



Article

The Influence of Adiposity Levels on the Relation between Perfluoroalkyl Substances and High Depressive Symptom Scores in Czech Adults

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Abstract: The extensive use and bioaccumulation of Perfluoroalkyl Substances (PFAS) over time raise concerns about their impact on health, including mental issues such as depression. This study aims to evaluate the association between PFAS and depression. In addition, considering the importance of PFAS as an endocrine disruptor and in adipogenesis, the analyses will also be stratified by body fat status. A cross-sectional study with 479 subjects (56.4% women, 25–89 years) was conducted. Four PFAS were measured: perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), and perfluorooctane sulfonate (PFOS). The Poisson regression model was applied using robust error variances. The fully adjusted model included age, sex, educational level, income, smoking, physical activity, body fat percentage, and the questionnaire to assess depression. The prevalence of depression and high body fat was 7.9% and 41.1%, respectively. Only PFOA was significantly associated with depression in the entire sample (prevalence rate (PR): 1.91; confidence interval (CI95%): 1.01–3.65). However, in the group with normal adiposity, PFOA (3.20, CI95%: 1.46–7.01), PFNA (2.54, CI95%: 1.29–5.00), and PFDA (2.09, CI95%: 1.09–4.00) were also significant. Future research should investigate the role of obesity as well as the biological plausibility and possible mechanisms increasing the limited number of evidences between PFAS and depression.

Keywords: perfluoroalkyl substances; PFOA; PFDA; PFNA; PFOS; depression; body fat; adults



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1. Introduction

For a period in excess of eight decades, per- and polyfluoroalkyl substances (PFAS) have undergone extensive synthesis and application in a myriad of commercial and industrial contexts [1]. These synthetic chemicals can be found in everyday items such as electronics, automotive supplies, and food packaging. Additionally, they can be present in non-stick cookware, stain- and water-resistant coatings, cleaning products, waxes, and fire-fighting foams [2]. Their exceptional durability and resistance to decomposition render PFAS compounds persistently impactful on the environment, thereby posing potential long-term ramifications for human health. The ongoing and widespread exposure to PFAS is principally facilitated through diverse pathways, namely, ingestion via drinking water and dietary intake; inhalation of outdoor air; and contact with indoor dust and soil [3,4]. Consequently, PFAS exposure predominantly occurs through the intricate interplay of

ingestion and absorption into the bloodstream via the gastrointestinal tract, though alternative routes such as inhalation and dermal absorption also contribute significantly [5]. The structural underpinning of PFAS lies in a succinct yet robust carbon-fluorine bond, endowing these compounds with chemical stability and remarkable resistance to organic degradation. This structural feature imparts bioaccumulation tendencies to substances containing PFAS, as they persist and accumulate over temporal scales [6]. The presence of PFAS in receptacles treated with these compounds raises considerable concerns within the area of human health, given the facile migration of these substances into consumables, thereby resulting in elevated PFAS levels in human consumption [7]. The multifaceted interaction of PFAS with environmental matrices and the consequential implications for human exposure underscore the imperative nature of comprehensive investigations into the ecological and health impacts of these persistent synthetic compounds.

Two types of PFAS, specifically perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), are of particular concern. Notably, these substances exhibit prolonged half-lives of four to five years in the human physiological milieu, coupled with the capacity to traverse the placental barrier, thereby instigating bioaccumulation processes [7]. The presence of PFAS in serum poses multifaceted implications for various physiological systems within diverse health conditions. Their impact encompasses the modulation of thyroid, kidney, liver, lung, and immune functions, as well as lipid metabolism, thereby elevating the risk of metabolic syndrome [8]. PFAS are also identified in the serum of individuals afflicted by anxiety and depression [9]. In fact, the current body of literature regarding the potential correlation between PFAS exposure and anxiety/depression-like behavior is still inconclusive and lacks consistency.

However, experimental evidence does suggest that there may be an impact on anxiety-like behavior resulting from exposure to PFAS [10] by interfering with the hypothalamic-pituitary-adrenal (HPA) axis [11,12]. Exposure to PFAS increases the risk of developing or worsening mental health disorders due to their neurotoxic effects [13–15]. Experimentally, these findings were also modeled specifically in PFOA-exposed mice, which exhibited anxiety-like behavior and increased corticotrophin-releasing hormone (CRH) expression in the basolateral amygdala complex (BLA), which have been found to participate in the pathogenesis of several psychiatric disorders [16]. In humans, prenatal PFAS exposure seems to be a significant risk factor for depressive symptoms in pregnant women [17], along with higher BASC-2 (Behavioral Assessment System for Children-2) scores for externalizing problems, hyperactivity, aggression, and conduct problems [18].

Depressive disorder stands as a significant contributor to the global burden of disability-adjusted life years, with over 300 million individuals affected in 2015, constituting 4.4% of the world's population [19,20]. In Europe, approximately 31 million adults suffer from depression [21]. However, there is a lack of research on the possible negative impact of PFAS on mental health. Thus, our goal is to examine the association between plasma PFAS levels and depression prevalence in a representative population-based sample of adults and older adults. Given the recognized role of PFAS as endocrine disruptors, with a plausible influence on adipose tissue mass [22,23], and the established interplay between depression and obesity, notably through the hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis [24,25], our inquiry extends to elucidate potential connections with a focus on body fat status. The intricate relationship between depression and obesity is particularly relevant in the context of stress-induced mechanisms [26]. Thus, we pay particular attention to the associations adjusted and stratified by body fat status.

