk of diabetes. A dose–response meta-analysis showed a "parabolic-shaped" association between perfluorooctanoate acid (PFOA) exposure and T2DM risk [27]. A prospective study in the Swedish population found no significant association between serum PFOS and the risk of type-2 diabetes [19]. Although the study adopted a prospective design, the study included 124 pairs of subjects, and the small sample size limited the stability of the conclusions. More prospective studies are needed to explore the relationship between serum PFOS levels and the risk of diabetes in the future.

To verify the causal relationship between PFOS exposure and diabetes, we carried out further experimental studies. We used the rat insulinoma cell line INS-1 as the experimental object and interfered with different concentrations of PFOS solution. In the 25 μmol/L exposure group, the proliferation ability of INS-1 cells decreased slightly, indicating that a low concentration of PFOS did not significantly decrease cell proliferation, but at the same low concentration, the ability of nerve cells [20] and hepatocytes [21] to reduce cell proliferation was very obvious, which may be due to the strong compensatory ability of INS-1 cells or because their secretory function is different from that of other cells. INS-1 cells maintain a slightly stable state of cell proliferation in low concentrations of PFOS solution. With increasing PFOS exposure concentration, the cell survival rate was approximately 50% in the 100 μmol/L exposure group and less than 20% in the 200 μmol/L exposure group, indicating that the proliferation ability decreased in a straight line after exceeding the cell compensatory capacity. Insufficient insulin secretion is the core mechanism of diabetes [22]. Insulin therapy is the main way to reduce blood sugar in patients with diabetes [24]. Clinically, patients with diabetes are also treated with insulin to reduce blood glucose concentrations [23]. PFOS could affect the normal physiological function of GSIS in INS-1 cells [25]. In this study, compared with the control group, the insulin secretion level decreased significantly with increasing PFOS exposure dose. At the same time, we detected the insulin mRNA and protein expression levels. The results showed that insulin mRNA and protein expression levels decreased gradually with increasing PFOS exposure dose, especially in the 50 μmol/L exposure group. It is suggested that under the influence of PFOS exposure, the expression of the insulin gene tends to decrease, which will increase the risk of elevated blood sugar and make the body more likely to develop diabetes.

Conclusion

In summary, through the verification of experimental studies, we found that there is a significant positive association between serum PFOS and the risk of diabetes, especially in people with hypertension and high cholesterol. More large-sample prospective studies are needed to verify the conclusions of this study in the future.

Acknowledgements

The authors would like to thank the participants for their contribution to this study.

Author contributions

KL and LS: conceptualization, methodology, writing–reviewing and editing. HX and ZL: software, data curation and substantive revision. KL, LS, LS and SL: cell culture, experimental operations. YT and LS: validation, supervision. HX: project administration, funding acquisition. All the authors have read and approved the final manuscript.

Funding

This study was funded by the Chunhui Project Foundation of the Education Department of China (Z2016038).

Availability of data and materials

All data analyzed or generated during this study are included in this published article.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of Ningxia Medical University. The approved ID is No. 2016-132.

Consent for publication

All participants provided written informed consent, and NHANES obtained approval from the Ethics Review Committee of the National Center for Health Statistics.

Competing interests

The authors report no competing interests.

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Received: 25 June 2023 Accepted: 21 October 2023
Published online: 28 October 2023

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