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The relationship between pesticide exposures and primary headaches in adults: A cross-sectional study based on Rafsanjan cohort study

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ABSTRACT

Objectives: Toxic substances can trigger headaches. The prevalence of pesticide use and headaches was high among the population of Rafsanjan.
Methods: A cross-sectional study was used to collect data from 9991 adults who participated via sampling people aged 35–70 years old of both genders from the Rafsanjan Cohort Study (RCS) in Iran. Demographic characteristics, habits, chronic primary headache (CPH), and episodic primary headache (EPH) were measured.
Results: The prevalence of CPH and EPH were 7.4 % and 29.9 % respectively. The multivariable model showed the odds of EPH increased significantly by the pesticide exposure on farm OR: 1.16 (1.02–1.34), in yard OR: 1.18 (1.01–1.39), duration of pesticide exposure in yard > median OR: 1.35 (1.06–1.73), at home OR: 1.31 (1.17–1.46), duration of pesticide exposure at home ≤ median OR: 1.24 (1.10–1.40) and > median OR: 1.38 (1.22–1.57). Also, pesticide preparation OR: 1.20 (1.03–1.39), duration of exposure in pesticide preparation ≤ median OR: 1.31 (1.09–1.57), and duration of exposure in managed spraying pesticide > median OR: 1.28 (1.04–1.57) increased odds of EPH. These results showed that the odds of CPH increased in participants using pesticides at home OR: 1.22 (1.02–1.48), duration of pesticide exposure at home > median OR: 1.37 (1.11–1.70), and duration of pesticide exposure in pesticide preparation > median OR: 0.47 (0.27–0.82). The odds of EPH increased with more pesticide exposures (18 %) and duration of pesticide exposure (25 %).
Conclusions: As evidenced by the obtained results, there is a relationship between pesticide exposure and headaches.

1. Introduction

Toxic substances such as lead, insecticides, organophosphate pesticides, chemical solvents, acetaldehyde from alcohol (a hangover), carbon tetrachloride, and various home cleaners can trigger headaches. This is often accompanied by disrupting the cell's magnesium metabolism, which sets off a chain of events that culminate in a variety of headaches, or more severe conditions (such as neurological deficit) (Cottingham, 2014). The least prevalent type of vascular headache is a toxic headache. Causes that originate within the body are notoriously difficult to identify. Disturbances in any organ of the body, including the liver, kidneys, and intestines, can result in the accumulation of toxins that are damaging to the body. When a toxic headache is induced by exposure to a toxin, it is considered an environmental disease

Abbreviations: RCS, Rafsanjan Cohort Study; PERSIAN, Prospective epidemiological research studies in Iran; CPH, chronic primary headache; EPH, episodic primary headache; RUMS, Rafsanjan University of Medical Sciences; WSI, Wealth score index; MET, Metabolic equivalent of task; BMI, body mass index; OR, odds ratios; Ops, organophosphates; ACHE, Acetylcholinesterase.

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(Cottingham, 2014).

Pesticides are primarily utilized in agriculture (Lu et al., 2010) and cause a variety of neurobehavioral problems, although migraine was found in many pesticide users (Chetty-Mhlanga, 2021). According to multiple researches, the most prevalent negative effect of pesticide use was headaches (Mattiazzi, xxxx). Pesticides are made up of chemicals from a variety of chemical groups that have strong organic development and a large range of linked rebellious actions (Mesnil, 2021). Herbicides are the most common pesticides, followed by bug sprays, anti-parasitic, and fungicides. Many of them are GJIC modulators and operate as endocrine disruptors (Mesnil, 2021).

However, few studies have looked into the impact of toxin consumption on headaches. The most common symptom of pesticide exposure, according to the Mattiazi 2020 study, was a headache, which occurred in 31 % of cases (Mattiazzi, xxxx). Chatty Mélanga proposed a prospective study protocol in 2018 that evaluates the side effects of pesticides over several years, and the headache was one of the aspects regarded as side effects in this cohort (Chetty-Mhlanga, 2018).

Mwabulambo estimated that 95 % of pesticide users in Tanzania used organophosphate pesticides in a 2018 research. The most common neurological symptoms reported were physical weakness (57.1 %) followed by sweating, headache (40.7 %), anorexia depression (29.3 %), and irritation (26.4 %). Pesticide applicants had acetylcholinesterase levels below the limit value in 27 percent of them (Mwabulambo, 2018).

In 2020, Burralli's study looked at the effects of toxins in Brazil, 50 percent of assistants and 31 % of applicators suffered from headaches (Buralli, 2020). Dizziness, tremor, and limb paresthesia were all prevalent symptoms. A higher percentage of cases, ranging from 50 to 60 percent, showed signs of despair and anxiety. Complications were more likely among assistants in general (Buralli, 2020).