2. Materials and Methods

2.1. Study Design and Population

The participants in this study are part of a probability population-based sample, which is representative of the Kardiovize study, an epidemiological cohort comprising 2430 individuals aged between 25 and 89. The study randomly selected 479 individuals, consisting of 279 from the youngest cohort and 200 aged 65 or older. Ethical considerations

adhered to the principles outlined in the Helsinki Declaration, ensuring the protection of participant rights and well-being. All individuals involved in the study provided explicit and informed consent before participation. The study protocol received approval from the ethics committee of St. Anne's University Hospital in Brno, Czech Republic.

2.2. Demographic Variables

Health professionals affiliated with the International Clinical Research Center at St. Anne University Hospital in Brno employed the Research Electronic Data Capture (REDCap), a web-based electronic survey tool, to facilitate face-to-face interviews with patients. This methodological approach was chosen to gather comprehensive data on various facets of the participants' demographic profile. The survey encompassed a spectrum of demographic variables, providing insights into crucial aspects of the participants' backgrounds. These variables included age, educational attainment, and socioeconomic status, as well as habits related to smoking and alcohol consumption. The educational level was stratified into three categories: primary, secondary, or higher education. Concurrently, the socioeconomic status was delineated based on monthly household income, with categorizations of low (<EUR 1200), middle (EUR 1200–1800), or high (>EUR 1800).

Smoking status was characterized as either "non-smokers" or "current smokers", the latter encompassing individuals who reported smoking daily or less than daily over the past year. Participants' alcohol consumption habits were dichotomized into "non-drinkers", which included abstainers and those who had refrained from drinking in the previous 12 months, and "drinkers", based on their reported alcohol intake over the last week, quantified in terms of standard drinks. A standard drink was standardized across various alcoholic beverages, equating to a glass of wine, a bottle of beer, or a shot of spirits, each containing approximately 10 g of ethanol.

Diabetes was operationally defined as either having a fasting blood glucose level equal to or exceeding 126 mg/dL (7.0 mmol/L) [27] or self-reporting a diagnosis of diabetes. Hypertension criteria included a systolic blood pressure of 140 mmHg or higher, a diastolic blood pressure of 90 mmHg or higher [27], a personal history of hypertension, or the use of antihypertensive medication. Waist circumference, a key anthropometric measure, was assessed midway between the bottom of the ribs and the top of the hips using a manual tape, providing an objective index of central adiposity. Physical activity was assessed through the Long version of the International Questionnaire of Physical Activity [28], where participants were considered "active" if they engaged in vigorous physical activity for three or more days per week, for at least 20 min per day, or moderate-intensity physical activity or walking for five or more days, for at least 30 min per day, or any combination of walking, moderate-intensity, or vigorous-intensity activities for five or more days per week, achieving a minimum of at least 600 metabolic equivalents for the task (MET)-min/week. Participants who did not perform any of the activities above were classified as "insufficiently active".

2.3. Depression

To assess depression symptoms in those under the age of 65, we employed the Patient Health Questionnaire (PHQ-9) [29]. This clinical screening instrument comprises nine questions designed to align with the symptoms of depression as delineated in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). The PHQ-9 generates a comprehensive score ranging from 0 to 27, with a designated depression cutoff score of ≥ 10 . For individuals over 65, we utilized the validated Center for Epidemiologic Studies Depression scale (CES-D), which evaluates the number and duration of depressive symptoms through 10 questions. A standard cutoff score of ≥ 10 out of 30 possible points applies to the CES-D [30].

2.4. Measurement of PFAS Serum Concentrations

Samples of frozen blood serum underwent meticulous analysis to ascertain the presence of four PFAS compounds: perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PFDA). This analytical procedure was conducted at the RECETOX laboratory, a highly accredited trace analytical facility. The serum samples were subjected to a systematic processing sequence, initiated by allowing them to attain room temperature and subsequently homogenizing them using a vortex. Subsequently, 200 μ L of each sample was meticulously transferred to a 96-well Phree Phospholipid Removal Plate (Phenomenex, Torrance, CA, USA), followed by filtration and relocation to glass vials. The samples were then evaporated under a nitrogen stream until the last drop of solvent was obtained. Finally, 50 μ L of methanol and 50 μ L of NH₄Ac in water were added before the samples underwent analysis utilizing an LC-MS/MS system—specifically, the LC Agilent 1290 connected with QTrap 5500 (ABSciex, Framingham, MA, USA). The chromatographic separation was facilitated by a SYNERGI 4 μ Fusion MAX-RP 80 \AA 100 mm \times 2 mm column (Phenomenex, Torrance, CA, USA), with a pre-column Phenomenex SecurityGuard C18 4 \times 2 mm. The analytical performance was carefully gauged, with the limit of quantitation (LOQ) for each compound set at 3 standard deviations (SD) of blank values and the limit of detection (LOD) at 1.5 SD. All four compounds (PFOA, PFOS, PFNA, and PFDA) were successfully detected in all samples using this robust methodology. Specifically, PFOA was found at a LOD of 0.020 ng/mL and a LOQ of 0.070 ng/mL, PFOS at a LOD = 0.030 ng/mL and a LOQ = 0.090 ng/mL, PFNA at a LOD = 0.004 ng/mL and a LOQ = 0.012 ng/mL, and PFDA at a LOD = 0.004 ng/mL and a LOQ = 0.010 ng/mL. The trace amounts detected underscore the sensitivity and precision of the analytical approach employed in elucidating the presence of these PFAS compounds in the blood serum samples.

