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ORIGINAL RESEARCH

The Association Between Long-Term Spicy-Food Consumption and the Incidence of Chronic Postsurgical Pain After Cesarean Delivery: An Observational Study

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Background: Our previous study found that a long-term diet incorporating spicy foods can reduce the human basal pain threshold. Capsaicin is the pungent ingredient in chili peppers. Transient receptor potential vanilloid type1 is the capsaicin receptor expressed in the oral cavity and is the primary sensory neuron of the "pain" pathway. Few studies have examined the association between long-term spicy diet and chronic postsurgical pain (CPSP). Women who underwent elective cesarean section (eCS) have consistent characteristics of CPSP. This study aimed to investigate the relationship between a long-term spicy diet and the incidence of CPSP after eCS.

Methods: Participants were divided into a low frequency group (LF, numerical rating scale (NRS)<5) for spicy food consumption and a high frequency group (HF, NRS≥5) by receiver operator characteristic analysis. The primary outcome was the incidence of CPSP three months after eCS. Propensity score matching (PSM) analysis was performed between the two frequency groups. Stepwise logistic regression analysis was then performed.

Results: Of the 1029 enrolled patients, data from 982 were analyzed 3 months after eCS. After PSM, the incidence of CPSP in the HF group (30.1% [108/359]) was higher than that in the LF group (19.8% [71/359]; $P = 0.001$). Compared with the LF group, the risk of CPSP in the HF group increased 1.61 times by 3 months (95% CI 1.18–2.20, $P = 0.003$). PSM results found that 1 year, the incidence of CPSP in the HF group (15.2% [56/369]) was higher than that in the LF group (8.1% [30/369], P = 0.003).

Conclusion: With an NRS≥5 as a boundary, women who consumed spicy food ≥ 2 days/week were more likely to have CPSP than those who consumed spicy food < 2 days/week.

Keywords: long-term spicy diet, chronic postsurgical pain, capsaicin, TRPV1, cesarean section

Introduction

The global taste for spicy foods is increasing, as demonstrated by an international survey that reported that nearly 70% of respondents listed "spicy" as one of their top three food choices, which fuels a worldwide trend towards greater consumption of spicy foods.[1] As such, there is a corresponding increasing scientific interest in spicy foods.[2] Our previous study found that a long-term spicy diet can reduce the human basal pain threshold.[3] Furthermore, some studies have found that the capsaicin receptor, transient receptor potential vanilloid type1 (TRPV1), is the primary sensory neuron of the "pain" pathway,[4,5] as well as the integration of diverse painful stimuli.[6] Another study showed that capsaicin is the pungent ingredient in chili pepper and TRPV1 is expressed in taste buds and epithelial keratinocytes

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throughout the oral cavity.[7] However, evidence related to the relationship between a long-term spicy diet and increased pain sensitivity is insufficient, especially in post-surgical populations.

Chronic postsurgical pain (CPSP) is a heightened pain sensitivity that is far more common than other postoperative complications.[8] The annual number of surgeries performed worldwide is approximately 320 million.[9] The National Bureau of Statistics of China has reported that the number of inpatient surgeries in 2019 exceeded 69.3 million.[10] This phenomenon indicates that a considerable number of patients suffer from CPSP, which can continue for months or years after surgery. Although pain is a psychological sensory experience, it is an integrated manifestation of physiological, genetic, and psychosocial backgrounds.[11] In terms of postoperative pain, the surgery itself is only a small part of the cause. Therefore, identification of high-risk patients is critical for early intervention in CPSP.[8] Many studies have analyzed the risk factors for CPSP[11] and established a predictive model of CPSP.[12] However, few studies have focused on the relationship between a long-term spicy diet and CPSP.

Women who underwent elective cesarean section (eCS) have relatively consistent characteristics for the investigation of CPSP. The incidence of CPSP after CS is as high as 15%-18.3%.[13,14] Therefore, optimizing the perioperative program for the unique CS population to reduce the occurrence of CPSP is a major issue worthy of attention. The purpose of this study was to evaluate the association between long-term spicy dietary habits and the incidence of CPSP after eCS to provide a reference for the identification of high-risk populations and the optimization of perioperative schemes.

Materials and Methods

Study Design

This investigation was a prospective cohort study of Chinese patients who underwent eCS at a tertiary referral hospital (the Second Affiliated Hospital of the Army Medical University) in Chongqing, China, from August 20, 2018, to March 5, 2020 (Figure 1). The protocol, including data and statistical analyses, was approved by the Medical Ethics Committee of the Second Affiliated Hospital, Army Military Medical University (approval ID:2018–030-01) before data were accessed. Written informed consent was obtained from all participants before the study. This manuscript adheres to STROBE guidelines.

Participants

The inclusion criteria were patients aged 20–40 years, American Society of Anesthesiologists class II, and singleton full-term pregnant women who underwent eCS. The exclusion criteria included a history of smoking, alcohol and opioid abuse, or chronic dysmenorrhea, use of analgesics in the past three months, history of chronic pain, and lack of cooperation with the research.