In this study, we looked at pesticides and headaches from a different angle. There have always been triggers for migraine and other primary headaches. Barometric pressure shifts, intense lights, noise, scents, and sunlight were examples of stimulators. Triggers can be found in the home or at work. The next point is that one of the cornerstones of treatment is reducing headache stimuli both at home and at work. it can reduce the morbidity of primary headaches, especially migraine, by regulating environmental stressors, and this helps to reduce primary headaches (Friedman and De Ver Dye, 2009). One of the causes of primary headaches and migraine is air pollution. Changes in air pressure, particles in the air, and types of toxic gases such as SO2, NO2, CO, and O3 in the air were effective factors. Other environmental factors that may trigger headaches in sensitive persons include pollution, exposure to environmental allergens, indoor illumination, indoor air quality, and exposure to chemicals or odors (Friedman and De Ver Dye, 2009).

Toxins' role in the emergence of neurodegenerative diseases like Alzheimer's and Parkinson's disease, as well as in migraine and depression, and neurodevelopmental disorders, like autism spectrum diseases, and ADHD, as well as epilepsy, has been discussed in some studies. Toxins contribute to the development of more of these diseases by interfering with the function of gap junctions and cannikins (Mesnil, 2021). Another study discovered a short-term link between ambient air pollution and migraine, which had a synergistic effect on migraine when combined with temperature (Lee, 2018).

Toxins and insecticides, as previously mentioned, may play a role in neurological illnesses. In this study, we wanted to see if there was a link between exposure to toxins in the farm, yard, and home and primary headaches, but we did not want to look at the consequence of toxins in general, including headaches.

Rafsanjan, in the south of Iran, has specific characteristics, with its largest pistachio jungle in the world. Therefore, farmers are the main residents of Rafsanjan who are highly exposed to various agricultural toxins (Hakimi, 2021). About 100,000 L of pesticides—mostly Organ phosphorus—each year are received in the 80,000 ha of pistachio orchards in Rafsanjan (Dehghani, 2011). Surprisingly, less than eighty percent of farmers, when applying pesticides, have no protection against them and more than fifty percent discard the pesticide containers in the environment (Tavakolian Ferdosieyeh, 2012). Toxins and insecticides, as previously mentioned, may play a role in neurological illnesses. In this study, we wanted to see if there was a link between exposure to toxins in the farm, yard, and home and primary headaches and we aimed to investigate the presence and extent of exposure to pesticides or its absence in participants with primary episodic and chronic headaches in the population of Rafsanjan cohort study (RCS).

2. Methods

2.1. Study population

The statistical population of this study was derived from the RCS population, launched in 2014 (Hakimi, 2021) as part of the prospective epidemiological studies of Iran (PERSIAN) (Poustchi, 2018). RCS included a total of 10,000 participants of both genders aged 35 to 70 years from four predetermined areas of Rafsanjan city both urban and suburban. Among all participants, 9991 people had a complete questionnaire and entered our study. Subjects with incomplete toxin-use questionnaires were excluded from the study (31 males and 25 females). The protocol of the present study was designed in accordance Persian cohort study. Accuracy and precision of all methods were performed by the relevant guidelines and regulations and all subjects signed the consent form to enter the study. The names of the participants were kept confidential and only the data were available to the study investigators. Also, this study was approved by the Ethics Committee of Rafsanjan University of Medical Sciences (RUMS) (Ethical code: IR.RUMS.REC.1400.016).

2.2. Data collection

Demographic and medical questionnaires were asked by expert interviewers. Demographic characteristics included age, sex, educational status, socioeconomic status (Wealth score index: WSI), anthropometric (body mass index: BMI), physical activity (Metabolic equivalent of task: MET) and medical characteristics included hypertension, chronic primary headache (CPH), episodic primary headache (EPH), and family history of headache. Also, habits included smoking, opium, and alcohol consumption (Hakimi, 2021). The question asked about the family history of headache was as follows Whether or not any first degree relatives have chronic recurrent headaches.

MET was calculated for 24 h, using the METs specified for each activity by a 22-item questionnaire. WSI was calculated by multiple correspondence analysis (MCA) of the economic and social characteristics of participants to determine socio-economic status by a 27-question questionnaire (Hakimi, 2021).

In the cohort questionnaire, the status of EPH and CPH was asked through interviews with questions about chronic and intermittent headaches a year before the enrollment date. CPH was defined as headaches occurring at least half of the month and lasting for at least three consecutive months. Migraine disease was considered as a type of both EPH and. EPH was defined as experiencing persistent headaches at least once in a lifetime with a duration of more than 4 h (Hakimi, 2021). Secondary causes of headaches such as headaches associated with head or neck injury, cranial or cervical vascular disorders, non-vascular intracranial disorders, infection, and psychiatric disorders (somatization or psychotic disorders) were not included in the answers to these questions. The sub-classification of primary headache types was not included in this interview (Hakimi, 2021).

