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Keywords:	tea, dysmenorrhea, women of reproductive age

Association of Tea Drinking and Dysmenorrhea among reproductive-age women in China

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ABSTRACT

Objectives: To investigate the association between tea drinking and dysmenorrhea among women of reproductive age.

Design: A cross-sectional study based on Shanghai Birth Cohort Study.

Setting: Two preconceptional care clinics in Shanghai, China.

Participants: 1183 women of reproductive age who sought preconceptional care were recruited from Aug 2013 to April 2015.

Primary and secondary outcome measures: Information on demographic, menstrual characteristics and lifestyle factors was collected at the enrollment. A multinomial logistic regression was performed to assess the relationship of tea drinking with dysmenorrhea.

Results: The prevalence of dysmenorrhea was 57.8%, among whom 10.4% and 3.5% had moderate and severe dysmenorrhea, respectively. Tea drinking was associated with a lower prevalence of dysmenorrhea (adjusted odds ratio [aOR]=0.68, 95%CI: 0.50-0.93 for mild dysmenorrhea; aOR=0.59 (0.32-1.04) for moderate-to-severe dysmenorrhea). Green tea and oolong tea appeared to have most reduction in the prevalence of dysmenorrhea [For mild dysmenorrhea: green tea: aOR=0.63 (0.44-0.90) and oolong tea: aOR=0.60 (0.35-1.03); for moderate-to-severe dysmenorrhea: green tea: aOR=0.42 (0.20-0.85) and oolong tea: aOR=0.34 (0.11-1.09)].

Conclusions: Consumptions of green tea and possibly oolong tea were associated with a lower prevalence of dysmenorrhea.

Keywords: tea; dysmenorrhea; women of reproductive age

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Article Summary

1. This was a large, population-based study, involving extensive potential confounders in the analyses.
2. This was a cross-sectional study, and therefore cannot establish a causal relationship.
3. The information on dysmenorrhea was based on participant's self-report.

INTRODUCTION

Dysmenorrhea, a common gynecological disorder, refers to painful cramps in the pelvis or lower abdomen beginning shortly before or during menstruation. Due to the lack of a standard method grading dysmenorrhea-related pain, the estimated prevalence of dysmenorrhea varied widely, ranging from 16.8% to 81%[1]. A study from China reported that 56.4% of female university students had dysmenorrhea, and among them, 6.5% had very severe (unbearable) symptoms[2]. Dysmenorrhea is not only a personal health problem, but also increases economic burden to the society. It was estimated that it costed $881.5 million on outpatient management and 600 million working hours lost in the US annually[3,4].

Overproduction of uterine prostaglandins from arachidonic acid through cyclo-oxygenase (COX) pathway has been commonly accepted as the etiology of primary dysmenorrhea[3]. The intensity of painful cramps and dysmenorrhea-related symptoms are proportional to the level of prostaglandin released[5]. Non-steroidal anti-inflammatory drugs (NSAIDs) is commonly prescribed as the first line of treatment for dysmenorrhea, due to its suppression of COX activity. However, the inhibitory effect of NSAIDs on COX-1 brings about several physiological concerns[6,7]. 10%-20% of women with primary dysmenorrhea fail to respond to or are intolerable to NSAIDs[6]. More and more women with dysmenorrhea resort to complementary and alternative medicine.

Tea has been considered as a medicinal staple for hundreds of years in China, thanks to the potential health benefits of tea flavonoids as antioxidants, anti-carcinogenic and anti-arteriosclerotic agent. Recently, green tea catechins have been demonstrated their inhibitory effect on COX-2 activity[8,9]. Hence, it is hypothesized that green tea may possibly decrease prostaglandin level and thereby relieve the severity of dysmenorrhea. However, there is a huge paucity of epidemiological evidence of the relationship of tea drinking with dysmenorrhea, especially green tea consumption and the association is still inconsistent. A cross-sectional study of 729 Turkish women of reproductive age showed no association between tea drinking and

dysmenorrhea[10], while another small study with 440 female university students suggested that students consuming >4 glasses of tea per day had a higher risk of primary dysmenorrhea than those who did not drink tea[11]. The present study aims to examine the relationship between tea drinking and dysmenorrhea in women of reproductive age in Chinese women.

MATERIALS AND METHODS

This study is based on the Shanghai Birth Cohort Study, which is a hospital-based, multi-center cohort study. It aims to assess the impacts of genetic, environmental and behavioral factors on reproductive health, pregnancy outcomes, child growth, development and risks of diseases.

Patient and participant involvement

Couples of reproductive age were recruited at either preconception or first trimester of pregnancy. Potential participants who agreed to participate in the study would signed an informed consent during recruitment. Women were followed at several time points, including preconception (if they were recruited before pregnancy), 1st, 2nd, 3rd trimesters and birth, and husbands were interviewed at preconception or at birth. Information on demographic characteristics, health behaviors, social support, reproductive and medical history, and family history of diseases was collected. Biological specimens were collected at each round of follow-up for further analyses.

This study used data from the preconception women who sought preconceptional care at 2 preconceptional care clinics in Shanghai, China, with the following inclusion criteria: 1) married women with age ≥ 20yrs (legal marriage age in China); 2) plan to be pregnant in the following year; 3) registered resident of Shanghai who do not plan to move out in the next 2 years; 4) plan to give birth in collaborating hospitals. Women who had tried to conceive for 12 months or longer were excluded from this study.

Socio-demographic characteristics

Participants provided information on demographic characteristics and lifestyle factors. Demographic characteristics include age, ethnicity, education level, income by herself, household

income, as well as height and weight. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Lifestyle factors included smoking history, alcohol intake, consumption of fruits and vegetables, use of dietary supplements and physical activity which was assessed by International Physical Activity Questionnaire short version[12].

In addition, the consumptions of caffeinated beverages, such as coffee, soda (Coca-Cola, Pepsi), and energy drink (e.g., Red Bull), were queried. Specifically, the consumption of tea was assessed by a structured questionnaire. Participants were asked whether they drank tea in their daily life. If yes, what type of tea they usually drank, including green, oolong and black tea, which are commonly consumed in China. They could choose one or multiple categories depending on their tea drinking habits. Participants were also asked about the number of years of tea drinking and the choices were “<1 year”, “1-5 years”, “6-10 years” and “>10 years”, and the number of cups per day.

Menstrual characteristics

Women were asked about menstrual characteristics including the onset of menarche, menstrual cycle length, bleeding duration, volume of menstrual flow and dysmenorrhea. If participants stated that they had pelvic pain associated with menstrual bleeding during the past 12 months, they were further asked to grade the intensity of menstrual cramp as mild, moderate and severe. Mild pain was defined as one could feel the pain but did not need further treatment. Moderate pain was defined as one needed to use therapy or treatment to relieve dysmenorrhea, and severe pain was referred as taking absence of work or bed rest besides treatment. The regularity of menstrual cycle length was assessed with the question: “Is your menstrual cycle length regular?”. Length variation of 8 days or more was considered as irregular. If irregular, the durations of the shortest and longest menstrual cycles were asked. If regular, participants stated the average length of their menstrual cycle. Participants were asked to state their volume of menstrual flow with four choices: “light”, “normal” and “heavy”.

Statistical analysis

All the analyses were performed using R studio (Version 1.0.136). The primary result was the relationship between tea drinking and dysmenorrhea, which was performed by multinomial logistic regression model. In addition, the difference in demographic characteristics and lifestyle factors according to the severity of dysmenorrhea was analyzed by Kruskal-Wallis test for categorical variables and one-way ANOVA for continuous variables. Variables with $P<0.05$ of the significance test for the difference were selected in the final logistic model. Other confounders were selected if they could change the coefficient by more than 10% compared with unadjusted coefficient. $P<0.05$ (two sides) was considered statistically significant.

RESULTS

A total of 1183 participants were recruited, of whom 23 did not finish the interview and 8 participants did not provide information on severity of dysmenorrhea, leaving 1152 women for the final analysis.

The prevalence of dysmenorrhea was 57.8% (666/1152). Among them, 86.2% (574) had mild, 10.4% (69) moderate, and 3.5% (23) severe dysmenorrhea. Since the total number of moderate and severe dysmenorrhea was only 99, we combined them together for further analyses.

The average age of all the 1152 participants was 29.4 ± 3.2 years, ranging from 21 to 44 years. 5% of women were 35 years or older. Women with moderate to severe dysmenorrhea had a mean age of 28.4 ± 2.4 years, in comparison to 29.9 ±3.5 years in women without dysmenorrhea ($P<0.001$). The average BMI was 21.0 ± 2.7 kg/m^2, with 7.2% being overweight or obese (BMI ≥ 25 kg/m^2). Non-dysmenorrhea group had a higher BMI than mild-dysmenorrhea group, followed by moderate-to-severe group ($P=0.021$). There was no difference in education, women's income and household income among the three groups.

The average age of the onset of menarche was 13.4 ± 1.3 years (Table 1). The average length of menstrual cycle and bleeding was 29.8 ± 3.5 days and 5.7 ± 1.3 days, respectively, among all the women of reproductive age. The prevalence of moderate-to-severe dysmenorrhea

was higher in women with heavy menstrual flow, compared with women with light and normal menses. Multiparous women were less likely to have dysmenorrhea (*P*<0.001).