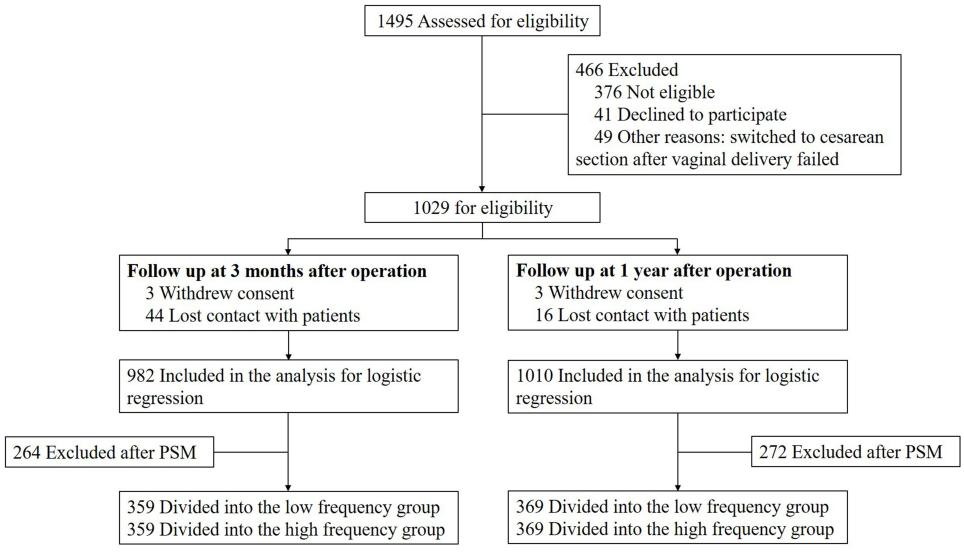

Figure 1 Trial flow chart.
Abbreviations: PSM, propensity score matching; low group, NRS < 5 of the frequency for spicy food consumption; high group, NRS ≥ 5 of the frequency for spicy food consumption.

Setting

This investigation was an observational study that did not interfere with any clinical decisions. An experienced anesthesiologist and obstetrician implemented a standardized CS under standard spinal anesthesia for each participant. When the patient was hospitalized before CS, sleep quality in the last week and the frequency of spicy food consumption were recorded. Sleep quality was self-reported by the patients and rated on five levels (very bad, bad, general, good, and very good). A numerical rating scale (NRS; 0, never eat, 1:1 day/month, 2:2 days/month, 3:3 days/month, 4:1 day/week, 5:2 days/week, 6:3 days/week, 7:4 days/week, 8:5 days/week, 9:6 days/week, 10:7 days/week) was used to quantify the self-reported frequency of spicy food consumption. At hospital admission, the preoperative Edinburgh Postpartum Depression Scale (EPDS) and Generalized Anxiety Disorder 7-item (GAD-7) questionnaires were administered by a professionally trained researcher in face-to-face interviews. The GAD-7 is a common tool for screening for GAD in general hospitals in China (a GAD-7 score > 9 indicates the presence of GAD).[15,16] Patient self-report EPDS is a commonly used instrument for screening perinatal depression.[17,18] The recommended cut-off score for screening depressive illness in the Chinese general postnatal population is equal to or greater than 10;[18] thus, an EPDS < 10 represents no state of antenatal depression (AD), and an EPDS ≥ 10 indicates a state of AD (no/yes). Other relevant data were collected from the electronic medical record system of the hospital, including age, body mass index (BMI), number of previous CSs, number of previous non-CS surgeries, complications (yes/no), and history of dysmenorrhea (yes/no). The operation duration was obtained from the electronic anesthesia recording system of the hospital. Pain intensity was quantified using an 11-point NRS (0 represents "no pain" and 10 represents "unbearable pain"). The main follow-up item during hospitalization was the incidence of inadequate analgesia (NRS score > 4) within 48 hours after surgery. At three months (± 3 days) and one year (± 7 days) after surgery, follow-up telephone calls were made to every participant to assess the presence of chronic pain. Patients who were not contacted within the time window were considered to be lost to follow-up. Moreover, patients who were lost to follow-up at three months still need to be followed up for one year. The items in the questionnaires mainly contained the following: (1) Do you still have any pain that you could link to your surgery or surgical procedures? (2) Location of the painful area, (3) immediate pain intensity and maximum pain intensity in the past week, (4) pain onset time, (5) duration of pain, (6) feeling of pain, (7) Was your mood affected? (8) Are your sleep quality affected? (9) Was your daily life affected? (10) Did you use analgesics? And (11) Did you seek medical attention? Participants who were lost to the three months follow-up were contacted for a one-year telephone follow-up.

Outcomes

The 11th revision of the International Classification of Diseases defines CPSP as pain developing or increasing in intensity after a surgical procedure, in the area of the surgery, persisting beyond the healing process (ie, at least three months), and that is not better explained by other causes such as infections, malignancies, or pre-existing pain conditions.[19] Therefore, the incidence of CPSP three months after eCS was the primary outcome. Participants who answered "yes" to the question, "Do you still have any pain that you could link to a surgery or surgical procedure?" were defined as pain cases. All adverse responses were classified as those without pain.