2.5. Body Composition

To assess weight and body composition, an InBody 370 scale equipped with multi-frequency bioelectrical impedance analysis (BIA) and an eight-point tactile electrode system (BIOSPACE Co., Ltd., Seoul, Republic of Korea) was employed. It utilizes a direct segmental multi-frequency technique predicated on the conceptualization of the human body as five interconnected cylinders. The device leverages direct impedance measurements to delineate various body compartments [31]. Operating at multiple frequencies (5, 50, and 250 kHz), the BIA technique provides a nuanced analysis of the body's composition. By assessing the spectrum of electrical frequencies, the technique extrapolates critical parameters such as the phase angle [32], intracellular water (ICW), and extracellular water (ECW) compartments within the total body water (TBW) across distinct body segments. Specifically, low frequencies are utilized to gauge the conductive properties of extracellular fluid, while high frequencies encompass the conductive properties of both intracellular and extracellular fluids. Lean body mass is derived by summing the intracellular and extracellular fluids and dividing the total by 0.73 [31]. The ensuing difference between total body weight and lean body mass yields the fat mass component. Moreover, the InBody 370 features an auto-calibration mechanism that activates each time the device is powered on, enhancing its reliability. This analytical method can function as a viable alternative to dual-energy X-ray absorptiometry (DXA), especially when the latter is unavailable [33]. High body fat cutoff points were established at 25% for men and 35% for women [34].

2.6. Statistical Analysis

In this study, a diverse array of methods was employed to represent both continuous and categorical variables. Continuous variables were characterized using the median and interquartile range, while categorical variables were presented as proportions in percentages. To enhance the normality of PFAS concentrations, a natural logarithm (ln) transformation was applied prior to analysis.

In addition to calculating the geometric mean, median, minimum, and maximum values of the transformed PFAS concentrations, the study utilized an adjusted Poisson regression model with robust error variances. This model was employed to assess prevalence rates (PR) concerning the association between continuous PFAS levels and dichotomous variables (presence/absence of depression). The utilization of the adjusted Poisson regression model facilitated the estimation of precise 95% confidence intervals (CI). To identify confounding variables, the researchers consulted existing literature [35] and systematically evaluated the available variables. The variable “type of questionnaire” was incorporated as a confounder, given the utilization of two different questionnaires to classify depression status. A covariate examination was conducted, and the outcomes were presented as PR. All statistical analyses were executed using STATA software (version 14.0, StataCorp, College Station, TX, USA), with a predetermined statistical significance level set at $\alpha \leq 0.05$.

3. Results

A group of 467 individuals underwent examination, and the median age was found to be 52 years (with an interquartile range of 30). The female population accounted for 56.3% of the total group. Depression was found to affect 7.9% of the population, with a higher prevalence observed among women. Individuals who were classified as having “insufficient physical activity” had a higher prevalence of depression, while those who engaged in high physical activity reported fewer cases. These findings were consistent with the data presented in Table 1. The median percentage of body fat was 28.3% (with a standard deviation of 10.2), and high body fat was prevalent in 41.1% of the population.

Table 1. Characteristics of the subjects in accordance with depression status (n = 467).

Variables	Depression (n = 37)	No Depression (n = 430)	<i>p</i>
Age	49 (32)	52 (30)	0.50
Women	73.0%	54.9%	0.03
Educational Level (%)			
Low	0.0%	3.5%	0.76
Middle	59.9%	56.3%	
High	40.5%	40.2%	
Household Income (EUR) (%)			
Low (<1200)	64.9%	53.9%	0.36
Middle (1200–1800)	13.5%	22.3%	
High (>1800)	21.6%	23.7%	
Smoking (%)	16.2%	16.5%	0.96
Alcohol (%)	86.5%	90.2%	0.47
Physical Activity Level			
Insufficient	32.4%	13.7%	0.001
Moderate	37.8%	38.4%	
High	29.7%	47.9%	
Body Fat Percentage	31.0 (22.2)	27.7 (16.3)	0.19
Waist Circumference (cm)	90 (24.5)	92.5 (21)	0.33
High Body Fat (%)	35.0%	25.5%	0.96
Diabetes (%)	21.6%	14.9%	0.28
Hypertension (%)	43.2%	37.9%	0.52

Age, body fat percentage, and waist circumference presented as median (interquartile).

In Table 2, the analysis of the four substances reveals that PFOS exhibited the highest concentration, with a median of 3.45 ng/mL, followed by PFOA with a median of 1.63 ng/mL, PFNA with a median of 0.58 ng/mL, and PFDA with a median of 0.18 ng/mL.

These values provide a quantitative overview of the distribution of these PFAS compounds within the studied population. Table 3 presents the prevalence ratio (PR) values derived from the associations between different PFAS concentrations and the occurrence of depression. The results are presented for the entire sample and are adjusted for high adiposity (adiposity status), as well as the unadjusted values.

Table 2. Descriptive statistics of perfluoroalkyl (PFAS) variables (ng/mL).

	Geometric Mean	Median	Minimum	Maximum
Perfluorooctanoic acid (PFOA)	1.58	1.63	0.26	6.72
Perfluorooctane sulfonate (PFOS)	3.50	3.45	0.68	128
Perfluorononanoic acid (PFNA)	0.58	0.58	0.14	3.43
Perfluorodecanoic acid (PFDA)	0.17	0.18	0.01	1.34

Table 3. Associations between serum PFAS levels (ng/mL) and depression prevalence unstratified and stratified by body fat status.