2.2.1. Exposure assessment

A self-report questionnaire asking about the quantity of exposure to pesticides with 38 questions about activities performed in a year before the enrollment date. The questions included the use of pesticides on the farm (applying pesticides in farms, greenhouses, or agricultural fields),

use in the yard (applying pesticides at home for plants), use at home (applying insecticides at home), pesticide preparation (mixing/loading pesticides or insecticides), manage spraying pesticide (directing spray operations), duration of exposure to pesticide questions (the number of times pesticides were applied in the year *average length of time (minutes) spent applying pesticides). The frequency of pesticide exposure was divided into three categories (no, ≤median, and >median minutes per year). Unfortunately, the type of agricultural pesticides was not asked.

Total exposure included subjects that had exposure to the pesticide on the farm or in the yard or at home or pesticide preparation or managed to spray pesticide.

The total duration of exposure included the sum of the duration of exposure on the farm and duration of exposure in the yard and duration of exposure at home and duration of exposure in pesticide preparation and duration of exposure in managed spraying pesticide.

2.3. Statistical analysis

Comparisons were made between participants with headaches and non-headaches using the chi-square test for categorical variables and the T-test for quantitative variables. Due to the non-normality of the distribution of the duration of pesticide exposure in people, we divided the people into 2 groups based on the median in Tables 2 and 3. To investigate the relationship between pesticide exposure and CPH or EPH used Logistic regression models. Confounders were sequentially used in models according to their purported strengths regarding pesticide exposure and headache. Afterward, variables with a p-value < 0.25 were considered for multivariate analysis (Mickey and Greenland, 1989; Bendel and Afifi, 1977). Adjusted model included age (continuous variable), gender (male/female), education years (continuous variable), BMI (continuous variable), hypertension (yes/no), family history of primary headache (yes/no), smoking (yes/no), opium consumption (yes/no), alcohol consumption (yes/no) and physical activity (continuous variable). P-values < 0.05 and 95 % confidence intervals were considered statistically significant.

Table 1
Prevalence of episodic primary headache and chronic primary headache based on general characteristics in adult population of Rafsanjan cohort study launched in 2014.

Demographic characteristics	*Male (n=4624)*						Female (n=5311)					
	CPH (n=193)	*No CPH (n=4431)*	P-value	EPH (n=887)	No EPH (n=3737)	P-value	CPH (n=548)	No CPH (n=4762)	P-value	EPH (n=2002)	No EPH (n=3309)	P-value
Age. years			0.94			<0.001			0.34			<0.001
Mean±SD	50.2 ±10.5	50.2±9.7		48.6±9.5	50.5±9.8		50.1±9.2	49.7±9.4		48.8±9.1	50.3±9.5	
Education. years			0.07			0.6			<0.001			0.17
Mean±SD	8.9±4.9	9.54±4.9		9.4±4.8	9.5±4.9		6.9±4.8	7.7±5.0		7.8±5.0	7.6±5.0	
BMI			0.5			0.21			0.32			<0.001
Mean±SD	26.3±4.3	26.1±4.3		26.0±4.5	26.2±4.3		29.5±4.9	29.3±4.9		29.0±4.8	29.5±5.0	
WSI			0.26			0.16			0.002			0.16
Mean±SD	0.1±0.9	0.2±1.0		0.1±1.0	0.2±1.0		-0.3±1.0	-0.1±1.0		-0.1±1.0	-0.2±1.0	
Physical activity			0.017			0.35			0.81			0.26
Mean±SD	38.6±7.5	40.1±8.4		40.3±8.1	40.0±8.5		37.7±3.4	37.7±3.3		37.8±3.2	37.7±3.4	
Hypertension- n (%)			0.007			0.06			0.001			0.14
Yes	52(26.9)	846(19.1)		192 (21.7)	706(18.9)		198 (36.2)	1396 (29.3)		577(28.9)	1017 (30.8)	
No	141 (73.1)	3584 (80.9)		695 (78.4)	3030 (81.1)		349 (63.8)	3364 (70.7)		1423 (71.2)	2290 (69.3)	
Family history of primary headache - n (%)			<0.001			<0.001			<0.001			<0.001
Yes	69(35.8)	878(19.8)		274 (30.9)	673(18.0)		243 (44.3)	1422 (29.9)		803(40.1)	862(26.1)	
No	124 (64.3)	3553 (80.2)		613 (69.1)	3064 (82.0)		305 (55.7)	3340 (70.1)		1199 (59.9)	2447 (74.0)	
Smoking- n (%)			0.93			0.04			0.003			0.18
Yes	100 (52.6)	2310 (52.3)		489 (55.4)	1921(51.6)		24(4.4)	110(2.3)		58(2.9)	76(2.3)	
No	90(47.4)	2108 (47.7)		393 (44.6)	1805 (48.4)		522 (95.6)	4650 (97.7)		1942 (97.1)	3230 (97.7)	
Opium consumption- n (%)			0.77			0.68			0.009			0.28
Yes	90(47.4)	2044 (46.3)		414 (46.9)	1720 (46.2)		33(6.0)	178(3.7)		72(3.6)	139(4.2)	
No	100 (52.6)	2374 (53.7)		468 (53.1)	2006 (53.8)		513 (94.0)	4582 (96.3)		1928 (96.4)	3167 (95.8)	
Alcohol consumption- n (%)			0.13			0.15			0.94			0.79
Yes	49(25.8)	935(21.2)		204 (23.1)	780(20.9)		1(0.2)	8(0.2)		3(0.2)	6(0.2)	
No	141 (74.2)	3483 (78.8)		678 (76.9)	2946 (79.1)		545 (99.8)	9752 (99.8)		1997 (99.9)	3300 (99.8)	