Considering that CPSP may last longer, we regarded the incidence of CPSP one year after CS as a secondary outcome to observe long-term effects. In addition, other secondary outcomes included the characteristics of pain at three months and one year after CS. Pain features included the pain site (wound, near the wound, intra-abdominal, wound and intra-abdominal, and unlocated), immediate pain intensity and maximum pain intensity in the past week (assessed using the numerical rating scale [NRS]), pain onset time (occasionally, during activities, at nighttime, in the daytime, during rainy weather, and during hot weather), duration of pain (occasionally, last week, last month, and from the operation to the present), feeling of pain (aching, stabbing, cramping, inexplicable, and others), whether it affected the patient's mood, quality of sleep, or daily life, and use of analgesic drugs or seeking of medical attention.

Statistical Analysis

Stata version 15.0 (StataCorp) and R software (version 3.0.1; http://www.Rproject.org) were used to perform statistical analyses. The "OptimalCutpoints" package in R was used for the receiver operator characteristic (ROC) analysis to determine the cut-off of the NRS scores of the frequency for spicy food consumption. To better understand the relationship between the frequency of spicy

food consumption and outcomes, participants were divided into a low-frequency group (NRS < cut-off value, LF group) and a high-frequency group (NRS ≥ cut-off value, HF group). A two-tailed P-value less than 0.05 was considered statistically significant. Data are summarized as the mean (standard deviation), number (frequency), or median (interquartile range). Considering the influence of bias and confounding variables in the observational study, the "MatchIt" package in R was used to perform propensity score matching (PSM) between the LF and HF groups in 1:1 nearest neighbor matching without replacement under a logit model (caliper = 0.2). The propensity score was calculated for the significantly different baseline variables between the LF and HF groups. Before and after PSM, the incidence of CPSP at three months and one year was compared between the two frequency groups. The data of participants who underwent CPSP after PSM were extracted to further investigate the pain features. Chi-square tests, nonparametric tests, Fisher's exact test, and analysis of variance statistical tests were performed to compare the two groups in terms of categorical and continuous variables. For sensitivity analyses, a stepwise logistic regression analysis was used to screen the optimal model at 10 levels of pe (0.2, 0.1, 0.01, 0.001, 0.0001), pr (0.02, 0.2, 0.1, 0.3), and pe (0.05) pr (0.2) to ensure that the factors included in the model are significant without serious multicollinearity. According to the principle of model selection, the model with the minimum Akaike information criterion (AIC) value and variable number was selected. As we excluded patients with missing essential data from our analysis, we did not impute missing data.

Power Analysis

At Three Months After CS

In this study, the incidence of CPSP three months after CS was considered the primary outcome. PASS software version 11.0 (NCSS, Kayesville, UT, USA) was used to calculate power. Group sample sizes of 359 in the HF group and 359 in the LF group after PSM achieved 90% power to detect an odds ratio in the group proportions of 1.75. The proportion in the HF group was assumed to be 0.198 under the null hypothesis and 0.30 under the alternative hypothesis. The proportion of patients in the LF group was 0.1980. The proportion of patients in the LF group was 0.08. The test statistic used is the two-sided Likelihood Ratio test. The significance level of the test was set at $P < 0.05$.

A logistic regression of a binary primary outcome on a binary independent variable (frequency for spicy consumption) with a sample size of 982 observations (of which 42% are in the group frequency for spicy consumption = 0 and 58% are in the group frequency for spicy consumption = 1) achieves 91% power at a 0.05 significance level to detect a change in Prob (Y=1) from the baseline value of 0.230 to 0.325. This change corresponded to an odds ratio (OR) of 1.610.

At One Year After CS

Group sample sizes of 369 in the HF group and 369 in the LF group after PSM achieved 84% power to detect an odds ratio in the group proportions of 2.02. The proportion in the HF group was assumed to be 0.08 under the null hypothesis and 0.15 under the alternative hypothesis. The proportion of patients in the LF group was 0.08. The two-sided Likelihood Ratio test was used with significance set at $P < 0.05$.

A logistic regression of a binary response variable on a binary independent variable (frequency for spicy consumption) with a sample size of 1010 observations (of which 42% are in the group frequency for spicy consumption = 0 and 58% are in the group frequency for spicy consumption = 1) achieves 92% power at a 0.05 significance level to detect a change in Prob (Y = 1) from the baseline value of 0.120 to 0.198. This change corresponded to an odds ratio (OR) of 1.810.

Results

Of the 1029 patients enrolled, 47 patients (4.6% [47/1029]) lacked data for the primary outcome, and data from 982 eligible patients were eventually collected at the three months after CS (Figure 1). 19 patients (1.9% [19/1029]) lacked data, and a total of 1010 eligible patients were collected at the one-year mark. Based on the ROC analysis, the cut-off value of the frequency for spicy food consumption was determined to be "NRS = 5", thus, an NRS score ≥ 5 indicates a high frequency (HF) group for spicy food consumption, and an NRS score < 5 indicates a low frequency (LF) group. The demographic and clinical data for all subjects at three months after eCS are shown in Table 1, and those at one year after CS are shown in Table 2.