PFAS	Entire Sample ^a PR (CI 95%)	Entire Sample ^b PR (CI 95%)	Normal Adiposity ^c PR (CI 95%)	High Adiposity ^c PR (CI 95%)
PFOA	1.92 (1.01–3.69)	1.91 (1.01–3.65)	3.20 (1.46–7.01)	0.78 (0.27–2.22)
PFOS	0.99 (0.56–1.76)	1.00 (0.56–1.79)	1.59 (0.76–3.30)	0.64 (0.26–1.58)
PFNA	1.73 (0.95–3.14)	1.74 (0.96–3.18)	2.54 (1.29–5.00)	0.84 (0.30–2.34)
PFDA	1.37 (0.84–2.23)	1.39 (0.85–2.27)	2.09 (1.09–4.00)	0.96 (0.50–1.82)

^a—adjusted by age, sex, educational level, household income, smoking, physical activity level, diabetes, hypertension, waist circumference, and type of questionnaire used to classify depression status; ^b—adjusted by age, sex, educational level, household income, smoking, alcohol, physical activity level, diabetes, hypertension, waist circumference, adiposity status, and type of questionnaire used to classify depression status; ^c—adjusted by age, sex, educational level, household income, smoking, alcohol, physical activity level, body fat percentage, diabetes, hypertension, waist circumference, and type of questionnaire used to classify depression status; PR—prevalence rate.

The study's findings present a significant association between PFOA and depression, both before and after adjusting for adiposity status. The prevalence ratio (PR) for PFOA was 1.97 (CI95%: 1.06–3.69) and 1.95 (CI95%: 1.04–3.65), respectively. While PFNA and PFDA exhibited positive associations with depression, these were not statistically significant. PFOS did not demonstrate any significant association with depression. Further exploration revealed that the significant associations between PFOA, PFNA, and PFDA and depression were observed exclusively in the normal adiposity group. For this subgroup, the PR values for PFOA, PFNA, and PFDA were 3.11 (CI95%: 1.53–6.34), 2.54 (CI95%: 1.32–4.90), and 2.10 (CI95%: 1.09–4.01), respectively. However, in the high-adiposity group, after additional analysis, it was observed that only physical activity level and body fat percentage retained statistical significance in relation to depression. Within this group, PFOA, PFNA, PFDA, and PFOS all exhibited a negative association with depression, with PR values of 0.43 (CI95%: 0.21–0.87), 0.43 (CI95%: 0.21–0.88), 0.44 (CI95%: 0.21–0.92), and 0.44 (CI95%: 0.21–0.91), respectively. Conversely, body fat percentage displayed a positive association with depression for all four variables, with PR values of 1.13 (CI95%: 1.04–1.22), 1.12 (CI95%: 1.04–1.21), 1.12 (CI95%: 1.04–1.21), and 1.11 (CI95%: 1.03–1.20), respectively.

4. Discussion

This study aimed to investigate the association between four PFAS compounds and depression, delving deep into the details of the relationship between these variables. The study's findings revealed that among the four PFAS compounds analyzed, PFOA is most likely associated with depression, even after adjusting for adiposity status. The study found a significant association between PFOA and depression. While PFNA and PFDA showed positive associations, they were not found to be statistically significant. In contrast,

PFOS did not exhibit any positive association with depression. These results suggest the importance of body fat status in the relationship between PFOA, PFNA, and PFDA with depression, with the strongest associations observed in individuals with normal adiposity. It is worth noting that the concentrations of PFAS found in the blood serum were lower than what is typically found in the literature, but they were consistent with the levels reported by the Czech national monitoring test [36]. In fact, although a cutoff for adverse health effects related to PFAS exposure is 2 nanograms per milliliter (ng/mL) of the sum of PFAS, there may not even be a level of PFAS exposure without some biological effect [37].

Disruption of neurotransmitters and neuromodulators by PFAS may contribute to an increased risk of neuropsychiatric disorders [10]. However, there are conflicting results in the literature regarding the association between depressive symptoms and serum levels of PFOS, PFOA, PFNA, and PFDA, among other PFAS. In a cross-sectional study by Berk et al. [38], which included 5400 subjects aged 18 years and older, unexpected associations were found between a lower risk of depression and higher levels of PFNA and PFDA. The study only considered the differences between the first and fourth quartiles of PFAS without adjusting or stratifying any variable related to body mass. In another cross-sectional study examining the relationship between PFAS exposure and CRH levels in mid-gestation according to different psychosocial stressors, the association between PFNA and CRH was stronger among women who experienced depression [39]. In older adults (55–74 years), no association was observed between depression and anxiety scores and PFOA [40]. Recently, PFOS was associated with higher depressive symptoms among immigrant women during pregnancy [17]. This highlights the importance of addressing the combined impact of PFAS exposure and social stress on health outcomes in marginalized communities [17].

Comparing studies is a challenge due to the varying characteristics of the sample, which is primarily composed of pregnant women [17,39]. However, in general terms, different PFAS seem to influence neurological health, confirming their action as endocrine disruptors. In some studies, neurotoxicity is linked to delayed gross motor development in infancy [41] and attention deficit hyperactivity in adolescents [42]. PFAS has been reported to exert significant toxic effects on HPA axis activity and on the dopaminergic system in several limbic brain regions [12,43], modifying the gene and protein expression of the glucocorticoid receptor (Gr) and the signaling of the brain-derived neurotrophic factor (Bdnf) [44]. Then, an association is suggested between PFAS and the activation of Gr signaling due to their direct Gr binding [45] and Bdnf signaling/HPA axis alterations in stress-related disorders, including depression [46]. Particularly, PFOA seems to activate the peroxisome proliferator-activated receptor α (PPAR α) [47], which increases the hepatic expression of fibroblast growth factor 21 (FGF21) [48]. FGF21 stimulates the expression of the hormone CRH, and the increased concentration of CRH contributes to the etiology of disorders such as anorexia nervosa, obsessive-compulsive disorder, anxiety, and depression [48]. These observations suggest that some PFAS may act centrally to influence psychiatric disorders and eating behavior. The anorexic effect of PFAS also involves the activation of hypothalamic urocortin-2, CRH receptor-2, and suppression of gastroduodenal motor activity [49]. After stratifying the sample in the present study, these associations became apparent. An adjustment in the measure referring to adiposity amount removed potential confounding but blocked its mediating effect, and this was more evident for the PFNA and PFDA.