Abbreviations: Chronic primary headache (CPH); Episodic primary headache (EPH); Body Mass Index (BMI); Wealth Score Index (WSI).
Results are expressed as mean ± standard deviation for continuous variables and as number of participants (column percentage) for categorical variables. Between-group comparisons were performed by Independent Samples T-test for continuous variables, and chi-square for categorical variables.

Table 2
Prevalence of Chronic primary headache and Episodic primary headache according to pesticide exposure in adult population of Rafsanjan cohort study launched in 2014.**

Pesticide Use	Male *n* (%)						Female *n* (%)					
	CPH (n=193)	No CPH (n=4431)	P-value	EPH (n=887)	No EPH (n=3737)	P-value	CPH (n=548)	No CPH (n=4762)	P-value	EPH (n=2002)	No EPH (n=3309)	P-value
Use in Farm			0.66			0.04			0.63			0.69
Yes	71(37.0)	1702 (38.6)		367 (41.5)	1406 (37.8)		11(2.0)	82(1.7)		37(1.8)	56(1.7)	
No	121 (63.0)	2710 (61.4)		518 (58.5)	2313 (62.2)		533 (98.0)	4655 (98.3)		1958 (98.2)	3231 (98.3)	
Duration of exposure in Farm (minutes/ year)			0.08			0.13			0.53			0.73
No	121 (63.0)	2710 (61.4)		518 (58.5)	2313 (62.2)		533 (98.0)	4655 (98.3)		1958 (98.2)	3231 (98.3)	
≤median	45(23.5)	844(19.1)		186 (21.0)	703(18.9)		7(1.3)	62(1.3)		29(1.4)	40(1.2)	
>median	26(13.5)	858(19.5)		181 (20.5)	703(18.9)		4(0.7)	19(0.4)		8(0.4)	15(0.5)	
Use in Yard			0.28			0.61			0.7			0.02
Yes	23(12.0)	654(14.8)		135 (15.3)	542(14.6)		29(5.3)	234(4.9)		118(5.9)	145(4.4)	
No	169 (88.0)	3758 (85.2)		750 (84.8)	3177 (85.4)		516 (94.7)	4503 (95.1)		1878 (94.1)	3142 (95.6)	
Duration of exposure in Yard (minutes/ year)			0.35			0.68			0.82			0.02
No	169 (88.0)	3758 (85.2)		750 (84.8)	31.77 (85.5)		516 (94.7)	4503 (95.1)		1878 (94.1)	3142 (95.6)	
≤median	17(8.8)	411(9.3)		82(9.2)	346(9.3)		17(3.1)	148(3.1)		68(3.4)	97(3.0)	
>median	6(3.2)	242(5.5)		53(6.0)	195(5.2)		12(2.2)	86(1.8)		50(2.5)	48(1.4)	
Use in Home			0.18			<0.001			0.08			0.001
Yes	134 (69.8)	2869 (65.0)		633 (71.6)	2370 (63.7)		460 (84.4)	3861 (81.5)		1679 (84.1)	2643 (80.4)	
No	58(30.2)	1542 (35.0)		251 (28.4)	1349 (36.3)		85(15.6)	876(18.5)		317(15.9)	644(19.6)	
Duration of exposure in Home (minutes/ year)			0.42			<0.001			<0.001			<0.001
No	58(30.4)	1542 (35.0)		251 (28.4)	1349 (36.3)		85(15.6)	876(18.5)		317(15.9)	644(19.6)	
≤median	76(93.8)	1622 (36.8)		350 (39.6)	1348 (36.3)		212 (39.0)	2151 (45.4)		877(44.0)	1487 (45.2)	
>median	57(29.8)	1245 (28.2)		282 (32.0)	1020 (27.4)		247 (45.4)	1710 (36.1)		801(40.1)	1156 (35.2)	
Pesticide Preparation			0.06			0.002			0.81			0.41
Yes	47(24.5)	1357 (30.8)		308 (34.8)	1096 (29.5)		9(1.8)	72(1.5)		27(1.3)	54(1.6)	
No	145 (75.5)	3054 (69.2)		576 (65.2)	2623 (70.5)		536 (98.4)	4665 (98.5)		1969 (98.7)	3233 (98.4)	
Duration of exposure in pesticide preparation (minutes/ year)			0.009			0.001			0.96			0.62
No	145 (75.5)	3054 (69.3)		576 (65.2)	2623 (70.5)		536 (98.4)	4665 (98.5)		1969 (98.7)	3233 (98.4)	
≤median	34(17.7)	709(16.0)		180 (20.4)	563(15.1)		8(1.5)	65(1.4)		25(1.2)	48(1.5)	
>median	13(6.8)	647(14.7)		127 (14.4)	533(14.4)		1(0.1)	7(0.1)		2(0.1)	6(0.1)	
Manage Spraying Pesticide			0.92			0.07			0.19			0.19
Yes	43(22.4)	975(22.1)		216 (24.4)	802(21.6)		23(4.2)	264(5.6)		98(4.9)	189(5.7)	
No	149 (77.6)	3437 (77.9)		669 (75.6)	2917 (78.4)		522 (95.8)	4473 (94.4)		1898 (95.1)	3098 (94.3)	
Duration of exposure in pesticide preparation (minutes/ year)			0.99			0.02			0.15			0.14
No	149 (77.6)	3437 (77.9)		669 (75.6)	2917 (78.4)		522 (95.8)	4473 (94.4)		1898 (95.1)	3098 (94.3)	