Table 1 Demographic and Clinical Characteristics at Baseline for the Data of 3 Months After CS

	Unmatched Cohort			Matched Cohort			
	LF Group (n=411)	HF Group (n=571)	P value	LF Group (n=359)	HF Group (n=359)	Standardized Differences	P value
Age*	30.88 (4.06)	31.04 (4.37)	0.553	30.83 (3.99)	30.70 (4.47)	0.032	0.685
BMI*	27.87 (3.24)	27.59 (3.29)	0.183	27.77 (3.24)	27.69 (3.28)	0.023	0.757
Occupation#			<0.001				0.588
Farmer	3 (0.7)	19 (3.3)		3 (0.8)	6 (1.7)	−0.098	
Worker	4 (1.0)	14 (2.5)		4 (1.1)	7 (1.9)	−0.085	
Student	0 (0.0)	1 (0.2)		0 (0.0)	0 (0.0)	0.000	
Soldier	0 (0.0)	1 (0.2)		0 (0.0)	0 (0.0)	0.000	
Staff or civil servant	133 (32.4)	224 (39.2)		122 (34.0)	117 (32.6)	0.030	
Others	271 (65.9)	312 (54.6)		230 (64.1)	229 (63.8)	0.006	
Educational level#			0.515				0.744
Illiteracy	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	0.000	
≤6 years	3 (0.7)	10 (1.8)		2 (0.6)	3 (0.8)	−0.033	
6–9 years	77 (18.7)	98 (17.2)		63 (17.5)	65 (18.1)	−0.014	
9–12 years	92 (22.4)	125 (21.9)		78 (21.7)	88 (24.5)	−0.067	
≥12 years	239 (58.2)	338 (59.2)		216 (60.2)	203 (56.5)	0.073	
Marital status#			0.409				>0.999
Married	407 (99.0)	567 (99.3)		358 (99.7)	357 (99.4)	0.028	
Unmarried	1 (0.2)	3 (0.5)		1 (0.3)	2 (0.6)	−0.057	
Divorced	3 (0.7)	1 (0.2)		0 (0.0)	0 (0.0)	0.000	
Monthly household income# (yuan)			<0.001				0.834
0–1500	2 (0.5)	2 (0.4)		0 (0.0)	1 (0.3)	−0.040	
1500–4500	53 (12.9)	49 (8.6)		45 (12.5)	40 (11.1)	0.042	
4500–9000	276 (67.2)	288 (50.4)		234 (65.2)	237 (66.0)	−0.018	
9000–35,000	77 (18.7)	228 (39.9)		77 (21.4)	77 (21.4)	0.000	
>35,000	3 (0.7)	4 (0.7)		3 (0.8)	4 (1.1)	−0.033	
Sleep quality in the last week#			0.003				0.629
Very bad	2 (0.5)	1 (0.2)		2 (0.6)	1 (0.3)	0.040	
Bad	80 (19.5)	161 (28.2)		78 (21.7)	82 (22.8)	−0.028	
General	181 (44.0)	254 (44.5)		156 (43.5)	168 (46.8)	−0.067	
Good	143 (34.8)	145 (25.4)		119 (33.1)	102 (28.4)	0.099	
Very good	5 (1.2)	10 (1.8)		4 (1.1)	6 (1.7)	−0.051	
Number of CS#			0.604				0.652
0	141 (34.3)	174 (30.5)		126 (35.1)	118 (32.9)	0.047	
1	252 (61.3)	369 (64.6)		218 (60.7)	224 (62.4)	−0.034	
2	17 (4.1)	25 (4.4)		14 (3.9)	17 (4.7)	−0.042	
3	1 (0.2)	3 (0.5)		1 (0.3)	0 (0.0)	0.057	
Complication#			0.138				0.649
No	177 (43.1)	219 (38.4)		150 (41.8)	143 (39.8)	0.039	
Yes	234 (56.9)	352 (61.7)		209 (58.2)	216 (60.2)	−0.039	
Surgery history#			0.928				0.854
0	323 (78.6)	443 (77.6)		282 (78.6)	281 (78.3)	0.007	
1	78 (19.00)	115 (20.1)		68 (18.9)	71 (19.8)	−0.021	
2	10 (2.4)	11 (1.9)		9 (2.5)	7 (1.9)	0.036	
3	0 (0.0)	1 (0.2)		0 (0.0)	0 (0.0)	0.000	
4	0 (0.0)	1 (0.2)		0 (0.0)	0 (0.0)	0.000	

(*Continued*)

Table 1 (Continued).