Table 2 presents the distribution of lifestyle factors according to the intensity of dysmenorrhea. Very few women smoked. There was no association between smoking and dysmenorrhea. However, women who were exposed to second-hand smoke from her husband, roommates or colleagues were more likely to have dysmenorrhea (*P*<0.001).

Table 1. Demographic and menstrual characteristics according to the severity of dysmenorrhea

Variables	Dysmenorrhea (N (%) or (Mean ± SD))			P-value
	No (486)	Mild (574)	Moderate-to-severe (92)	
Age	29.9 ± 3.5	29.2± 3.0	28.4 ± 2.4	<0.001
BMI	21.2 ± 2.9	20.9 ± 2.5	20.3 ± 3.0	0.021
Race				0.733
Han	474 (42.2)	559 (49.8)	89 (7.9)	
Others	12 (40.0)	15 (50.0)	3 (10.0)	
Education				0.533
Junior college	96 (42.7)	113 (50.2)	16 (7.1)	
Undergraduate	302 (43.0)	346 (49.2)	55 (7.8)	
Graduate	88 (39.3)	115 (51.3)	21 (9.4)	
Home income				0.646
＜￥100K	31 (36.9)	48 (57.1)	5 (6.0)	
￥100-150K	77 (41.4)	96 (51.6)	13 (7.0)	
≥￥150K	357 (43.9)	392 (48.2)	65 (8.0)	
Personal income				0.622
＜￥100K	241 (40.3)	315 (52.7)	42 (7.0)	
￥100-150K	159 (45.2)	161 (45.7)	32 (9.1)	
≥￥150K	62 (43.7)	68 (47.9)	12 (8.5)	
Having had a pregnancy				<0.001
No	244 (37.2)	344 (52.4)	68 (10.4)	
Yes	241 (48.7)	230 (46.5)	24 (4.8)	
Volume of menstrual flow				<0.001
Light	48(48.0)	44(44.0)	8(8.0)	
Normal	419(43.2)	487(50.2)	65(6.7)	
Heavy	18(23.1)	41(52.6)	19(24.4)	
Regularity of menstrual cycle				0.773
Regular	393 (41.7)	479 (50.8)	71 (7.5)	
Irregular	93 (44.5)	95 (45.5)	21 (10.0)	
Length of menstrual cycle	29.8 ± 2.9	29.7 ± 2.9	30.3 ± 7.7	0.308
Bleeding duration	5.6 ± 1.4	5.7 ± 1.2	5.7 ± 1.3	0.268
Onset of menarche	13.4 ± 1.4	13.4 ± 1.3	13.4 ± 1.3	0.763

P-value was obtained by Krustal-Wallis test for categorical variables and one-way ANOVA for continuous variables

Table 2. Lifestyle factors according to the severity of dysmenorrhea

Variables	Dysmenorrhea (N (%))			P-value
	No (486)	Mild (574)	Moderate-to-severe (92)	
Smoking now				0.193
No	481 (42.3)	569 (50.0)	88 (7.7)	
Yes	5 (35.7)	5 (35.7)	4 (28.6)	
Used to smoke				0.604
No	471 (42.2)	557 (50.0)	87 (7.8)	
Yes	9 (47.4)	9 (47.4)	1 (5.3)	
Second-hand smoke				<0.001
No	365 (46.5)	363 (46.2)	57 (7.3)	
Yes	121 (33.2)	209 (57.3)	35 (9.6)	
Alcohol drinking within one year				0.110
No	325 (43.6)	366 (49.1)	54 (7.2)	
Yes	160 (39.4)	208 (51.2)	38 (9.4)	
Current alcohol drinking				0.676
No	469 (42.3)	551 (49.7)	88 (7.9)	
Yes	17 (39.5)	22 (51.2)	4 (9.3)	
Vitamin E				0.065
No	392 (41.3)	474 (49.9)	84 (8.8)	
Yes	81 (46.8)	85 (49.1)	7 (4.0)	
Supplementation of fish oil				0.874
No	438 (42.0)	519 (49.8)	85 (8.2)	
Yes	33 (42.9)	38 (49.4)	6 (7.8)	
Leaf vegetables				0.359
<1 per week	8 (57.1)	6 (42.9)	0 (0)	
1-3 per week	73 (42.4)	81 (47.1)	18 (10.5)	
4-7 per week	264 (40.7)	330 (50.9)	54 (8.3)	
≥ 2 per day	137 (44.1)	154 (49.5)	20 (6.4)	
Fruits				0.262
<1 per week	8 (32.0)	15 (60.0)	2 (8.0)	
1-3 per week	90 (39.1)	113 (49.1)	27 (11.7)	
4-7 per week	286 (43.4)	331 (50.2)	42 (6.4)	
≥ 2 per day	99 (43.2)	109 (47.6)	21 (9.2)	
Vigorous physical activity				0.460
No	393 (41.6)	475 (50.3)	77(8.1)	
Yes	85 (44.7)	90 (47.4)	15(7.9)	
Moderate physical activity				0.456
No	300 (41.3)	366 (50.3)	61 (8.4)	
Yes	171 (43.4)	193 (49.0)	30 (7.6)	
Walk				0.195
No	24 (57.1)	12 (28.6)	6 (14.3)	
Yes	409 (41.6)	495 (50.4)	78 (7.9)	

P-value was obtained by Krustal-Wallis test

Consumptions of vegetables, fruits, dietary supplements of Vitamin E and fish oil were not associated with the severity of menstrual pain (Table 2). However, the prevalence of moderate-to-severe dysmenorrhea was slightly higher in women who did not take Vitamin E, compared with Vitamin E consumers (8.8% versus 4.0%, *P*=0.065). Physical activity (vigorous, moderate or walking) was not associated with the severity of dysmenorrhea.

Table 3. Caffeinated beverages according to the severity of dysmenorrhea

Variables	Dysmenorrhea		
	No (486)	Mild (574)	Moderate-to-severe (92)
Tea			
No	308 (40.8)	384 (50.9)	62 (8.2)
Yes	178 (44.7)	190 (47.7)	30 (7.5)
Green tea			
No	347 (40.2)	443 (51.3)	74 (8.6)
Yes	139 (48.3)	131 (45.5)	18 (6.3)
Black tea			
No	413 (42.7)	481 (49.7)	74 (7.6)
Yes	73 (39.7)	93 (50.5)	18 (9.8)
Oolong tea			
No	434 (41.3)	528 (50.3)	88 (8.4)
Yes	52 (51.0)	46 (45.1)	4 (3.9)
Coffee			
No	275 (43.9)	317 (50.6)	34 (5.4)
Yes	211 (40.1)	257 (48.9)	58 (11.0)
Soda (Coca-Cola, Pepsi)			
No	335 (43.7)	381 (49.7)	51 (6.6)
Yes	151 (39.2)	193 (50.1)	41 (10.6)
Energy beverages			
No	462 (42.7)	539 (49.8)	81 (7.5)
Yes	24 (34.3)	35 (50.0)	11 (15.7)

P-value was obtained by Krustal-Wallis test

The prevalence of tea drinking was 34.5% (398 of 1152) among women with reproductive age, and the number of tea drinkers arrcoding to the severity of dysmenorrhea was shown in table 3. Table 4 shows the association between tea drinking and dysmenorrhea. After adjusting for age, BMI, personal income, ever pregnant, consumption of caffeinated beverages (coffee, Soda or energy drink), alcohol drinking during last 12 months, second-hand smoke, supplementation of fish oil, consumption of leaf vegetable, moderate physical activity and walking,

tea drinking was associated with a lower prevalence of mild dysmenorrhea [aOR=0.68 (0.50-0.93)]. The aOR [0.49 (0.31-0.79)] of mild dysmenorrhea was attenuated by half in women who drank tea for 3-5 cups per day compared with women who did not drink tea, whereas we did not find such relationship in higher tea consumers (≥6 cups/day). We did not find a relationship between number of years of tea drinking and severity of dysmenorrhea among tea drinkers, which may be a result of small sample size. Consumption of green tea was associated with a lower prevalence of dysmenorrhea, and the relationship was stronger in moderate-to-severe dysmenorrhea [aOR=0.42 (0.20-0.85)] than in mild dysmenorrhea [aOR=0.63 (0.44-0.90)], which is shown in table 5. Consumption of oolong tea was slightly associated with prevalence of dysmenorrhea [aOR=0.60 (0.35-1.03), *P*=0.063 for mild dysmenorrhea; aOR=0.34 (0.11-1.09), *P*=0.070 for moderate-to-severe dysmenorrhea], which may be ascribed to a small sample size since only 4 oolong tea-drinkers had moderate-to-severe dysmenorrhea.