(*continued on next page*)

Table 2 (*continued*)

Pesticide Use	Male *n* (%)						Female *n* (%)					
	CPH (n=193)	No CPH (n=4431)	P-value	EPH (n=887)	No EPH (n=3737)	P-value	CPH (n=548)	No CPH (n=4762)	P-value	EPH (n=2002)	No EPH (n=3309)	P-value
≤median	19(9.9)	441(10.0)		84(9.5)	376(10.1)		16(2.9)	219(4.6)		85(4.3)	150(4.6)	
>median	24(12.5)	534(12.1)		132 (14.9)	426(11.5)		7(1.3)	45(1.0)		13(0.6)	39(1.1)	
Total exposures			0.68			0.36			0.16			0.001
Yes	158 (82.3)	3681 (83.4)		747 (84.4)	3092 (83.1)		467 (85.7)	3946 (83.3)		1710 (85.7)	2704 (82.3)	
No	34(17.7)	731(16.6)		138 (15.6)	627(16.9)		78(14.3)	791(16.7)		286(14.3)	583(17.7)	
Total duration of exposures (minutes/ year)			0.88			0.35			0.03			<0.001
No	34(17.7)	731(16.6)		138 (15.6)	627(16.9)		78(14.3)	791(16.7)		286(14.3)	583(17.7)	
≤median	52(27.1)	1170 (26.5)		225 (25.4)	997(26.8)		292 (53.7)	2680 (56.6)		1118 (56.1)	1855 (56.5)	
>median	106 (55.2)	2510 (56.9)		522 (59.0)	2094 (56.3)		174 (32.0)	1266 (26.7)		591(29.6)	849(25.8)	

Abbreviations: Chronic primary headache (CPH); Episodic primary headache (EPH).
Results are expressed as number of participants (column percentage). Between-group comparisons were performed by chi-square test.

3. Results

The age of participants was 35–70 years with a mean of 50.1 ± 9.8 in men and 49.7 ± 9.4 in women. The results of the statistical analysis are presented in Tables 1–3.

Table 1 presented CPH and EPH among men and women based on general characteristics. According to this table, 7.4 % (193 males and 548 females) and 29.9 % (887 males and 2002 females) of this population had CPH and EPH respectively. The average age in the EPH group was lower than healthy people and this difference was significant in both genders ($P < 0.001$), also, BMI in the EPH group ($P < 0.001$), education ($P < 0.001$) and WSI ($P = 0.002$) in CPH group in females; and physical activity in men with CPH ($P = 0.017$) were significantly lower than healthy participants (Table 1).

The prevalence of hypertension in the CPH group was higher in both genders (26.9 % in men and 36.2 % in women) than in healthy individuals, and this difference was significant ($P = 0.007$ in men and $P = 0.001$ in women). Also, in the CPH group, the prevalence of a family history of primary headache was significantly more than no CPH group in both genders (men = 35.8 % and women = 44.3 %) and similar results were observed in the EPH group (men = 30.9 % and women = 40.1 %) ($P < 0.001$). In the EPH group, the percentage of male smokers (55.4 %) was higher than in the no EPH group, and in the CPH group, the percentage of female smokers (4.4 %) was higher than healthy group and these differences were significant ($P = 0.04$ in men and $P = 0.003$ in women). It is noteworthy that, the prevalence of CPH was significantly more in opium consumption in females ($P = 0.009$) (Table 1).