	Unmatched Cohort			Matched Cohort			
	LF Group (n=411)	HF Group (n=571)	P value	LF Group (n=359)	HF Group (n=359)	Standardized Differences	P value
Dysmenorrhea[#]			0.698				0.846
No	338 (82.2)	475 (83.2)		293 (81.6)	296 (82.5)	−0.022	
Yes	73 (17.8)	96 (16.8)		66 (18.4)	63 (17.5)	0.022	
State of AD[#]			0.001				0.923
No	340 (82.7)	419 (73.4)		293 (81.6)	295 (82.2)	−0.015	
Yes	71 (17.3)	152 (26.6)		66 (18.4)	64 (17.8)	0.015	
State of GAD[#]			0.261				0.602
No	404 (98.3)	555 (97.2)		353 (98.3)	350 (97.5)	0.065	
Yes	7 (1.7)	16 (2.8)		6 (1.7)	9 (2.5)	−0.065	
Operation duration* (min)	86.44 (24.93)	82.64 (26.56)	0.023	85.39 (24.09)	83.81 (24.80)	0.064	0.385
Intraoperative blood loss[#]			0.262				0.367
<1000mL	400 (97.3)	548 (96.0)		349 (97.2)	351 (97.8)	−0.035	
≥1000mL	8 (1.9)	15 (2.6)		8 (2.2)	8 (2.2)	0.000	
≥1500mL	2 (0.5)	8 (1.4)		2 (0.6)	0 (0.0)	0.080	
≥2500mL	1 (0.2)	0 (0.0)		0 (0.0)	0 (0.0)	0.000	
Inadequate analgesia within after operation[#]			0.483				0.900
No	370 (90.0)	506 (88.6)		323 (90.0)	325 (90.5)	−0.019	
Yes	41 (10.0)	65 (11.4)		36 (10.0)	34 (9.5)	0.019	

Notes: Data are described as *mean ± standard deviation, or [#]number (percentage). *Analyzed by the analysis of variance. [#]Analyzed by the Chi-square test or Fisher's exact test. Number of CS and surgery history refer to the number of previous cesarean section and the number of previous surgery except cesarean section, respectively; "YES" indicates the EPDS (Preoperative Edinburgh Postpartum Depression Scale) ≥10 in the state of AD, GAD-7 (Generalized Anxiety Disorder 7-item) >9 in the state of GAD, and NRS (numerical rating scale) score > 4 in the inadequate analgesia within after operation.

Abbreviations: LF, low frequency; HF, high frequency; BMI, body mass index; CS, cesarean section; AD, antenatal depression; GAD, generalized anxiety disorder; CPSP, chronic postsurgical pain; OR, odds ratio; CI, confidence interval.

Short-Term Outcomes

The incidence of CPSP at three months after CS was 23.1% (227/982). In the unmatched cohort, we identified 411 patients in the low frequency group and compared them with 571 patients in the high group. As shown in Table 1, the significantly different factors between the LF and HF groups were the occupation ($P < 0.001$), monthly household income ($P < 0.001$), sleep quality in the last week before CS ($P = 0.003$), state of AD ($P = 0.001$), operation duration ($P = 0.023$). The propensity score was calculated for all baseline variables. After PSM, in the matched cohort, the analysis compared 359 subjects in the LF group and 359 subjects in the HF group (Table 1). There were no significant differences in the demographic and clinical data between the two groups. The incidence of CPSP at the three months after CS in the HF group (30.1% [108/359]) was significantly higher than that in the LF group (19.8% [71/359], P=0.001, Table 3). To further investigate the pain features, the data of subjects with CPSP (71 in the LF group and 108 in the HF group) after PSM were extracted, with no statistical difference in the baseline data between the two groups. The results are shown in Figure S1. The immediate NRS scores (2 [1, 5]) at three months after CS in the HF group were significantly higher than that (2 [1, 3]) in the LF group ($P = 0.018$), as were the maximum NRS scores (2 [1, 5]; 2 [1, 4]; P=0.014). There were no significant differences in the other pain characteristics.

Sensitivity analyses were performed through the stepwise logistic regression. The optimal model filtered is shown in Figure 2. Compared to the low frequency group (NRS < 5), the risk of CPSP in the group of high frequency increased 1.61 times by three months after CS (NRS ≥ 5, OR 1.61, 95% CI 1.18–2.20, $P = 0.003$). Moreover, the occurrence of insufficient analgesia within 48 h after CS (OR 1.94, 95% CI 1.25–3.01, $P = 0.003$), fewer CS times in the past (OR 0.75, 95% CI 0.56–0.99, $P = 0.04$), and younger age (OR 0.96, 95% CI 0.93–1.00, $P = 0.03$) were also high-risk factors for CPSP at three months after surgery.

Table 2 Demographic and Clinical Characteristics at Baseline for the Data of 1 Year After CS