The relationship between high adiposity and depression is complex and requires further exploration. Among individuals with high adiposity, physical activity levels and body fat percentage were found to be the most important factors associated with depression. It was only possible to confirm the association between body fat percentage and depression in this group, which is consistent with previous research [50,51]. Also, a few studies conceptualized the body mass index (BMI) as a proxy for dietary and physical behavior characteristics before pregnancy [52,53]. That would generate a potential “collider bias” when there are other causes common to adiposity levels [54]. In the current research, there was an attempt to minimize this by also adjusting the physical activity level. It can be

reinforced by the fact that there was an inverse association between depression and physical activity level only in the group with high adiposity.

It is important to note that the current study has certain limitations that must be acknowledged. Specifically, no consideration was given to comorbidities such as neurodevelopmental and behavioral disorders or a prior history of mental illness. Also, although there are differences in serum PFAS levels among races in the general population [55], this variable was not collected. It is important to note that the Czech population is largely homogenous, with only approximately 5.3% of the population being made up of foreigners (primarily Ukrainians, Slovaks, Vietnamese, and Russians), and the ethnic minority Roma comprising just 2.2% of the overall population [56].

It is worth mentioning that the sample size was relatively small, and, as the study was cross-sectional, we cannot determine causation. Thus, further research, such as a longitudinal study, is required to confirm our findings. The previous studies' mixed results indicate a need for diverse approaches when investigating the link between PFAS and mental health-related factors. A notable strength of this study is the inclusion of a sample that was not highly exposed to PFAS.

5. Conclusions

The present analysis suggests a distinctive association between PFAS levels in the blood and the prevalence of depression. Remarkably, among the four analyzed PFAS compounds, perfluorooctanoic acid (PFOA) emerged as the sole significant association before adjustments for adiposity levels. However, subsequent stratified analyses revealed that PFOA, along with perfluorononanoic acid (PFNA) and perfluorodecanoic acid (PFDA), demonstrated associations exclusively in individuals with a normal amount of adiposity. To our knowledge, this study is the first to establish a connection between PFAS levels and depression that is contingent upon body fat status. The identification of these associations highlights the need for further investigations to unravel the intricate mechanisms underlying the impact of PFAS on mental health. Depression remains a pervasive global concern, and elucidating the environmental factors contributing to its prevalence is of paramount importance. Moreover, these findings underscore the significance of considering individual factors, such as body composition, when evaluating the mental health consequences of environmental pollutants. This study contributes to a growing body of evidence suggesting that the impact of environmental pollutants on mental health outcomes is complex and multifaceted. As PFAS continue to be ubiquitous in contemporary life, understanding the interplay between PFAS exposure, body fat status, and mental health is crucial for comprehensive risk assessment and public health interventions.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the ethics committee of St. Anne's University Hospital, Brno, Czech Republic (Ref. Number: 2G/2012).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available upon request from the corresponding author. The data are not publicly available.