Table 2 shows the prevalence of CPH and EPH according to pesticide exposure by gender. The prevalence of EPH was significantly higher in men who were exposed to pesticides on the farm ($P = 0.04$), at home ($P < 0.001$), in the preparation of pesticides ($P = 0.002$), and also, the duration of exposure to the pesticide at home ≤ median ($P < 0.001$), the duration of pesticide exposure in pesticide preparation ≤ median ($P = 0.001$) and duration of pesticide exposure for manage spraying pesticide > median ($P = 0.02$). The prevalence of EPH was significantly higher in women who were exposed to pesticides in the yard ($P = 0.02$), at home ($P = 0.001$), the duration of exposure to pesticides in the yard ≤ median ($P = 0.02$), and the duration of exposure to pesticides at home ≤ median ($P < 0.001$).

The prevalence of CPH was significantly higher in women who were exposed to pesticides at home > median ($P < 0.001$) and in the men who were exposed to pesticides during the preparation of pesticides ≤ median ($P = 0.009$) (Table 2). The prevalence of EPH was significantly higher in women who have more pesticide exposures ($P = 0.001$). Also, the percentage of women who have CPH and EPH were significantly higher in total duration of pesticide exposures > median ($P = 0.03$ and $P = 0.001$ respectively).

In Table 3, the relationship between headaches and pesticide exposure was examined. The odds ratios (OR) of CPH were associated with pesticide exposure on the farm, in the yard, at home, pesticide preparation, managed spraying of pesticide, and duration of exposure in all of them in the Univariate model. The multivariable model has been examined by adjusting for confounding variables age, gender, education years, BMI, hypertension, family history of primary headache, smoking, opium consumption, Alcohol consumption, and physical activity. According to the data in Table 3, none of the variables had a significant relationship with the prevalence of CPH except pesticide use at home (OR: 1.22; 95 % CI 1.02 to 1.48), duration of exposure to pesticide at home > median (OR: 1.37, 95 % CI 1.11 to1.70) and duration of pesticide exposure in pesticide preparation > median (OR: 0.47, 95 % CI 0.27 to 0.82). These results showed that the odds of CPH increased in participants using pesticides at home and the duration of exposure to pesticides at home was 22 % and 37 % respectively.

There was a relationship between the prevalence of EPH and the exposure to pesticides on the farm, at home, pesticide preparation, managed spraying pesticide, and duration of exposure in all of them in the Univariate model. After adjusting the confounders in the multivariable model, the relationship between the EPH with the exposure to pesticides on the farm (OR: 1.16; 95 % CI 1.02 to 1.34), in the yard (OR: 1.18, 95 % CI 1.01 to 1.39), duration of exposure to pesticide in yard > median (OR: 1.35, 95 % CI 1.06 to 1.73), at home (OR: 1.31, 95 % CI 1.17 to 1.46), duration of exposure to pesticide at home ≤ median (OR: 1.24, 95 % CI 1.10 to 1.40) and > median (OR: 1.38, 95 % CI 1.22 to 1.57) was significant and exposure to pesticides increased odds of EPH. Also, pesticide preparation (OR: 1.20, 95 % CI 1.03 to 1.39), duration of exposure in pesticide preparation ≤ median (OR: 1.31, 95 % CI 1.09 to 1.57) and duration of exposure in manage spraying pesticide > median (OR: 1.28, 95 % CI 1.04 to 1.57) increased odds EPH 20 %, 31 % and 28 % respectively (Table 3).

The odds ratios of EPH had a significant association with total pesticide exposures (OR: 1.18, 95 % CI 1.04 to 1.33) and total duration of pesticide exposures > median (OR: 1.25, 95 % CI 1.09 to 1.43) in the multivariable model. These results showed that the odds of EPH increased in those who have more total pesticide exposures and duration of exposure to pesticides by 18 % and 25 % respectively.

Table 3
The relationship between pesticide exposure with chronic primary headache and episodic primary headache in adult population of Rafsanjan cohort study, launched in 2014.