Table 4. Relationship of tea drinking and dysmenorrhea

Variable	Crude model (cOR)			Adjusted model (aOR) [a]	
	No (486)	Mild (574)	Moderate-to-severe (92)	Mild (574)	Moderate-to-severe (92)
Tea					
No	1	1	1	1	1
Yes	1	0.86(0.66-1.10)	0.84(0.52-1.34)	0.68(0.50-0.93)	0.59(0.32-1.04)
Number of cups/day					
0 per day	1	1	1	1	1
1-2 cups/day	1	0.97(0.71-1.33)	1.06(0.61-1.84)	0.80(0.55-1.17)	0.71(0.36-1.41)
3-5 cups/day	1	0.66(0.44-0.98)	0.57(0.25-1.31)	0.49(0.31-0.79)	0.39(0.15-1.00)
≥ 6 cups/day	1	0.80(0.43-1.50)	0.71(0.21-2.45)	0.75(0.37-1.53)	0.77(0.21-2.86)
Number of years of tea drinking					
<1 year	1	1	1	1	1
1-5 years	1	0.64(0.36-1.13)	1.41(0.44-4.50)	0.53(0.26-1.07)	2.13(0.40-11.2)
≥ 6 years	1	0.61(0.33-1.14)	0.71(0.18-2.73)	0.54(0.24-1.25)	1.67(0.25-11.2)

[a] model 1 was a crude multinomial logistic regression which was used for each outcome
[b] model 2 was an adjusted multinomial logistic regression model for each outcome, and was adjusted for age, BMI, personal income, ever pregnant, caffeinated beverages drinking, alcohol drinking now and during last one year, second-hand smoke, supplementation of fish oil, consumption of leaf vegetables, moderate- and walk-intensity physical activity.

Table 5. Odds ratios for dysmenorrhea according to consumption of type of tea beverage

Variable	Crude model (cOR) [a]			Adjusted model (aOR) [b]	
	No (486)	mild (574)	Moderate-to-severe (92)	Mild (574)	Moderate-to-severe (92)
Green tea	1	0.74(0.56-0.97)	0.61(0.35-1.05)	0.63(0.44-0.90)	0.42(0.20-0.85)
Black tea	1	1.09(0.78-1.53)	1.38(0.78-2.44)	1.27(0.81-2.00)	1.96(0.94-4.10)
Oolong tea	1	0.73(0.48-1.10)	0.38(0.13-1.08)	0.60(0.35-1.03)	0.34(0.11-1.09)

[a] model 1 was a crude multinomial logistic regression model which was used for each type of tea beverage separately

[b] model 2 was an adjusted multinomial logistic regression model including three types of tea beverages as independent variables, and was adjusted for age, BMI, personal income, ever pregnant, caffeinated beverages drinking, alcohol drinking now and during last one year, second-hand smoke, supplementation of fish oil, consumption of leaf vegetables, moderate- and walk-intensity physical activity

As for the relationship between each caffeine-contained beverage (coffee, Soda and energy drink) and severity of dysmenorrhea (Table 6), women with moderate-to-severe dysmenorrhea were twice more likely to be coffee drinkers than women without dysmenorrhea (adjusted odds ratio [aOR]=2.11, 95%CI:1.22-3.62). However, after adjusting for potential confounders, consumption of neither soda nor energy beverages was associated with prevalence of moderate-to-severe dysmenorrhea.

Table 6. Odds ratios for dysmenorrhea according to consumption of caffeinated beverage

Variable	Crude model (cOR) [a]			Adjusted model (aOR) [b]	
	No (486)	mild (574)	Moderate-to-severe (92)	Mild (574)	Moderate-to-severe (92)
Coffee	1	1.06(0.83-1.35)	2.22(1.40-3.52)	1.08(0.80-1.44)	2.11(1.22-3.62)
Soda	1	1.12(0.87-1.45)	1.78(1.13-2.81)	1.05(0.76-1.44)	1.20(0.69-2.10)
Energy beverages	1	1.25(0.73-2.13)	2.61(1.23-5.54)	0.91(0.50-1.69)	1.65(0.66-4.15)

[a] model 1 was a crude multinomial logistic regression model which was used for each caffeinated beverage separately

[b] model 2 was an adjusted multinomial logistic regression model including three caffeinated beverages as independent variables, and was adjusted for age, BMI, personal income, ever pregnant, second-hand smoke, walk-intensity physical activity, tea drinking

DISCUSSION

The present study found that more than half of Chinese reproductive age women (57.8%) had some degree of dysmenorrhea. Exposure to second-hand smoke or consumption of coffee

were positively associated with moderate-to-severe dysmenorrhea. After adjustment for the potential confounders, consumptions of green tea and possibly oolong tea were associated with lower prevalence of dysmenorrhea.

The prevalence of dysmenorrhea in our population was consistent with previous studies. It was reported that at least 50% of women around the world[13] and 56.4% of university students in China suffered from dysmenorrhea[2]. However, the prevalence of severe dysmenorrhea in this study was slightly lower than the previous study (3.5% vs 6.5%, respectively)[2], which may be explained by the age difference between the study populations (29.4 ± 3.2 years in the current study versus 20.3 ± 1.3 in Zhou's study[2]). Previous literature indicated that menstrual pain was alleviated to some degree with advancing age[10,14,15].

The relationship between dysmenorrhea and menstrual characteristics (such as onset of menarche, regular menses, bleeding duration) is still uncertain[16]. Some studies reported that older age at menarche was associated with a decreased risk of dysmenorrhea[14,17], while others showed no association[10,18]. Unsal et al. found that menstrual irregularity was one of risk factors for dysmenorrhea [OR=1.90 (1.22-32.95)][10]. As for blood flow, some studies showed that reduced menstrual flow may be a sign of uterine constriction and it was associated with cramp pain[5,19] while others showed that the severity of dysmenorrhea increased with increasing volume of blood flow[2,20]. Our study was consistent with the latter finding, that is, women with heavy blood flow were more likely to have dysmenorrhea. However, we did not find any other relationship between menstrual health and dysmenorrhea. Interestingly, our result showed that pregnancy history was inversely associated with dysmenorrhea, in line with previous studies[10,14].

Our results showed a tendency towards dysmenorrhea relief when women drank tea in daily life. Those who consumed 3-5 cups/day of tea were 51% less likely to report having mild dysmenorrhea than non-drinkers. The observation of no relationship between high tea drinking (≥6 cups/day) and dysmenorrhea may be true or due to chance; only 45 participants stated tea

consumption of ≥6 cups/day. In contrast, a small cross-sectional study with randomly selected 440 female university students in Ethiopia suggested that people drinking tea for more than 4 glasses/day has 19 times higher prevalence of dysmenorrhea than non-drinkers, the corresponding aOR was 18.94 (2.19-163.73)[11]. However, the very wide confidence interval indicates that the conclusion is uncertain.

Among three types of tea, our study showed that consumption of green tea may be beneficial for relief of dysmenorrhea while consumption of black tea was not. The latter finding is consistent with the results from a Turkey study - a cross-sectional study with 729 reproductive-age women, which found no association between tea consumption and dysmenorrhea[10], as the traditional tea in Turkey is black tea.

To explore whether caffeine in tea was responsible to the relief of dysmenorrhea, we examined the association between consumption of caffeinated beverages, especially coffee, and dysmenorrhea. Unlike tea, consumption of coffee was positively related to the severity of dysmenorrhea in this study after adjustment of potential confounders. Previous studies showed that the risk of dysmenorrhea was twice as high in high caffeine consumers (≥300 mg/day) compared with low/moderate caffeine consumers (<300 mg/day) [OR=1.97 (1.09-3.59)][21]and in coffee consumers [OR=2.08 (1.34-3.24)][10]. The mechanism through which caffeine could aggravate cramp-like pain is uncertain and further studies are warranted. One possible mechanism is the vasoconstricting action of caffeine[22]. A study in pregnant women indicated that caffeine stimulated uterine muscle and, consequently, caused increased uterine contraction[23]. Uterine hypercontraction reduces blood flow and results in pain[5].

Instead, catechins in green tea might partly explain the observed relationship with relieved severity of dysmenorrhea. The extent of the oxidative processing (also called “fermentation”) differs among three types of tea - green tea is minimally processed, while black tea is completed fermented. Hence, catechins are rich in green tea followed by oolong tea, while much lower in black tea, as it is unstable and sensitive to oxidization. A number of animal and *in vitro* studies

suggested that green tea extract (catechins) was an effective inhibitor of COX-2 but not COX-1[8,9], thereby preventing overproduction of uterine prostaglandin levels, a major pathogenesis of primary dysmenorrhea. In addition, catechins inhibit the activity of phospholipase A2, an enzyme involved in the production of arachidonic acid, and consequently decreases the production of additional prostaglandin from arachidonic acid[24]. Given the high catechins content in green tea, it is convincingly expected green tea may be beneficial to relieve menstrual cramp by inhibiting prostaglandin level. Further studies are needed to specify the role of catechins in dysmenorrhea. Despite the promising effect of tea drinking in dysmenorrhea, tea drinking during menstrual period may also have unwanted side effects. Catechins and tannic acid rich in tea can chelate iron, thus tend to interfere with iron absorption[25, 26]. As menstruating women lose iron through bleeding, caution of drinking too much tea during menstruation may be warranted.

Several limitations of our study are worth mentioning. First, as our study collected data from the study population at a single point of time, it may be difficult to establish a causal relationship between tea drinking and dysmenorrhea. Second, this study did not distinguish secondary dysmenorrhea from primary dysmenorrhea. However, secondary dysmenorrhea may share some of the same pathways of pain as the primary dysmenorrhea, with an evidence of an increased level of prostaglandin in endometriosis and adenomyosis[27, 28]. On the other hand, an animal study has showed that green tea catechins were able to inhibit the development of endometriosis through anti-angiogenic effects[29]. Thus, it is possible that green tea may potentially be benefit to both primary and secondary dysmenorrhea. Third, we did not include information on oral contraceptive pills use, which may cause potential bias due to residual confounding. However, this study recruited women of reproductive age who were planning to become pregnant. Therefore, the number of participants using oral contraceptive pills was negligible. Fourth, the size of a tea serving and the biochemical quantity in a tea serving vary widely with different methods of preparing tea between individuals in China. We were unable to standardize the size

of tea cups. Finally, the information on dysmenorrhea was based on participants' self-report and, as such, it was subject to information bias. However, it is difficult to explain why such a bias only occurred in certain types of tea but not all types.