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References

1. EFSA Panel on Contaminants in the Food Chain (CONTAM); Knutsen, H.K.; Alexander, J.; Barregard, L.; Bignami, M.; Bruschweiler, B.; Ceccatelli, S.; Cottrill, B.; Dinovi, M.; Edler, L.; et al. Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food. *EFSA J.* **2018**, *16*, e05194.
2. Diaz, L.M.; Stewart, M.R. “Forever Chemicals”: Forever Altering the Legal Landscape. *Belmont Law Rev.* **2019**, *7*, 308.
3. Fromme, H.; Tittlemier, S.A.; Völkel, W.; Wilhelm, M.; Twardella, D. Perfluorinated compounds—Exposure assessment for the general population in Western countries. *Int. J. Hyg. Environ. Health* **2009**, *212*, 239–270. [[CrossRef](#)] [[PubMed](#)]
4. Xie, X.; Weng, X.; Liu, S.; Chen, J.; Guo, X.; Gao, X.; Fei, Q.; Hao, G.; Jing, C.; Feng, L. Perfluoroalkyl and polyfluoroalkyl substance exposure and association with sex hormone concentrations: Results from the NHANES 2015–2016. *Environ. Sci. Eur.* **2021**, *33*, 69. [[CrossRef](#)] [[PubMed](#)]
5. Di Law, H.; Armstrong, B.; D’Este, C.; Randall, D.; Hosking, R.; Lazarevic, N.; Trevenar, S.; Smurthwaite, K.; Lal, A.; Lucas, R. *PFAS Health Study*; Australian National University: Canberra, Australia, 2021.
6. Ross, I.; Hurst, J. Managing risks and liabilities associated with per- and polyfluoroalkyl substances (PFASs). In *Contaminated Land: Applications in Real Environments*; CL:AIRE: London, UK, 2019.
7. Buoso, E.; Masi, M.; Racchi, M.; Corsini, E. Endocrine-Disrupting Chemicals’ (EDCs) Effects on Tumour Microenvironment and Cancer Progression: Emerging Contribution of RACK1. *Int. J. Mol. Sci.* **2020**, *21*, 9229. [[CrossRef](#)]
8. Cakmak, S.; Lukina, A.; Karthikeyan, S.; Atlas, E.; Dales, R. The association between blood PFAS concentrations and clinical biochemical measures of organ function and metabolism in participants of the Canadian Health Measures Survey (CHMS). *Sci. Total Environ.* **2022**, *827*, 153900. [[CrossRef](#)]
9. Calloway, E.E.; Chiappone, A.L.; Schmitt, H.J.; Sullivan, D.; Gerhardtstein, B.; Tucker, P.G.; Rayman, J.; Yaroch, A.L. Exploring Community Psychosocial Stress Related to Per- and Poly-Fluoroalkyl Substances (PFAS) Contamination: Lessons Learned from a Qualitative Study. *Int. J. Environ. Res. Public Health* **2020**, *17*, 8706. [[CrossRef](#)]
10. Starnes, H.M.; Rock, K.D.; Jackson, T.W.; Belcher, S.M. A Critical Review and Meta-Analysis of Impacts of Per- and Polyfluorinated Substances on the Brain and Behavior. *Front. Toxicol.* **2022**, *4*, 881584. [[CrossRef](#)]
11. Pereiro, N.; Moyano, R.; Blanco, A.; Lafuente, A. Regulation of corticosterone secretion is modified by PFOS exposure at different levels of the hypothalamic-pituitary-adrenal axis in adult male rats. *Toxicol. Lett.* **2014**, *230*, 252–262. [[CrossRef](#)]
12. Salgado-Freiria, R.; López-Doval, S.; Lafuente, A. Perfluorooctane sulfonate (PFOS) can alter the hypothalamic-pituitary-adrenal (HPA) axis activity by modifying CRF1 and glucocorticoid receptors. *Toxicol. Lett.* **2018**, *295*, 1–9. [[CrossRef](#)]
13. Piekarski, D.; Diaz, K.; Mc Nerney, M. Perfluoroalkyl chemicals in neurological health and disease: Human concerns and animal models. *Neurotoxicology* **2020**, *77*, 155–168. [[CrossRef](#)] [[PubMed](#)]
14. Foguth, R.M.; Sepúlveda, M.S.; Cannon, J.R. Per- and Polyfluoroalkyl Substances (PFAS) Neurotoxicity in Sentinel and Non-Traditional Laboratory Model Systems: Potential Utility in Predicting Adverse Outcomes in Human Health. *Toxics* **2020**, *8*, 42. [[CrossRef](#)] [[PubMed](#)]
15. Cao, Y.; Ng, C. Absorption, distribution, and toxicity of per- and polyfluoroalkyl substances (PFAS) in the brain: A review. *Environ. Sci. Process. Impacts* **2021**, *23*, 1623–1640. [[CrossRef](#)] [[PubMed](#)]
16. Merrill, A.K.; Conrad, K.; Marvin, E.; Sobolewski, M. Effects of gestational low dose perfluorooctanoic acid on maternal and “anxiety-like” behavior in dams. *Front. Toxicol.* **2022**, *4*, 971970. [[CrossRef](#)] [[PubMed](#)]
17. Aung, M.T.; Eick, S.M.; Padula, A.M.; Smith, S.; Park, J.S.; DeMicco, E.; Woodruff, T.J.; Morello-Frosch, R. Maternal per- and poly-fluoroalkyl substances exposures associated with higher depressive symptom scores among immigrant women in the Chemicals in Our Bodies cohort in San Francisco. *Environ. Int.* **2023**, *172*, 107758. [[CrossRef](#)]
18. Wang, J.; Pan, Y.; Cui, Q.; Yao, B.; Wang, J.; Dai, J. Penetration of PFASs Across the Blood Cerebrospinal Fluid Barrier and Its Determinants in Humans. *Environ. Sci. Technol.* **2018**, *52*, 13553–13561. [[CrossRef](#)]
19. Formánek, T.; Kagström, A.; Cermakova, P.; Csémy, L.; Mladá, K.; Winkler, P. Prevalence of mental disorders and associated disability: Results from the cross-sectional CZEch mental health Study (CZEMS). *Eur. Psychiatry* **2019**, *60*, 1–6. [[CrossRef](#)]
20. World Health Organization. *Depression and Other Common Mental Disorders: Global Health Estimates*; World Health Organization: Geneva, Switzerland, 2017.
21. Eurostat. *Mental Health and Related Issues Statistics*; Eurostat: Luxembourg, 2020.
22. Lind, P.M.; Lind, L.; Salihovic, S.; Ahlström, H.; Michaelsson, K.; Kullberg, J.; Strand, R. Serum levels of perfluoroalkyl substances (PFAS) and body composition—A cross-sectional study in a middle-aged population. *Environ. Res.* **2022**, *209*, 112677. [[CrossRef](#)]
23. Speed, M.S.; Jefsen, O.H.; Børghlum, A.D.; Speed, D.; Østergaard, S.D. Investigating the association between body fat and depression via Mendelian randomization. *Transl. Psychiatry* **2019**, *9*, 184. [[CrossRef](#)]
24. Milaneschi, Y.; Simmons, W.K.; van Rossum, E.F.C.; Penninx, B.W. Depression and obesity: Evidence of shared biological mechanisms. *Mol. Psychiatry* **2019**, *24*, 18–33. [[CrossRef](#)]