	Unmatched Cohort			Matched Cohort			
	LF Group (n=424)	HF Group (n=586)	P value	LF Group (n=369)	HF Group (n=369)	Standardized Differences	P value
Age*	30.84 (4.09)	31.04 (4.36)	0.472	30.89 (4.13)	30.90 (4.52)	−0.001	0.986
BMI*	27.86 (3.22)	27.58 (3.27)	0.185	27.79 (3.28)	27.64 (3.28)	0.045	0.552
Occupation#			<0.001				0.958
Farmer	3 (0.7)	20 (3.4)		3 (0.8)	4 (1.1)	−0.032	
Worker	5 (1.2)	13 (2.2)		5 (1.4)	4 (1.1)	0.025	
Student	0 (0.0)	1 (0.2)		0 (0.0)	0 (0.0)	0.000	
Soldier	0 (0.0)	2 (0.3)		0 (0.0)	0 (0.0)	0.000	
Staff or civil servant	135 (31.8)	232 (39.6)		122 (33.1)	125 (33.9)	−0.018	
Others	281 (66.3)	318 (54.3)		239 (64.8)	236 (64.0)	0.017	
Educational level#			0.588				0.807
Illiteracy	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	0.000	
≤6 years	4 (0.9)	10 (1.7)		3 (0.8)	2 (0.5)	0.028	
6–9 years	81 (19.1)	98 (16.7)		73 (19.8)	75 (20.3)	−0.014	
9–12 years	96 (22.6)	133 (22.7)		84 (22.8)	93 (25.2)	−0.058	
≥12 years	243 (57.3)	345 (58.9)		209 (56.6)	199 (53.9)	0.055	
Marital status#			0.328				>0.999
Married	420 (99.1)	581 (99.1)		368 (99.7)	367 (99.5)	0.028	
Unmarried	1 (0.2)	4 (0.7)		1 (0.3)	1 (0.3)	0.000	
Divorced	3 (0.7)	1 (0.2)		0 (0.0)	1 (0.3)	−0.032	
Monthly household income# (yuan)			<0.001				0.953
0–1500	2 (0.5)	2 (0.3)		1 (0.3)	1 (0.3)	0.000	
1500–4500	57 (13.4)	52 (8.9)		48 (13.0)	43 (11.7)	0.040	
4500–9000	283 (66.8)	297 (50.7)		241 (65.3)	242 (65.6)	−0.006	
9000–35,000	79 (18.6)	230 (39.2)		77 (20.9)	80 (21.7)	−0.021	
>35,000	3 (0.7)	5 (0.9)		2 (0.5)	3 (0.8)	−0.032	
Sleep quality in the last week#			0.001				0.550
Very bad	2 (0.5)	1 (0.2)		1 (0.3)	1 (0.3)	0.000	
Bad	82 (19.3)	166 (28.3)		80 (21.7)	87 (23.6)	−0.048	
General	185 (43.6)	261 (44.5)		159 (43.1)	173 (46.9)	−0.077	
Good	150 (35.4)	148 (25.3)		125 (33.9)	104 (28.2)	0.119	
Very good	5 (1.2)	10 (1.7)		4 (1.1)	4 (1.1)	0.000	
Number of CS#			0.911				0.956
0	141 (33.3)	187 (31.9)		121 (32.8)	126 (34.1)	−0.029	
1	265 (62.5)	373 (63.7)		232 (62.9)	226 (61.2)	0.034	
2	17 (4.0)	23 (3.9)		15 (4.1)	16 (4.3)	−0.014	
3	1 (0.2)	3 (0.5)		1 (0.3)	1 (0.3)	0.000	
Complication#			0.066				0.453
No	185 (43.6)	222 (37.9)		154 (41.7)	143 (38.8)	0.060	
Yes	239 (56.4)	364 (62.1)		215 (58.3)	226 (61.2)	−0.060	
Surgery history#			0.680				0.888
0	335 (79.0)	456 (77.8)		292 (79.1)	297 (80.5)	−0.033	
1	78 (18.4)	116 (19.8)		68 (18.4)	64 (17.3)	0.028	
2	11 (2.6)	11 (1.9)		9 (2.4)	8 (2.2)	0.017	
3	0 (0.0)	2 (0.3)		0 (0.0)	0 (0.0)	0.000	
4	0 (0.0)	1 (0.2)		0 (0.0)	0 (0.0)	0.000	

(*Continued*)

Table 2 (Continued).

	Unmatched Cohort			Matched Cohort			
	LF Group (n=424)	**HF Group (n=586)**	**P value**	**LF Group (n=369)**	**HF Group (n=369)**	**Standardized Differences**	**P value**
Dysmenorrhea[#]			0.928				0.848
No	350 (82.5)	485 (82.8)		304 (82.4)	301 (81.6)	0.021	
Yes	74 (17.5)	101 (17.2)		65 (17.6)	68 (18.4)	−0.021	
State of AD[#]			0.001				>0.999
No	346 (81.6)	424 (72.4)		293 (79.4)	292 (79.1)	0.007	
Yes	78 (18.4)	162 (27.6)		76 (20.6)	77 (20.9)	−0.007	
State of GAD[#]			0.256				>0.999
No	417 (98.3)	570 (97.3)		362 (98.1)	362 (98.1)	0.000	
Yes	7 (1.7)	16 (2.7)		7 (1.9)	7 (1.9)	0.000	
Operation duration* (min)	86.72 (25.55)	82.16 (26.38)	0.006	85.84 (25.12)	84.07 (26.94)	0.069	0.357
Intraoperative blood loss[#]			0.227				0.925
<1000mL	413 (97.4)	562 (95.9)		360 (97.6)	358 (97.0)	0.034	
≥1000mL	8 (1.9)	16 (2.7)		7 (1.9)	9 (2.4)	−0.040	
≥1500mL	2 (0.5)	8 (1.4)		2 (0.5)	2 (0.5)	0.000	
≥2500mL	1 (0.2)	0 (0.0)		0 (0.0)	0 (0.0)	0.000	
Inadequate analgesia within after operation[#]			0.394				>0.999
No	384 (90.6)	521 (88.9)		332 (90.0)	331 (89.7)	0.009	
Yes	40 (9.4)	65 (11.1)		37 (10.0)	38 (10.3)	−0.009	