The strengths of this study are also worth noting. The large sample size made the results more precise. In addition, this study was based on a large cohort, which enables us to involve more potential confounders in the analyses. The study population was women who were planning to be pregnant, so they were more likely to remember their health-related behaviors and characteristics, especially those related to reproduction, such as menstrual characteristics.

In conclusion, our study suggests that drinking green tea was associated with lower prevalence of dysmenorrhea among reproductive-age women in China. On the other hand, excessive tea drinking may not be advisable, either, as tea may inhibit iron absorption.This finding will be of considerable clinical and publich health significance if the observed association can be confirmed in future prospective studies.

AUTHOR STATEMENT

J.Z, P.Z and Y.T contributed to study conception and design, and contributed to acquisition of data. X.Z, D.C and R.H contributed to analysis and interpretation of data. X.Z and R.Z contributed to drafting article. J.Z, and P.Z contributed to revising the article critically. All authors reviewed the final version of the manuscript and gave final approval of the version to be published.

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DECLARATION OF INTEREST

There is no conflict of interest that could be perceived.

DATA SHARING

Currently, the Shanghai Birth Cohort data are not yet open to public due to the confidentiality agreement. Data used in this analysis and computing programs are available from the corresponding author upon request.

ETHICAL APPROVAL

This study is based on the Shanghai Birth Cohort which was approved by the Institutional Review Board of Xinhua Hospital affiliated to the Shanghai Jiao Tong University School of Medicine, and no additional review was needed for this analysis. All participants signed an informed consent.

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-10
		(b) Indicate number of participants with missing data for each variable of interest	7-10
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Association of Tea Drinking and Dysmenorrhea among reproductive-age women in Shanghai, China (2013-2015): a cross-sectional study

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Association of Tea Drinking and Dysmenorrhea among reproductive-age women in Shanghai, China (2013-2015): a cross-sectional study

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ABSTRACT

Objectives: To investigate the association between tea drinking and dysmenorrhea among women of reproductive age.

Design: A cross-sectional study based on Shanghai Birth Cohort Study.

Setting: Two preconceptional care clinics in Shanghai, China.

Participants: 1183 women of reproductive age who sought preconceptional care were recruited from Aug 2013 to April 2015.

Primary and secondary outcome measures: Participants were asked if they had pelvic pain associated with menstrual bleeding during the past 12 months and further grade the intensity of menstrual cramp as mild, moderate and severe. Multinomial logistic regression was performed to assess the association of tea drinking and dysmenorrhea. Other information such as demographic and lifestyle factors were also collected and assessed in relation to dysmenorrhea.

Results: The prevalence of dysmenorrhea was 57.8%, among whom 10.4% and 3.5% had moderate and severe dysmenorrhea, respectively. Tea drinking was associated with a lower prevalence of dysmenorrhea [adjusted odds ratio (aOR)=0.68, 95%CI: 0.50-0.93 for mild dysmenorrhea; aOR=0.59 (0.32-1.04) for moderate-to-severe dysmenorrhea]. Green tea and oolong tea appeared to have most reduction in the prevalence of dysmenorrhea [For mild dysmenorrhea: green tea: aOR=0.63 (0.44-0.90) and oolong tea: aOR=0.60 (0.35-1.03); for moderate-to-severe dysmenorrhea: green tea: aOR=0.42 (0.20-0.85) and oolong tea: aOR=0.34 (0.11-1.09)].

Conclusions: Consumptions of green tea and possibly oolong tea were associated with a lower prevalence of dysmenorrhea.

Keywords: tea; dysmenorrhea; reproductive age

Word accounts: 3117

Strengths and limitations of this study

- This was a large, population-based study, involving extensive potential confounders in the analyses.
- This was a cross-sectional study, and therefore cannot establish a causal relationship.
- The information on dysmenorrhea was based on participants' self-report.

INTRODUCTION

Dysmenorrhea refers to pelvic pain during menstruation and can be classified as primary and secondary. Primary dysmenorrhea begins at or shortly after menarche without any evidence of pathology. Pain usually occurs just before or during menstrual period, lasting for 2-3 days.[1] Secondary dysmenorrhea is caused by specific pathological conditions, such as adenomyosis and fibroids, endometriosis, and pelvic inflammatory disease. The onset of secondary dysmenorrhea begins later than the primary dysmenorrhea, usually more than 2 years after menarche.[2] Due to the lack of a standard method grading dysmenorrhea-related pain, the estimated prevalence of dysmenorrhea varied widely, ranging from 16.8% to 81%.[3, 4] A study from China reported that 56.4% of female university students had dysmenorrhea, and among them, 6.5% had very severe (unbearable) symptoms.[5] Dysmenorrhea limits women's daily activity and is associated with absenteeism from school or work.[6] Furthermore, women with primary or secondary dysmenorrhea have higher total health care costs than those without syndromes.[7]

Overproduction of uterine prostaglandins from arachidonic acid through cyclo-oxygenase (COX) pathway has been commonly accepted as the etiology of primary dysmenorrhea.[8] The intensity of painful cramps and dysmenorrhea-related symptoms are proportional to the level of prostaglandin released.[1] Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed as the first line of treatment for dysmenorrhea, due to its suppression of COX activity. However, the inhibitory effect of NSAIDs on COX-1 brings about several physiological concerns.[2, 9] 10%-20% of women with primary dysmenorrhea fail to respond to or are intolerable to NSAIDs.[2] More and more women with dysmenorrhea resort to complementary and alternative medicine.

Tea has been considered as a medicinal staple for hundreds of years in China, thanks to the potential health benefits of tea flavonoids as antioxidants, anti-carcinogenic and anti-arteriosclerotic agent. Recently, green tea catechins have been demonstrated their inhibitory

effect on COX-2 activity.[10, 11] Hence, it is hypothesized that green tea may possibly decrease prostaglandin level and thereby relieve the severity of dysmenorrhea. However, there is a huge paucity of epidemiological evidence of the association of tea drinking with dysmenorrhea, especially green tea consumption, and the results of association are still inconsistent. A cross-sectional study of 729 Turkish women of reproductive age showed no association between tea drinking and dysmenorrhea,[12] while another small study with 440 female university students suggested that students consuming >4 glasses of tea per day had a higher risk of primary dysmenorrhea than those who did not drink tea.[13] To fill in the knowledge gap, the present study aims to examine the relationship between tea drinking and dysmenorrhea in Chinese women of reproductive age.

MATERIALS AND METHODS

This study is based on the Shanghai Birth Cohort Study (SBC), which is a hospital-based, multi-center cohort study. It aims to assess the impacts of genetic, environmental and behavioral factors on reproductive health, pregnancy outcomes, child growth, development and risks of diseases. The reader is referred to cohort profile for more details about SBC.[14]

Patient and participant involvement

In SBC, couples of reproductive age were recruited at either preconception or first trimester of pregnancy. Potential participants who agreed to participate in the study would sign an informed consent during recruitment. Women were followed at several time points, including preconception (if they were recruited before pregnancy), 1st, 2nd, 3rd trimesters and birth, and husbands were interviewed at preconception or at birth. Information on demographic characteristics, health behaviors, social support, reproductive and medical history, and family history of diseases was collected. Biological specimens were collected at each round of follow-up for further analyses.

This study used data from the preconception women who sought preconceptional care at 2 preconceptional care clinics in Shanghai, China, with the following inclusion criteria: 1) married women with age ≥ 20yrs (legal marriage age in China); 2) plan to be pregnant in the following

year; 3) registered residents of Shanghai who do not plan to move out in the next 2 years; 4) plan to give birth in collaborating hospitals. Women who had tried to conceive for 12 months or longer were excluded from this study.

Socio-demographic characteristics

Participants provided information on demographic characteristics and lifestyle factors. Demographic characteristics include age, ethnicity, education level, income by herself, household income, as well as height and weight. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Lifestyle factors included smoking history, alcohol intake, consumption of fruits and vegetables, use of dietary supplements and physical activity which was assessed by International Physical Activity Questionnaire short version.[15]

In addition, the consumptions of caffeinated beverages, such as coffee, soda (Coca-Cola, Pepsi), and energy drink (e.g., Red Bull), were queried. Specifically, the consumption of tea was assessed by a structured questionnaire. Participants were asked whether they drank tea in their daily life. If yes, what type of tea they usually drank, including green, oolong and black tea, which are commonly consumed in China. They could choose one or multiple categories depending on their tea drinking habits. Participants were also asked about the number of years of tea drinking and the choices were “<1 year”, “1-5 years”, “6-10 years” and “>10 years”, and the number of cups per day.