25. Wester, V.L.; Staufenbiel, S.M.; Veldhorst, M.A.; Visser, J.A.; Manenschijn, L.; Koper, J.W.; Klessens-Godfroy, F.J.; van den Akker, E.L.; van Rossum, E.F. Long-term cortisol levels measured in scalp hair of obese patients. *Obesity* **2014**, *22*, 1956–1958. [[CrossRef](#)] [[PubMed](#)]
26. Fulton, S.; Décarie-Spain, L.; Fioramonti, X.; Guiard, B.; Nakajima, S. The menace of obesity to depression and anxiety prevalence. *Trends Endocrinol. Metab.* **2022**, *33*, 18–35. [[CrossRef](#)] [[PubMed](#)]
27. Visseren, F.L.; Mach, F.; Smulders, Y.M.; Carballo, D.; Koskinas, K.C.; Bäck, M.; Benetos, A.; Biffi, A.; Boavida, J.-M.; Capodanno, D. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies with the special contribution of the European Association of Preventive Cardiology (EAPC). *Eur. J. Prev. Cardiol.* **2022**, *29*, 5–115. [[PubMed](#)]
28. Craig, C.L.; Marshall, A.L.; Sjöström, M.; Bauman, A.E.; Booth, M.L.; Ainsworth, B.E.; Pratt, M.; Ekelund, U.; Yngve, A.; Sallis, J.F.; et al. International physical activity questionnaire: 12-Country reliability and validity. *Med. Sci. Sports Exerc.* **2003**, *35*, 1381–1395. [[CrossRef](#)] [[PubMed](#)]
29. Kroenke, K.; Spitzer, R.L.; Williams, J.B. The PHQ-9: Validity of a brief depression severity measure. *J. Gen. Intern. Med.* **2001**, *16*, 606–613. [[CrossRef](#)] [[PubMed](#)]
30. Andresen, E.M.; Malmgren, J.A.; Carter, W.B.; Patrick, D.L. Screening for depression in well older adults: Evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). *Am. J. Prev. Med.* **1994**, *10*, 77–84. [[CrossRef](#)] [[PubMed](#)]
31. Ling, C.H.; de Craen, A.J.; Slagboom, P.E.; Gunn, D.A.; Stokkel, M.P.; Westendorp, R.G.; Maier, A.B. Accuracy of direct segmental multi-frequency bioimpedance analysis in the assessment of total body and segmental body composition in middle-aged adult population. *Clin. Nutr.* **2011**, *30*, 610–615. [[CrossRef](#)]
32. Hui, D.; Dev, R.; Pimental, L.; Park, M.; Cerana, M.A.; Liu, D.; Bruera, E. Association between Multi-frequency Phase Angle and Survival in Patients with Advanced Cancer. *J. Pain Symptom Manag.* **2017**, *53*, 571–577. [[CrossRef](#)]
33. McLester, C.N.; Nickerson, B.S.; Kliszczewicz, B.M.; McLester, J.R. Reliability and Agreement of Various InBody Body Composition Analyzers as Compared to Dual-Energy X-Ray Absorptiometry in Healthy Men and Women. *J. Clin. Densitom.* **2020**, *23*, 443–450. [[CrossRef](#)]
34. World Health Organization. *Physical Status: The Use of and Interpretation of Anthropometry, Report of a WHO Expert Committee*; World Health Organization: Geneva, Switzerland, 1995.
35. Maranhao Neto, G.A.; Polcrova, A.B.; Pospisilova, A.; Blaha, L.; Klanova, J.; Bobak, M.; Gonzalez-Rivas, J.P. Associations between Per- and Polyfluoroalkyl Substances (PFAS) and Cardiometabolic Biomarkers in Adults of Czechia: The KardioVize Study. *Int. J. Environ. Res. Public Health* **2022**, *19*, 13898. [[CrossRef](#)]
36. National Institute of Public Health. *Environmental Health Monitoring System in the Czech Republic—Summary Report 2020*, 1st ed.; National Institute of Public Health: Saitama, Japan, 2021.
37. National Academies of Sciences, Engineering, and Medicine. *Guidance on PFAS Exposure, Testing, and Clinical Follow-Up*; National Academies of Sciences, Engineering, and Medicine: Washington, DC, USA, 2022.
38. Berk, M.; Williams, L.J.; Andreazza, A.C.; Pasco, J.A.; Dodd, S.; Jacka, F.N.; Moylan, S.; Reiner, E.J.; Magalhaes, P.V. Pop, heavy metal and the blues: Secondary analysis of persistent organic pollutants (POP), heavy metals and depressive symptoms in the NHANES National Epidemiological Survey. *BMJ Open* **2014**, *4*, e005142. [[CrossRef](#)]
39. Eick, S.M.; Goin, D.E.; Cushing, L.; DeMicco, E.; Smith, S.; Park, J.S.; Padula, A.M.; Woodruff, T.J.; Morello-Frosch, R. Joint effects of prenatal exposure to per- and poly-fluoroalkyl substances and psychosocial stressors on corticotropin-releasing hormone during pregnancy. *J. Expo. Sci. Environ. Epidemiol.* **2022**, *32*, 27–36. [[CrossRef](#)]
40. Shrestha, S.; Bloom, M.S.; Yucel, R.; Seegal, R.F.; Rej, R.; McCaffrey, R.J.; Wu, Q.; Kannan, K.; Fitzgerald, E.F. Perfluoroalkyl substances, thyroid hormones, and neuropsychological status in older adults. *Int. J. Hyg. Environ. Health* **2017**, *220*, 679–685. [[CrossRef](#)]
41. Fei, C.; McLaughlin, J.K.; Lipworth, L.; Olsen, J. Prenatal exposure to perfluorooctanoate (PFOA) and perfluorooctanesulfonate (PFOS) and maternally reported developmental milestones in infancy. *Environ. Health Perspect.* **2008**, *116*, 1391–1395. [[CrossRef](#)]
42. Hoffman, K.; Webster, T.F.; Weisskopf, M.G.; Weinberg, J.; Vieira, V.M. Exposure to polyfluoroalkyl chemicals and attention deficit/hyperactivity disorder in U.S. children 12–15 years of age. *Environ. Health Perspect.* **2010**, *118*, 1762–1767. [[CrossRef](#)] [[PubMed](#)]
43. Salgado, R.; López-Doval, S.; Pereiro, N.; Lafuente, A. Perfluorooctane sulfonate (PFOS) exposure could modify the dopaminergic system in several limbic brain regions. *Toxicol. Lett.* **2016**, *240*, 226–235. [[CrossRef](#)] [[PubMed](#)]
44. Jantzen, C.E.; Annunziato, K.M.; Cooper, K.R. Behavioral, morphometric, and gene expression effects in adult zebrafish (*Danio rerio*) embryonically exposed to PFOA, PFOS, and PFNA. *Aquat. Toxicol.* **2016**, *180*, 123–130. [[CrossRef](#)] [[PubMed](#)]
45. Masi, M.; Maddalon, A.; Iulini, M.; Linciano, P.; Galbiati, V.; Marinovich, M.; Racchi, M.; Corsini, E.; Buoso, E. Effects of endocrine disrupting chemicals on the expression of RACK1 and LPS-induced THP-1 cell activation. *Toxicology* **2022**, *480*, 153321. [[CrossRef](#)]
46. Brivio, P.; Buoso, E.; Masi, M.; Gallo, M.T.; Gruca, P.; Lason, M.; Litwa, E.; Papp, M.; Fumagalli, F.; Racchi, M.; et al. The coupling of RACK1 with the beta isoform of the glucocorticoid receptor promotes resilience to chronic stress exposure. *Neurobiol. Stress* **2021**, *15*, 100372. [[CrossRef](#)]