Pesticide Use	CPH		EPH	
	Univarate	Multivariable	Univarate	Multivariable
	OR (95 %Ci) [a]	OR (95 %Ci) [b]	OR (95 %Ci) [a]	OR (95 %Ci) [b]
Use in Farm				
No	1	1	1	1
Yes	0.52 (0.41–0.65)	1.00 (0.76–1.33)	0.62 (0.55–0.70)	1.16 (1.02–1.34)
Duration of exposure on Farm (minutes/year)				
No	1	1	1	1
≤median	0.65 (0.48–0.86)	1.17 (0.85–1.62)	0.65 (0.55–0.76)	1.16 (0.97–1.39)
>median	0.39 (0.27–0.56)	0.79 (0.52–1.19)	0.59 (0.50–0.70)	1.16 (0.96–1.40)
Use in Yard				
No	1	1	1	1
Yes	0.71 (0.53–0.94)	0.96 (0.71–1.30)	0.89 (0.76–1.03)	1.18 (1.01–1.39)
Duration of exposure in Yard (minutes/year)				
No	1	1	1	1
≤median	0.73 (0.51–1.05)	1.00 (0.70–1.44)	0.81 (0.67–0.99)	1.09 (0.89–1.33)
>median	0.66 (0.41–1.07)	0.89 (0.55–1.45)	0.02 (0.81–1.29)	1.35 (1.06–1.73)
Use in Home				
No	1	1	1	1
Yes	1.49 (1.24–1.80)	1.22 (1.02–1.48)	1.62 (1.46–1.80)	1.31 (1.17–1.46)
Duration of exposure at Home (minutes/year)				
No	1	1	1	1
≤median	1.29 (1.05–1.59)	1.08 (0.87–1.34)	1.52 (1.35–1.70)	1.24 (1.10–1.40)
>median	1.74 (1.42–2.14)	1.37 (1.11–1.70)	1.75 (1.55–1.97)	1.38 (1.22–1.57)
Pesticide preparation				
No	1	1	1	1
Yes	0.44 (0.34–0.59)	0.81 (0.59–1.10)	0.67 (0.59–0.76)	1.20 (1.03–1.39)
Duration of exposure in Pesticide preparation (minutes/year)				
No	1	1	1	1
≤median	0.62 (0.45–0.85)	1.04 (0.74–1.46)	0.77 (0.65–0.91)	1.31 (1.09–1.57)
>median	0.24 (0.14–0.41)	0.47 (0.27–0.82)	55 (0.45–0.67)	1.06 (0.85–1.31)
Manage Spraying Pesticide				
No	1	1	1	1
Yes	0.63 (0.48–0.81)	0.91 (0.69–1.19)	0.74 (0.65–0.85)	1.08 (0.93–1.24)
Duration of exposure in Manage Spraying Pesticide (minutes/year)				
No	1	1	1	1
≤median	0.63 (0.44–0.89)	0.79 (0.56–1.13)	0.75 (0.63–0.90)	0.95 (0.79–1.15)
>median	0.63 (0.44–0.91)	1.09 (0.74–1.61)	0.73 (0.60–0.89)	1.28 (1.04–1.57)
Total exposures				
No	1	1	1	1
Yes	1.11 (0.90–1.37)	1.09 (0.88–1.34)	1.21 (1.07–1.36)	1.18 (1.04–1.33)
Total duration of exposures (minutes/year)				
No	1	1	1	1
≤median	1.21 (0.97–1.52)	1.04 (0.83–1.30)	1.34 (1.18–1.53)	1.12 (0.98–1.28)
>median	1.01 (0.80–1.26)	1.15 (0.91–1.45)	1.08 (0.95–1.23)	1.25 (1.09–1.43)

Abbreviations: Chronic primary headache (CPH); Episodic primary headache (EPH).

[a] The Univariate model is stratified on the status of pesticide use.

[b] The Multivariable is adjusted for confounding variables age (continuous variable), gender (male/female), education years (continuous variable), BMI (continuous variable), hypertension (yes/no), Family history of primary headache (yes/no), smoking (yes/no), opium consumption (yes/no), Alcohol consumption (yes/no) and physical activity (continuous variable).

4. Discussion

In this study, we examined the population of RCS for exposure to pesticides on the farm, in the yard, at home, and the duration of pesticide exposure with the rate of CPH and EPH. As shown in the results, the relationship between EPH in people using pesticides was stronger than CPH. On the other hand, the duration of pesticide exposure at home and pesticide preparation were associated with CPH. This result confirms that CPH require long-term contact with pesticides, to be more effective, especially indoors and in their place of residence. Because pesticide preparation has a shorter contact time, probably it couldn't play as a risk factor for CPH compared to other kinds of contact that have a longer contact period. While, EPH can be associated with the use of pesticides at any place of the activity, regardless of how long it lasts and whether it occurred indoors or outdoors. Duration of exposure in managing spraying pesticide > median was associated with EPH.

People are exposed to a combination of different pesticides daily (Dalvie, 2011; English, 2012). Organophosphates (OPs) are mostly used for outdoor spaces but are also used indoors (Fenske, 2000). OP's, especially Chlorifyros, acutely affect the brain and irreversibly prevent acetylcholinesterase (ACHE) from breaking down neurotransmitters, but at the same time, chronic exposure to this pesticide may also interfere with less intense structural processes in the brain (Li, 2019). In addition, the occurrence of headaches with occupational OP exposure suggests subsequent chronic CNS effects of pesticides (Rastogi et al., 2010). In line with our results, Shala Chetty-Mhlanga et al demonstrated long-term effects of pesticide exposure on headache and cognition (Chetty-Mhlanga, 2021).