Menstrual characteristics

Women were asked about menstrual characteristics including the onset of menarche, menstrual cycle length, bleeding duration, volume of menstrual flow and dysmenorrhea. If participants stated that they had pelvic pain associated with menstrual bleeding during the past 12 months, they were further asked to grade the intensity of menstrual cramp as mild, moderate and severe. Mild pain was defined as one could feel the pain but did not need further treatment. Moderate pain was defined as one needed to use therapy or treatment to relieve dysmenorrhea,

and severe pain was referred as taking absence of work or bed rest besides treatment. The method grading pain intensity in this study was modified based on verbal rating scale - a validated pain scale to evaluate dysmenorrhea.[16] Although verbal rating scale is not as sensitive as the visual scale or numerical rating scale, which offer a broader spectrum of differentiating pain intensity, it is easier for participants to fill out and thereby limits missing data. The regularity of menstrual cycle length was assessed with the question: “Is your menstrual cycle length regular?”. Length variation of 8 days or more was considered as irregular. If irregular, the durations of the shortest and longest menstrual cycles were asked. If regular, participants stated the average length of their menstrual cycle. Participants were asked to state their volume of menstrual flow with four choices: “light”, “normal” and “heavy”.

Statistical analysis

All the analyses were performed using R studio (Version 1.0.136). We described the distribution of continuous variables (including mean and standard error) according to the severity of dysmenorrhea, and described the relationship of categorical variables with severity of dysmenorrhea using contingency tables. In addition, the differences in demographic characteristics and lifestyle factors according to the severity of dysmenorrhea were analyzed by Kruskal-Wallis test for categorical variables and one-way ANOVA for continuous variables. The primary result was the relationship between tea drinking and dysmenorrhea, which was performed by multinomial logistic regression model. Variables with $P<0.05$ of the significance test for the difference were selected in the final logistic model. Other confounders were selected if they could change the coefficient by more than 10% compared with unadjusted coefficient. $P<0.05$ (two sides) was considered statistically significant.

RESULTS

A total of 1183 participants were recruited, of whom 23 did not finish the interview and 8 participants did not provide information on severity of dysmenorrhea, leaving 1152 women for the final analysis.

The prevalence of dysmenorrhea was 57.8% (666/1152). Among them, 86.2% (574) had mild, 10.4% (69) moderate, and 3.5% (23) severe dysmenorrhea. Since the total number of moderate and severe dysmenorrhea was only 99, we combined them together for further analyses.

Table 1. Demographic and menstrual characteristics according to the severity of dysmenorrhea

Variables	Dysmenorrhea (N (%) or (Mean ± SD))			P-value
	No (486)	Mild (574)	Moderate-to-severe (92)	
Age (years)	29.9 ± 3.5	29.2 ± 3.0	28.4 ± 2.4	<0.001
BMI (kg/m²)	21.2 ± 2.9	20.9 ± 2.5	20.3 ± 3.0	0.021
Race				0.733
Han	474 (42.2)	559 (49.8)	89 (7.9)	
Others	12 (40.0)	15 (50.0)	3 (10.0)	
Education				0.533
Junior college	96 (42.7)	113 (50.2)	16 (7.1)	
Undergraduate	302 (43.0)	346 (49.2)	55 (7.8)	
Graduate	88 (39.3)	115 (51.3)	21 (9.4)	
Home income				0.646
＜￥100K	31 (36.9)	48 (57.1)	5 (6.0)	
￥100-150K	77 (41.4)	96 (51.6)	13 (7.0)	
≥ ￥150K	357 (43.9)	392 (48.2)	65 (8.0)	
Personal income				0.622
＜￥100K	241 (40.3)	315 (52.7)	42 (7.0)	
￥100-150K	159 (45.2)	161 (45.7)	32 (9.1)	
≥ ￥150K	62 (43.7)	68 (47.9)	12 (8.5)	
Onset of menarche (years)	13.4 ± 1.4	13.4 ± 1.3	13.4 ± 1.3	0.763
Length of menstrual cycle (days)	29.8 ± 2.9	29.7 ± 2.9	30.3 ± 7.7	0.308
Bleeding duration (days/month)	5.6 ± 1.4	5.7 ± 1.2	5.7 ± 1.3	0.268
Volume of menstrual flow				<0.001
Light	48(48.0)	44(44.0)	8(8.0)	
Normal	419(43.2)	487(50.2)	65(6.7)	
Heavy	18(23.1)	41(52.6)	19(24.4)	
Regularity of menstrual cycle				0.773
Regular	393 (41.7)	479 (50.8)	71 (7.5)	
Irregular	93 (44.5)	95 (45.5)	21 (10.0)	
Having had a pregnancy				<0.001
No	244 (37.2)	344 (52.4)	68 (10.4)	
Yes	241 (48.7)	230 (46.5)	24 (4.8)	

P-value was obtained by Kruskal-Wallis test for categorical variables and one-way ANOVA for continuous variables

Table 1 presents the demographic and menstrual characteristics of the study population according to the severity of dysmenorrhea. The average age of all the 1152 participants was 29.4 ± 3.2 years, ranging from 21 to 44 years. 5% of women were 35 years or older. Women with moderate to severe dysmenorrhea had a mean age of 28.4 ± 2.4 years, in comparison to 29.9 ±3.5 years in women without dysmenorrhea. The average BMI was 21.0 ± 2.7 kg/m^2, with 7.2% being overweight or obese (BMI ≥ 25 kg/m^2). Non-dysmenorrhea group had a higher BMI than mild-dysmenorrhea group, followed by moderate-to-severe group. There was no difference in education, women's income and household income among the three groups.

The average age of the onset of menarche was 13.4 ± 1.3 years. The average length of menstrual cycle and bleeding was 29.8 ± 3.5 days and 5.7 ± 1.3 days, respectively, among all the women of reproductive age. The prevalence of moderate-to-severe dysmenorrhea was higher in women with heavy menstrual flow, compared with women with light and normal menses. Multiparous women were less likely to have dysmenorrhea.

Table 2 presents the distribution of lifestyle factors according to the intensity of dysmenorrhea. Very few women smoked. There was no association between smoking and dysmenorrhea. However, women who were exposed to second-hand smoke from her husband, roommates or colleagues were more likely to have dysmenorrhea.

Consumptions of vegetables, fruits, dietary supplements of Vitamin E and fish oil were not associated with the severity of menstrual pain (Table 2). However, the prevalence of moderate-to-severe dysmenorrhea was slightly higher in women who did not take Vitamin E, compared with Vitamin E consumers (8.8% versus 4.0%). Physical activity (vigorous, moderate or walking) was not associated with the severity of dysmenorrhea.

The prevalence of tea drinking was 34.5% (398 of 1152) among women with reproductive age, and the number of tea drinkers according to the severity of dysmenorrhea was shown in Table 3. Table 4 shows the association between tea drinking and dysmenorrhea. After adjusting for age, BMI, personal income, ever pregnant, consumption of caffeinated beverages (coffee,

Table 2. Lifestyle factors according to the severity of dysmenorrhea

Variables	Dysmenorrhea (N (%))			P-value
	No (486)	Mild (574)	Moderate-to-severe (92)	
Smoking now				0.193
No	481 (42.3)	569 (50.0)	88 (7.7)	
Yes	5 (35.7)	5 (35.7)	4 (28.6)	
Used to smoke				0.604
No	471 (42.2)	557 (50.0)	87 (7.8)	
Yes	9 (47.4)	9 (47.4)	1 (5.3)	
Second-hand smoke				<0.001
No	365 (46.5)	363 (46.2)	57 (7.3)	
Yes	121 (33.2)	209 (57.3)	35 (9.6)	
Alcohol drinking within one year				0.110
No	325 (43.6)	366 (49.1)	54 (7.2)	
Yes	160 (39.4)	208 (51.2)	38 (9.4)	
Current alcohol drinking				0.676
No	469 (42.3)	551 (49.7)	88 (7.9)	
Yes	17 (39.5)	22 (51.2)	4 (9.3)	
Vitamin E				0.065
No	392 (41.3)	474 (49.9)	84 (8.8)	
Yes	81 (46.8)	85 (49.1)	7 (4.0)	
Supplementation of fish oil				0.874
No	438 (42.0)	519 (49.8)	85 (8.2)	
Yes	33 (42.9)	38 (49.4)	6 (7.8)	
Leaf vegetables				0.359
＜1 per week	8 (57.1)	6 (42.9)	0 (0)	
1-3 per week	73 (42.4)	81 (47.1)	18 (10.5)	
4-7 per week	264 (40.7)	330 (50.9)	54 (8.3)	
≥ 2 per day	137 (44.1)	154 (49.5)	20 (6.4)	
Fruits				0.262
＜1 per week	8 (32.0)	15 (60.0)	2 (8.0)	
1-3 per week	90 (39.1)	113 (49.1)	27 (11.7)	
4-7 per week	286 (43.4)	331 (50.2)	42 (6.4)	
≥ 2 per day	99 (43.2)	109 (47.6)	21 (9.2)	
Vigorous physical activity				0.460
No	393 (41.6)	475 (50.3)	77(8.1)	
Yes	85 (44.7)	90 (47.4)	15(7.9)	
Moderate physical activity				0.456
No	300 (41.3)	366 (50.3)	61 (8.4)	
Yes	171 (43.4)	193 (49.0)	30 (7.6)	
Walk				0.195
No	24 (57.1)	12 (28.6)	6 (14.3)	
Yes	409 (41.6)	495 (50.4)	78 (7.9)	

P-value was obtained by Kruskal-Wallis test

Soda or energy drink), alcohol drinking during last 12 months, second-hand smoke, supplementation of fish oil, consumption of leaf vegetable, moderate physical activity and walking, tea drinking was associated with a 32% lower prevalence of mild dysmenorrhea. The aOR of mild dysmenorrhea was attenuated by half in women who drank tea for 3-5 cups per day compared with women who did not drink tea, whereas we did not find such relationship in higher tea consumers (≥6 cups/day). We did not find a relationship between number of years of tea drinking and severity of dysmenorrhea among tea drinkers. Consumption of green tea was associated with a lower prevalence of dysmenorrhea, and the relationship was stronger in moderate-to-severe dysmenorrhea than in mild dysmenorrhea, which is shown in Table 5. Consumption of oolong tea was associated with a lower prevalence of dysmenorrhea but the association did not reach statistical significance.