47. Abbott, B.D.; Wood, C.R.; Watkins, A.M.; Tatum-Gibbs, K.; Das, K.P.; Lau, C. Effects of perfluorooctanoic acid (PFOA) on expression of peroxisome proliferator-activated receptors (PPAR) and nuclear receptor-regulated genes in fetal and postnatal CD-1 mouse tissues. *Reprod. Toxicol.* **2012**, *33*, 491–505. [[CrossRef](#)]
48. Wang, Y.; Zhang, Y.; Shi, Z.; Di, T.; Yu, W.; Chen, L. Exposure of male mice to perfluorooctanoic acid induces anxiety-like behaviors by increasing corticotropin-releasing factor in the basolateral amygdala complex. *Chemosphere* **2022**, *287*, 132170. [[CrossRef](#)] [[PubMed](#)]
49. Asakawa, A.; Toyoshima, M.; Fujimiya, M.; Harada, K.; Ataka, K.; Inoue, K.; Koizumi, A. Perfluorooctane sulfonate influences feeding behavior and gut motility via the hypothalamus. *Int. J. Mol. Med.* **2007**, *19*, 733–739. [[CrossRef](#)] [[PubMed](#)]
50. Ouakinin, S.R.S.; Barreira, D.P.; Gois, C.J. Depression and Obesity: Integrating the Role of Stress, Neuroendocrine Dysfunction and Inflammatory Pathways. *Front. Endocrinol.* **2018**, *9*, 431. [[CrossRef](#)] [[PubMed](#)]
51. Afari, N.; Noonan, C.; Goldberg, J.; Roy-Byrne, P.; Schur, E.; Golnari, G.; Buchwald, D. Depression and obesity: Do shared genes explain the relationship? *Depress. Anxiety* **2010**, *27*, 799–806. [[CrossRef](#)]
52. Bjerregaard-Olesen, C.; Bach, C.C.; Long, M.; Ghisari, M.; Bossi, R.; Bech, B.H.; Nohr, E.A.; Henriksen, T.B.; Olsen, J.; Bonefeld-Jørgensen, E.C. Time trends of perfluorinated alkyl acids in serum from Danish pregnant women 2008–2013. *Environ. Int.* **2016**, *91*, 14–21. [[CrossRef](#)] [[PubMed](#)]
53. Ballesteros, V.; Costa, O.; Iñiguez, C.; Fletcher, T.; Ballester, F.; Lopez-Espinosa, M.-J. Exposure to perfluoroalkyl substances and thyroid function in pregnant women and children: A systematic review of epidemiologic studies. *Environ. Int.* **2017**, *99*, 15–28. [[CrossRef](#)]
54. Inoue, K.; Goto, A.; Sugiyama, T.; Ramlau-Hansen, C.H.; Liew, Z. The Confounder-Mediator Dilemma: Should We Control for Obesity to Estimate the Effect of Perfluoroalkyl Substances on Health Outcomes? *Toxics* **2020**, *8*, 125. [[CrossRef](#)]
55. Boronow, K.E.; Brody, J.G.; Schaidler, L.A.; Peaslee, G.F.; Havas, L.; Cohn, B.A. Serum concentrations of PFASs and exposure-related behaviors in African American and non-Hispanic white women. *J. Expo. Sci. Environ. Epidemiol.* **2019**, *29*, 206–217. [[CrossRef](#)]
56. Pavlovska, I.; Polcrova, A.; Mechanick, J.I.; Brož, J.; Infante-Garcia, M.M.; Nieto-Martínez, R.; Maranhao Neto, G.A.; Kunzova, S.; Skladana, M.; Novotny, J.S.; et al. Dysglycemia and Abnormal Adiposity Drivers of Cardiometabolic-Based Chronic Disease in the Czech Population: Biological, Behavioral, and Cultural/Social Determinants of Health. *Nutrients* **2021**, *13*, 2338. [[CrossRef](#)]

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