Migraine may have evolved as an evolutionary protection mechanism, according to some experts (Jay, 2021). Similarly, increased odor sensitivity may serve as a warning indicator for numerous environmental contaminants. Martin et al. described the safe nature of low-level chemical exposure and the headache syndrome that was the result of chemical exposure (Martin and Becker, 1993). The high-level chemical exposures in their study could make the argument that chemical headaches may have a certain survival value and that severe exposure could lead to severe headaches (Jay, 2021; Martin and Becker, 1993; Blau and Common headaches: type, duration, 1990). Our results suggest using various pesticide-related activities and behaviors for long-term pesticide exposure, had an overall detrimental effect on CPH and EPH, which is mostly significant for the latter.

A recent study showed that short-term exposure to pesticides may trigger migraine. This relationship was especially pronounced on high-temperature days (Lee, 2018). Although limited studies have

examined the relationship between pesticide exposure and migraine, the findings have been mixed in this regard. A study conducted in Edmonton, Canada reported a significantly increased risk of migraine associated with exposure to pesticides (Szyszkowicz et al., 2009). Hyewon Lee et al. found that short-term exposure to higher concentrations of PM2.5, PM10, NO2, O3, and CO immediately increased the risk of migraine (Lee, 2018). Our results also showed that the use of pesticides at home increased the types of headaches and this observation was more in women. Johnsen (2018) showed that there was no strong evidence that headaches were associated with smoking in smokers. The findings from this study do not support that there was a strong causal relationship between smoking intensity and any type of headache (Johnsen, 2018). Considering that in our study demographic table, a relationship was observed between headache and smoking, but after controlling the effect of smoking in the model, the relationship between headache and pesticide exposure was significant.

In another study ten trigger factors were examined and compared in migraine patients, but toxins and pesticides were not discussed as a trigger (Karsan, 2021). Schulte et al in another study looking at the connections between reported trigger factors and premonitory symptoms in migraine, discussed 24 triggers, but again no mention of toxins as a trigger in this study (Schulte et al., 2015). As we checked other previous studies, toxins were not common migraine triggers and were not described in many studies (Hoffmann and Recober, 2013; Hindiyeh, 2020). This may be because the use of pesticides was so widespread in our area therefore toxins have been specifically studied.

The main limitation of our study was its cross-sectional design which refrained us from deriving any causal inferences. One of the limitations of our study was the lack of measurement of pesticide level in the body of cases and lack of detail on the type of pesticides, since active ingredients may have very different effects depending on whether they were insecticides or herbicides, for example. Another limitation of our study was its dependence on the questionnaire, which reduced the accuracy of the results of this study. Another limitation of the study was the lack of a detailed questionnaire to determine the type of acute or chronic headache and the year of EPH onset, which has reduced the scope of discussion on the types of headaches and their relationship to pesticides. Since the occupation of most of the people is agriculture and they were exposed to agricultural pesticides and the use of pesticides is critical for farmers and their products and there is no other potent biological way for this problem, its use has continued permanently during the past 40 years, the exact year of using agricultural pesticides was not asked.

Our study advantages are the participants' number, the cohort–based study, a detailed questionnaire about the use of pesticides, and a trained cohort team that has improved the quality of the study. We recommend that follow-up of our cohort study cases with a high number of pesticide exposures for many years and collect more information about our participants and new events in them that could be related to pesticide exposure.

5. Conclusion

In general, it can be concluded that the use of pesticides outdoors is associated more with EPH, and indoors, such as those used at home, we can face a higher risk of CPH. CPH is less likely to occur when preparing pesticides is considered, which takes less time than using pesticides. The importance of our findings is due to the reference to specific activities related to pesticide exposure in adults.

6. Ethics approval and consent to participate

The ethics committee of RUMS approved this study (Ethical codes: ID: IR.RUMS.REC.1400.016). Participants entered the study with informed consent. The names of the participants were kept confidential and only the data were available to the study investigators.

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CRediT authorship contribution statement

Alireza Vakilian: Writing – review & editing, Methodology, Formal analysis, Data curation. **Parvin Khalili:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Zahra Jamali:** Writing – review & editing, Writing – original draft. **Amir Moghadam -Ahmadi:** Writing – review & editing, Writing – original draft. **Nazanin Jalali:** Writing – review & editing, Writing – original draft, Data curation. **Movahedeh Mohamadi:** Writing – review & editing, Methodology, Data curation. **Seyed Hamid Pakzadmoghadam:** Writing – review & editing, Writing – original draft. **Fatemeh Ayoobi:** Writing – review & editing, Methodology, Formal analysis, Data curation.

Declaration of competing interest

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

Data availability

Data will be made available on request.

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Author contributions

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Alireza Vakilian, Fatemeh Ayoobi, Parvin Khalili, Nazanin Jalali, and Movahedeh Mohamadi. The first draft of the manuscript was written by Fatemeh Ayoobi, Zahra Jamali, Seyed Hamid Pakzadmoghadam, and Amir Moghadam-Ahmadi, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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