Table 3. Caffeinated beverages according to the severity of dysmenorrhea

Variables	Dysmenorrhea			
	No (486)	Mild (574)	Moderate-to-severe (92)	P-value
Tea				0.216
No	308 (40.8)	384 (50.9)	62 (8.2)	
Yes	178 (44.7)	190 (47.7)	30 (7.5)	
Green tea				0.012
No	347 (40.2)	443 (51.3)	74 (8.6)	
Yes	139 (48.3)	131 (45.5)	18 (6.3)	
Black tea				0.337
No	413 (42.7)	481 (49.7)	74 (7.6)	
Yes	73 (39.7)	93 (50.5)	18 (9.8)	
Oolong tea				0.033
No	434 (41.3)	528 (50.3)	88 (8.4)	
Yes	52 (51.0)	46 (45.1)	4 (3.9)	
Coffee				0.027
No	275 (43.9)	317 (50.6)	34 (5.4)	
Yes	211 (40.1)	257 (48.9)	58 (11.0)	
Soda (Coca-Cola, Pepsi)				0.047
No	335 (43.7)	381 (49.7)	51 (6.6)	
Yes	151 (39.2)	193 (50.1)	41 (10.6)	
Energy beverages				0.050
No	462 (42.7)	539 (49.8)	81 (7.5)	
Yes	24 (34.3)	35 (50.0)	11 (15.7)	

P-value was obtained by Kruskal-Wallis test

Table 4. Relationship of tea drinking and dysmenorrhea

Variable	Crude model (cOR)			Adjusted model (aOR) [a]	
	No (486)	Mild (574)	Moderate-to-severe (92)	Mild (574)	Moderate-to-severe (92)
Tea					
No	1	1	1	1	1
Yes	1	0.86(0.66-1.10)	0.84(0.52-1.34)	0.68(0.50-0.93)	0.59(0.32-1.04)
Number of cups/day					
0 per day	1	1	1	1	1
1-2 cups/day	1	0.97(0.71-1.33)	1.06(0.61-1.84)	0.80(0.55-1.17)	0.71(0.36-1.41)
3-5 cups/day	1	0.66(0.44-0.98)	0.57(0.25-1.31)	0.49(0.31-0.79)	0.39(0.15-1.00)
≥ 6 cups/day	1	0.80(0.43-1.50)	0.71(0.21-2.45)	0.75(0.37-1.53)	0.77(0.21-2.86)
Number of years of tea drinking					
< 1 year	1	1	1	1	1
1-5 years	1	0.64(0.36-1.13)	1.41(0.44-4.50)	0.53(0.26-1.07)	2.13(0.40-11.2)
≥ 6 years	1	0.61(0.33-1.14)	0.71(0.18-2.73)	0.54(0.24-1.25)	1.67(0.25-11.2)

[a] model 1 was a crude multinomial logistic regression which was used for each outcome

[b] model 2 was an adjusted multinomial logistic regression model for each outcome, and was adjusted for age, BMI, personal income, ever pregnant, caffeinated beverages drinking, alcohol drinking now and during last one year, second-hand smoke, supplementation of fish oil, consumption of leaf vegetables, moderate- and walk-intensity physical activity.

Table 5. Odds ratios for dysmenorrhea according to consumption of type of tea beverage/caffeinated beverage

Variable	Crude model (cOR)			Adjusted model (aOR)	
	No (486)	mild (574)	Moderate-to-severe (92)	Mild (574)	Moderate-to-severe (92)
[a] **Model 1**					
Green tea	1	0.74(0.56-0.97)	0.61(0.35-1.05)	0.63(0.44-0.90)	0.42(0.20-0.85)
Black tea	1	1.09(0.78-1.53)	1.38(0.78-2.44)	1.27(0.81-2.00)	1.96(0.94-4.10)
Oolong tea	1	0.73(0.48-1.10)	0.38(0.13-1.08)	0.60(0.35-1.03)	0.34(0.11-1.09)
[b] **Model 2**					
Coffee	1	1.06(0.83-1.35)	2.22(1.40-3.52)	1.08(0.80-1.44)	2.11(1.22-3.62)
Soda	1	1.12(0.87-1.45)	1.78(1.13-2.81)	1.05(0.76-1.44)	1.20(0.69-2.10)
Energy beverages	1	1.25(0.73-2.13)	2.61(1.23-5.54)	0.91(0.50-1.69)	1.65(0.66-4.15)

[a] model 1 was a multinomial logistic regression model which was used for each type of tea beverage separately, and was further adjusted for other types of tea beverages, age, BMI, personal income, ever pregnant, caffeinated beverages drinking, alcohol drinking now and during last one year, second-hand smoke, supplementation of fish oil, consumption of leaf vegetables, moderate- and walk-intensity physical activity

[b] model 2 was a multinomial logistic regression model which was used for each caffeinated beverage separately, and was further adjusted for other caffeinated beverages, age, BMI, personal income, ever pregnant, second-hand smoke, walk-intensity physical activity and tea drinking

As for the relationship between each caffeine-contained beverage (coffee, Soda and energy drink) and severity of dysmenorrhea (Table 5), women with moderate-to-severe dysmenorrhea were twice more likely to be coffee drinkers than women without dysmenorrhea. However, after adjusting for potential confounders, consumption of neither soda nor energy beverages was associated with prevalence of moderate-to-severe dysmenorrhea.

DISCUSSION

The present study found that more than half of Chinese reproductive age women (57.8%) had some degree of dysmenorrhea. Exposure to second-hand smoke or consumption of coffee were positively associated with moderate-to-severe dysmenorrhea. After adjustment for the potential confounders, consumptions of green tea and possibly oolong tea were associated with lower prevalence of dysmenorrhea.

The prevalence of dysmenorrhea in our population was consistent with previous studies. It was reported that at least 50% of women around the world[17] and 56.4% of university students in China suffered from dysmenorrhea.[5] However, the prevalence of severe dysmenorrhea in this study was slightly lower than the previous study (3.5% vs 6.5%, respectively),[5] which may be explained by the age difference between the study populations (29.4 ± 3.2 years in the current study versus 20.3 ± 1.3 in Zhou's study[5]). Previous literature indicated that menstrual pain was alleviated to some degree with advancing age.[12, 18, 19]

The relationships between dysmenorrhea and menstrual characteristics (such as onset of menarche, regular menses, bleeding duration) are still uncertain.[20] Some studies reported that older age at menarche was associated with a decreased risk of dysmenorrhea,[18, 21] while others showed no association.[12, 22] Unsal et al. found that menstrual irregularity was one of risk factors for dysmenorrhea [OR=1.90 (1.22-32.95)].[12] As for blood flow, some studies showed that reduced menstrual flow may be a sign of uterine constriction and it was associated with cramp pain[1, 23] while others showed that the severity of dysmenorrhea increased with increasing volume of blood flow.[5, 24] Our study was consistent with the latter finding, that is,

women with heavy blood flow were more likely to have dysmenorrhea. However, we did not find any other relationship between menstrual health and dysmenorrhea. Interestingly, our result showed that pregnancy history was inversely associated with dysmenorrhea, in line with previous studies.[12, 18]

Our results showed a tendency towards dysmenorrhea relief when women drank tea in daily life. Those who consumed 3-5 cups/day of tea were 51% less likely to report having mild dysmenorrhea than non-drinkers. The observation of no relationship between high tea drinking (≥6 cups/day) and dysmenorrhea may be true or due to chance; only 45 participants stated tea consumption of ≥6 cups/day. In contrast, a small cross-sectional study with randomly selected 440 female university students in Ethiopia suggested that people drinking tea for more than 4 glasses/day has 19 times higher prevalence of dysmenorrhea than non-drinkers, the corresponding aOR was 18.94 (2.19-163.73).[13] However, the very wide confidence interval indicates that the conclusion is uncertain.

Among three types of tea, our study showed that consumption of green tea may be beneficial for relief of dysmenorrhea while consumption of black tea was not. The latter finding is consistent with the results from a Turkey study - a cross-sectional study with 729 reproductive-age women, which found no association between tea consumption and dysmenorrhea,[12] as the traditional tea in Turkey is black tea. Consumption of oolong tea had a boardline association with a lower prevalence of dysmenorrhea, which may be ascribed to a small sample size. Our study may be underpowered to detect the desired difference between oolong tea drinkers and non-drinkers.