Notes: Data are described as *mean ± standard deviation, or [#]number (percentage). *Analyzed by the analysis of variance. [#]Analyzed by the Chi-square test or Fisher's exact test. Number of CS and surgery history refer to the number of previous cesarean section and the number of previous surgery except cesarean section, respectively; "YES" indicates the EPDS (Preoperative Edinburgh Postpartum Depression Scale) ≥10 in the state of AD, GAD-7 (Generalized Anxiety Disorder 7-item) >9 in the state of GAD, and NRS (numerical rating scale) score > 4 in the inadequate analgesia within after operation.

Abbreviations: LF, low frequency; HF, high frequency; BMI, body mass index; CS, cesarean section; AD, antenatal depression; GAD, generalized anxiety disorder; CPSP, chronic postsurgical pain; OR, odds ratio; CI, confidence interval.

Table 3 The Incidence of CPSP Between the Low and High Group

3 Months	**Unmatched Cohort**			**Matched Cohort**			
	LF Group (NRS<5) N=411	**HF Group (NRS≥5) N=571**	***P* value**	**LF Group (NRS<5) N=359**	**HF Group (NRS≥5) N=359**	**OR (95% CI)**	***P* value**
CPSP at 3 months after CS*							
Yes	76 (18.5)	151 (26.4)	0.004	71 (19.8)	108 (30.1)	1.75 (1.24, 2.46)	0.001
No	335 (81.5)	420 (73.6)		288 (80.2)	251 (69.9)		
1 year	**N=424**	**N=586**		**N=369**	**N=369**		
CPSP at 1 year after CS*							
Yes	38 (9.0)	84 (14.3)	0.010	30 (8.1)	56 (15.2)	2.02 (1.26, 3.23)	0.003
No	386 (91.0)	502 (85.7)		339 (91.9)	313 (84.8)		

Notes: Data are described as number (percentage). *Analyzed by the Chi-square test.

Abbreviations: LF, low frequency; HF, high frequency; CPSP, chronic postsurgical pain; PSM, propensity score matching; CS, cesarean section.

Long-Term Outcomes

The incidence of CPSP at one year after CS was 12.1% (112/1010). In the unmatched cohort, we identified 424 patients in the low frequency group and compared them with 586 patients in the high group. As shown in Table 2, monthly household income ($P < 0.001$), occupation ($P < 0.001$), sleep quality in the last week before CS ($P = 0.001$), state of AD

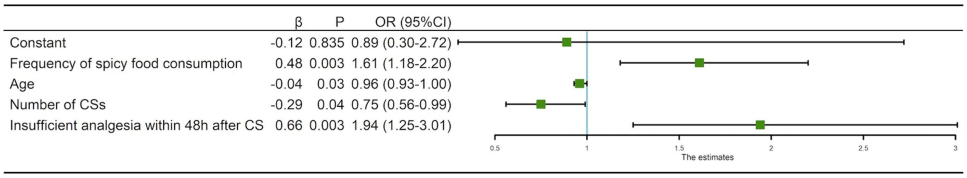

Figure 2 Risk factors for the incidence of CPSP at three months after CS (all demographic and clinical data were entered in a step-by-step logistic regression model, and finally the AIC value of the optimal model was 1043.659; R^2 = 0.027).
Abbreviations: CPSP, chronic postsurgical pain; CS, cesarean section; AIC, Akaike information criterion.

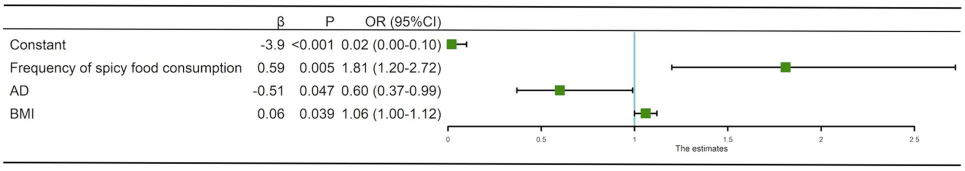

Figure 3 Risk factors for the incidence of CPSP at one year after CS (all demographic and clinical data were entered in a step-by-step logistic regression model, and finally the AIC value of the optimal model was 763.7911; R^2 = 0.03).
Abbreviations: CPSP, chronic postsurgical pain; CS, cesarean section; AD, antenatal depression; AIC, Akaike information criterion.