To explore whether caffeine in tea was responsible to the relief of dysmenorrhea, we examined the association between consumption of caffeinated beverages, especially coffee, and dysmenorrhea. Unlike tea, consumption of coffee was positively related to the severity of dysmenorrhea in this study after adjustment of potential confounders. Previous studies showed that the risk of dysmenorrhea was twice as high in high caffeine consumers (≥300 mg/day) compared with low/moderate caffeine consumers (<300 mg/day) [OR=1.97 (1.09-3.59)][25] and

in coffee consumers [OR=2.08 (1.34-3.24)].[12] The mechanism through which caffeine could aggravate cramp-like pain is uncertain and further studies are warranted. One possible mechanism is the vasoconstricting action of caffeine.[26] A study in pregnant women indicates that caffeine stimulates uterine muscle and, consequently, causes increased uterine contraction.[27] Uterine hypercontraction reduces blood flow and results in pain.[1]

Instead, catechins in green tea might partly explain the observed relationship with relieved severity of dysmenorrhea. The extent of the oxidative processing (also called “fermentation”) differs among three types of tea - green tea is minimally processed, while black tea is completed fermented. Hence, catechins are rich in green tea followed by oolong tea, while much lower in black tea, as it is unstable and sensitive to oxidization. A number of animal and *in vitro* studies suggest that green tea extract (catechins) is an effective inhibitor of COX-2 but not COX-1[10, 11] thereby preventing overproduction of uterine prostaglandin levels, a major pathogenesis of primary dysmenorrhea. In addition, catechins inhibit the activity of phospholipase A2, an enzyme involved in the production of arachidonic acid, and consequently decreases the production of additional prostaglandin from arachidonic acid.[28] Given the high catechins content in green tea, it is convincingly expected green tea may be beneficial to relieve menstrual cramp by inhibiting prostaglandin level.

Further studies are needed to specify the role of catechins in dysmenorrhea. Despite the promising effect of tea drinking in dysmenorrhea, tea drinking during menstrual period may also have unwanted side effects. Catechins and tannic acid rich in tea can chelate iron, thus tend to interfere with iron absorption.[29-31] As menstruating women lose iron through bleeding, caution of drinking too much tea during menstruation may be warranted.

Several limitations of our study are worth mentioning. First, as our study collected data from the study population at a single point of time, it may be difficult to establish a causal relationship between tea drinking and dysmenorrhea. Second, this study did not distinguish secondary dysmenorrhea from primary dysmenorrhea. However, secondary dysmenorrhea may share some

of the same pathways of pain as the primary dysmenorrhea, with an evidence of an increased level of prostaglandin in endometriosis and adenomyosis.[32, 33] On the other hand, an animal study has shown that green tea catechins inhibited the development of endometriosis through anti-angiogenic effects.[34] Thus, it is possible that green tea may potentially be beneficial to both primary and secondary dysmenorrhea. Third, we did not include information on oral contraceptive pills use, which may cause potential bias due to residual confounding. However, this study recruited women of reproductive age who were planning to become pregnant. Therefore, the number of participants using oral contraceptive pills was negligible. Fourth, the size of a tea serving and the biochemical quantity in a tea serving vary widely with different methods of preparing tea between individuals in China. We were unable to standardize the size of tea cups. Finally, the information on dysmenorrhea was based on participants' self-report and, as such, it was subject to information bias. However, it is difficult to explain why such a bias only occurred in certain types of tea but not all types.

The strengths of this study are also worth noting. The large sample size made the results more precise. In addition, this study was based on a large cohort, which enables us to involve more potential confounders in the analyses. The study population was women who were planning to be pregnant, so they were more likely to remember their health-related behaviors and characteristics, especially those related to reproduction, such as menstrual characteristics.

In conclusion, our study suggests that drinking green tea was associated with a lower prevalence of dysmenorrhea among reproductive-age women in China. On the other hand, excessive tea drinking may not be advisable, either, as tea may inhibit iron absorption. Given the scarcity of epidemiological evidence of tea drinking and dysmenorrhea, this study gives new insights in the possible role of green tea on the relief of dysmenorrhea. Cohort studies and subsequent randomized controlled trials are needed to confirm this finding, which may have important clinical and publich health significance.

AUTHOR STATEMENT

J.Z, P.Z and Y.T contributed to study conception and design, and contributed to acquisition of data. X.Z, D.C and R.H contributed to analysis and interpretation of data. X.Z and R.Z contributed to drafting article. J.Z, and P.Z contributed to revising the article critically. All authors reviewed the final version of the manuscript and gave final approval of the version to be published.

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DECLARATION OF INTEREST

There is no conflict of interest that could be perceived.

DATA SHARING

Currently, the Shanghai Birth Cohort data are not yet open to public due to the confidentiality agreement. Data used in this analysis and computing programs are available from the corresponding author upon request.

ETHICAL APPROVAL

This study is based on the Shanghai Birth Cohort which was approved by the Institutional Review Board of Xinhua Hospital affiliated to the Shanghai Jiao Tong University School of Medicine, and no additional review was needed for this analysis. All participants signed an informed consent.

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-10
		(b) Indicate number of participants with missing data for each variable of interest	7-10
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association of tea drinking and dysmenorrhea among reproductive-age women in Shanghai, China (2013-2015): a cross-sectional study

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Association of tea drinking and dysmenorrhea among reproductive-age women in Shanghai, China (2013-2015): a cross-sectional study

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ABSTRACT

Objectives: To investigate the association between tea drinking and dysmenorrhea among women of reproductive age.

Design: A cross-sectional study based on Shanghai Birth Cohort Study.

Setting: Two preconceptional care clinics in Shanghai, China.

Participants: 1183 women of reproductive age who sought preconceptional care were recruited from Aug 2013 to April 2015.

Primary and secondary outcome measures: Participants were asked if they had pelvic pain associated with menstrual bleeding during the past 12 months and to further grade the intensity of menstrual cramp as mild, moderate and severe. Multinomial logistic regression was performed to assess the association of tea drinking and dysmenorrhea. Other information such as demographic and lifestyle factors were also collected and assessed in relation to dysmenorrhea.

Results: The prevalence of dysmenorrhea was 57.8%, among whom 10.4% and 3.5% had moderate and severe dysmenorrhea, respectively. Tea drinking was associated with a lower prevalence of dysmenorrhea [adjusted odds ratio (aOR)=0.68, 95%CI: 0.50-0.93 for mild dysmenorrhea; aOR=0.59 (0.32-1.04) for moderate-to-severe dysmenorrhea]. Green tea and oolong tea appeared to have most reduction in the prevalence of dysmenorrhea [For mild dysmenorrhea: green tea: aOR=0.63 (0.44-0.90) and oolong tea: aOR=0.60 (0.35-1.03); for moderate-to-severe dysmenorrhea: green tea: aOR=0.42 (0.20-0.85) and oolong tea: aOR=0.34 (0.11-1.09)].

Conclusions: Consumptions of green tea and possibly oolong tea were associated with a lower prevalence of dysmenorrhea.

Keywords: tea; dysmenorrhea; reproductive age

Word accounts: 3151

Strengths and limitations of this study

- This was a large, population-based study, involving extensive potential confounders in the analyses.
- This was a cross-sectional study, and therefore cannot establish a causal relationship.
- The information on dysmenorrhea was based on participants' self-report.

INTRODUCTION

Dysmenorrhea refers to pelvic pain during menstruation and can be classified as primary and secondary. Primary dysmenorrhea begins at or shortly after menarche without any evidence of pathology. Pain usually occurs just before or during menstrual period, lasting for 2-3 days.[1] Secondary dysmenorrhea is caused by specific pathological conditions, such as adenomyosis and fibroids, endometriosis, and pelvic inflammatory disease. The onset of secondary dysmenorrhea begins later than the primary dysmenorrhea, usually more than 2 years after menarche.[2] Due to the lack of a standard method grading dysmenorrhea-related pain, the estimated prevalence of dysmenorrhea varied widely, ranging from 16.8% to 81%.[3, 4] A study from China reported that 56.4% of female university students had dysmenorrhea, and among them, 6.5% had very severe (unbearable) symptoms.[5] Dysmenorrhea limits women's daily activity and is associated with absenteeism from school or work.[6] Furthermore, women with primary or secondary dysmenorrhea have higher total health care costs than those without syndromes.[7]

Overproduction of uterine prostaglandins from arachidonic acid through cyclo-oxygenase (COX) pathway has been commonly accepted as the etiology of primary dysmenorrhea.[8] The intensity of painful cramps and dysmenorrhea-related symptoms are proportional to the level of prostaglandin released.[1] Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed as the first line of treatment for dysmenorrhea, due to its suppression of COX activity. However, the inhibitory effect of NSAIDs on COX-1 brings about several physiological concerns.[2, 9] 10%-20% of women with primary dysmenorrhea fail to respond to or are intolerable to NSAIDs.[2] More and more women with dysmenorrhea resort to complementary and alternative medicine.

Tea has been considered as a medicinal staple for hundreds of years in China, thanks to the potential health benefits of tea flavonoids as antioxidants, anti-carcinogenic and anti-arteriosclerotic agent. Recently, green tea catechins have been demonstrated their inhibitory

effect on COX-2 activity.[10, 11] Hence, it is hypothesized that green tea may possibly decrease prostaglandin level and thereby relieve the severity of dysmenorrhea. However, there is a huge paucity of epidemiological evidence of the association of tea drinking with dysmenorrhea, especially green tea consumption, and the results of association are still inconsistent. A cross-sectional study of 729 Turkish women of reproductive age showed no association between tea drinking and dysmenorrhea,[12] while another small study with 440 female university students suggested that students consuming >4 glasses of tea per day had a higher risk of primary dysmenorrhea than those who did not drink tea.[13] To fill in the knowledge gap, the present study aims to examine the relationship between tea drinking and dysmenorrhea in Chinese women of reproductive age.