(P = 0.001), and operation duration (P = 0.006) were significantly different between the LF and HF groups. The propensity score was calculated for all baseline variables. After PSM, the analysis compared 369 subjects in the LF group and 369 subjects in the HF group (Table 2). All covariates were not statistically different between the two groups. The incidence of CPSP at one year after CS in the HF group (15.2% [56/369]) was significantly higher than that in the LF group (8.1% [30/369], P=0.003). To further investigate the pain features, the data of subjects with CPSP (30 in the low group and 56 in the high group) after PSM were extracted, with no statistical difference found in the baseline data between the two groups. The results are shown in Figure S2. The onset time of CPSP was significantly different between the two groups (P = 0.02). There were no significant differences in the other pain features. It is worth noting that in the overall population, a total of 15 people (12.3% [15/122]) sought medical advice for CPSP at one year after the operation; however, 0 subjects sought medical advice after three months.

A stepwise logistic regression analysis was also performed, and the optimal model is shown in Figure 3. As the result of 3 months after the operation, the spicy frequency was also a high-risk factor for CPSP at one year. The risk of CPSP in the group with high frequency was 1.81 times higher than that of the low frequency group at one year after CS (OR 1.81, 95% CI 1.20–2.72, P = 0.005). Furthermore, with an increase in BMI (OR 1.06, 95% CI 1.00–1.12, P = 0.04), the risk of CPSP also increased at one year after CS.

Discussion

With NRS ≥ 5 as a boundary, women who consumed spicy food ≥ 2 days/week were more likely to have CPSP than those who consumed spicy food < 2 days/week, and the maximum degree of pain of CPSP was also significantly higher at three months after eCS. Furthermore, younger age, fewer CSs, and poor postoperative analgesia within 48 hours were risk factors for CPSP at 3 months.

Central sensitization[8] and ongoing inflammation[11] are two important mechanisms of CPSP. Capsaicin is a classic agonist of the transient receptor potential vanilloid subtype 1 (TRPV1),[20] which is the nociceptor and downstream integrator of many inflammatory pathways.[21] TRPV1 promotes nociception and neurogenic inflammation by regulating $CD4^+$ T cells[22] and enhancing interleukin-4.[23] TRPV1 is widely distributed throughout the human gastrointestinal tract.[24] Moreover, a study reported that capsaicin injection produced a wide dose-dependent area of hyperalgesia to mechanical stimuli via a central sensitization mechanism.[25] This central sensitization induced by TRPV1 has been verified in many animal and human experiments.[21,24,26] Therefore, we speculated that ongoing stimulation of TRPV1 via persistent intake of capsaicin through the gastrointestinal tract can result in ongoing inflammation that can sensitize nociceptive neurons,

which can promote central sensitization and long-term potentiation to produce hyperalgesia and pain hypersensitivity. Several studies have reported the use of capsaicin-induced analgesia for chronic pain.[27] Our previous study also found that a long-term spicy diet can reduce the body's basic pain threshold.[3] This finding may be the reason for the increased incidence of CPSP after CS in people who frequently consumed spicy food in this study, as well as the reason for the higher immediate and maximum pain of their CPSP.

The risks and predictors of CPSP in previous research[11,12,14] include age, sex, type of surgery, extent of preoperative pain, acute postoperative pain on movement, preoperative depression, and level of anxiety. Few studies have examined the association between long-term spicy eating habits and CPSP. There have been many studies on the application and exploration of capsaicin in chronic pain management,[28] and the capsaicin receptor TRPV1 plays an important role in the mechanism of pain.[29] Combined with the results of this study, spicy eating habits are one of the factors that cannot be ignored in the management of CPSP, especially in the context of a global pandemic. Although CPSP occurs far outside the perioperative period, perioperative physicians should continue to optimize perioperative pain management to reduce its occurrence. The comprehensive and accurate recognition of high-risk groups is an advance guard for developing individualized multi-mode pain management programs. The finding that women who frequently consume spicy foods are more likely to experience CPSP and higher pain intensity provides insight for identifying high-risk mothers. In summary, CPSP that occurs after planning surgical events has the potential to be prevented and controlled better in a plan.

This study has some limitations. First, we included a number of risk factors in the analysis for CPSP; other risk factors may exist (eg, gene mutation, degree of nerve injury caused by surgical technique, and preceding pain). Second, the complication is only classified as either "yes" or "no"; thus, a more detailed classification should be performed. Third, our findings were only evaluated in women who underwent eCS and were not generalizable to all patients who undergo other types of surgery or are men. Fourth, whether our findings apply to other ethnic backgrounds and provinces/geographical locations requires further validation.

Conclusion

The incidence of CPSP in women who frequently (≥ 2 days/week) consume spicy food is significantly higher than in women who seldom (< 2 days/week) consume spicy food at three months and one year after CS. The frequency of a personal spicy diet is an important factor in the identification stage, when clinicians optimize management schemes for the complex, multifaceted pain syndrome of CPSP.

Data Sharing Statement

The datasets generated during or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

The study is an observational research adhering to the applicable STROBE guidelines. The protocol including data analysis and statistical plan was approved by the Medical Ethics Committee of the Second Affiliated Hospital, Army Military Medical University (approved ID: 2018-030-01) before data were accessed. All subjects provided written informed consent and the study complied with the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. And all authors declare that they have no conflict of interest.

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