MATERIALS AND METHODS

This study is based on the Shanghai Birth Cohort Study (SBC), which is a hospital-based, multi-center cohort study. It aims to assess the impacts of genetic, environmental and behavioral factors on reproductive health, pregnancy outcomes, child growth, development and risks of diseases. The reader is referred to cohort profile for more details about SBC.[14]

Patient and participant involvement

In SBC, couples of reproductive age were recruited at either preconception or first trimester of pregnancy. Potential participants who agreed to participate in the study would sign an informed consent during recruitment. Women were followed at several time points, including preconception (if they were recruited before pregnancy), 1st, 2nd, 3rd trimesters and birth, and husbands were interviewed at preconception or at birth. Information on demographic characteristics, health behaviors, social support, reproductive and medical history, and family history of diseases was collected. Biological specimens were collected at each round of follow-up for further analyses.

This study used data from the preconception women who sought preconceptional care at 2 preconceptional care clinics in Shanghai, China, with the following inclusion criteria: 1) married women with age ≥ 20yrs (legal marriage age in China); 2) plan to be pregnant in the following

year; 3) registered residents of Shanghai who do not plan to move out in the next 2 years; 4) plan to give birth in collaborating hospitals. Women who had tried to conceive for 12 months or longer were excluded from this study.

Socio-demographic characteristics

Participants provided information on demographic characteristics and lifestyle factors. Demographic characteristics include age, ethnicity, education level, income by herself, household income, as well as height and weight. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Lifestyle factors included smoking history, alcohol intake, consumption of fruits and vegetables, use of dietary supplements and physical activity which was assessed by International Physical Activity Questionnaire short version.[15]

In addition, the consumptions of caffeinated beverages, such as coffee, soda (Coca-Cola, Pepsi), and energy drink (e.g., Red Bull), were queried. Specifically, the consumption of tea was assessed by a structured questionnaire. Participants were asked whether they drank tea in their daily life. If yes, what type of tea they usually drank, including green, oolong and black tea, which are commonly consumed in China. They could choose one or multiple categories depending on their tea drinking habits. Participants were also asked about the number of years of tea drinking and the choices were “<1 year”, “1-5 years”, “6-10 years” and “>10 years”, and the number of cups per day.

Menstrual characteristics

Women were asked about menstrual characteristics including the onset of menarche, menstrual cycle length, bleeding duration, volume of menstrual flow and dysmenorrhea. If participants stated that they had pelvic pain associated with menstrual bleeding during the past 12 months, they were further asked to grade the intensity of menstrual cramp as mild, moderate and severe. Mild pain was defined as one could feel the pain but did not need further treatment. Moderate pain was defined as one needed to use therapy or treatment to relieve dysmenorrhea,

and severe pain was referred as taking absence of work or bed rest besides treatment. The method grading pain intensity in this study was modified based on verbal rating scale - a validated pain scale to evaluate dysmenorrhea.[16] Although verbal rating scale is not as sensitive as the visual scale or numerical rating scale, which offer a broader spectrum of differentiating pain intensity, it is easier for participants to fill out and thereby limits missing data. The regularity of menstrual cycle length was assessed with the question: “Is your menstrual cycle length regular?”. Length variation of 8 days or more was considered as irregular. If irregular, the durations of the shortest and longest menstrual cycles were asked. If regular, participants stated the average length of their menstrual cycle. Participants were asked to state their volume of menstrual flow with four choices: “light”, “normal” and “heavy”.

Statistical analysis

All the analyses were performed using R studio (Version 1.0.136). We described the distribution of continuous variables (including mean and standard error) according to the severity of dysmenorrhea, and described the relationship of categorical variables with severity of dysmenorrhea using contingency tables. In addition, the differences in demographic characteristics and lifestyle factors according to the severity of dysmenorrhea were analyzed by Kruskal-Wallis test for categorical variables and one-way ANOVA for continuous variables. The primary result was the relationship between tea drinking and dysmenorrhea, which was performed by multinomial logistic regression model. Variables with $P<0.05$ of the significance test for the difference were selected in the final logistic model. Other confounders were selected if they could change the coefficient by more than 10% compared with unadjusted coefficient. $P<0.05$ (two sides) was considered statistically significant.

Patient and public involvement statement

Patients or the public were not involved in the design or conduct of the study. Participants will be able to view the study results once the study is published.

RESULTS

A total of 1183 participants were recruited, of whom 23 did not finish the interview and 8 participants did not provide information on severity of dysmenorrhea, leaving 1152 women for the final analysis. The prevalence of dysmenorrhea was 57.8% (666/1152). Among them, 86.2% (574) had mild, 10.4% (69) moderate, and 3.5% (23) severe dysmenorrhea. Since the total number of moderate and severe dysmenorrhea was only 99, we combined them together for further analyses.

Table 1. Demographic and menstrual characteristics according to the severity of dysmenorrhea

Variables	Dysmenorrhea (N (%) or (Mean ± SD))			P-value
	No (486)	Mild (574)	Moderate-to-severe (92)	
Age (years)	29.9 ± 3.5	29.2 ± 3.0	28.4 ± 2.4	<0.001
BMI (kg/m²)	21.2 ± 2.9	20.9 ± 2.5	20.3 ± 3.0	0.021
Race				0.733
Han	474 (42.2)	559 (49.8)	89 (7.9)	
Others	12 (40.0)	15 (50.0)	3 (10.0)	
Education				0.533
Junior college	96 (42.7)	113 (50.2)	16 (7.1)	
Undergraduate	302 (43.0)	346 (49.2)	55 (7.8)	
Graduate	88 (39.3)	115 (51.3)	21 (9.4)	
Home income				0.646
＜￥100K	31 (36.9)	48 (57.1)	5 (6.0)	
￥100-150K	77 (41.4)	96 (51.6)	13 (7.0)	
≥￥150K	357 (43.9)	392 (48.2)	65 (8.0)	
Personal income				0.622
＜￥100K	241 (40.3)	315 (52.7)	42 (7.0)	
￥100-150K	159 (45.2)	161 (45.7)	32 (9.1)	
≥￥150K	62 (43.7)	68 (47.9)	12 (8.5)	
Onset of menarche (years)	13.4 ± 1.4	13.4 ± 1.3	13.4 ± 1.3	0.763
Length of menstrual cycle (days)	29.8 ± 2.9	29.7 ± 2.9	30.3 ± 7.7	0.308
Bleeding duration (days/month)	5.6 ± 1.4	5.7 ± 1.2	5.7 ± 1.3	0.268
Volume of menstrual flow				<0.001
Light	48(48.0)	44(44.0)	8(8.0)	
Normal	419(43.2)	487(50.2)	65(6.7)	
Heavy	18(23.1)	41(52.6)	19(24.4)	
Regularity of menstrual cycle				0.773
Regular	393 (41.7)	479 (50.8)	71 (7.5)	
Irregular	93 (44.5)	95 (45.5)	21 (10.0)	
Having had a pregnancy				<0.001
No	244 (37.2)	344 (52.4)	68 (10.4)	
Yes	241 (48.7)	230 (46.5)	24 (4.8)	

P-value was obtained by Kruskal-Wallis test for categorical variables and one-way ANOVA for continuous variables

Table 1 presents the demographic and menstrual characteristics of the study population according to the severity of dysmenorrhea. The average age of all the 1152 participants was 29.4 ± 3.2 years, ranging from 21 to 44 years. 5% of women were 35 years or older. Women with moderate to severe dysmenorrhea had a mean age of 28.4 ± 2.4 years, in comparison to 29.9 ±3.5 years in women without dysmenorrhea. The average BMI was 21.0 ± 2.7 kg/m^2, with 7.2% being overweight or obese (BMI ≥ 25 kg/m^2). Non-dysmenorrhea group had a higher BMI than mild-dysmenorrhea group, followed by moderate-to-severe group. There was no difference in education, women's income and household income among the three groups.

The average age of the onset of menarche was 13.4 ± 1.3 years. The average length of menstrual cycle and bleeding was 29.8 ± 3.5 days and 5.7 ± 1.3 days, respectively, among all the women of reproductive age. The prevalence of moderate-to-severe dysmenorrhea was higher in women with heavy menstrual flow, compared with women with light and normal menses. Multiparous women were less likely to have dysmenorrhea.

Table 2 presents the distribution of lifestyle factors according to the intensity of dysmenorrhea. Very few women smoked. There was no association between smoking and dysmenorrhea. However, women who were exposed to second-hand smoke from her husband, roommates or colleagues were more likely to have dysmenorrhea.

Consumptions of vegetables, fruits, dietary supplements of Vitamin E and fish oil were not associated with the severity of menstrual pain (Table 2). However, the prevalence of moderate-to-severe dysmenorrhea was slightly higher in women who did not take Vitamin E, compared with Vitamin E consumers (8.8% versus 4.0%). Physical activity (vigorous, moderate or walking) was not associated with the severity of dysmenorrhea.

The prevalence of tea drinking was 34.5% (398 of 1152) among women with reproductive age, and the number of tea drinkers according to the severity of dysmenorrhea was shown in Table 3. Table 4 shows the association between tea drinking and dysmenorrhea. After adjusting for age, BMI, personal income, ever pregnant, consumption of caffeinated beverages (coffee,

Table 2. Lifestyle factors according to the severity of dysmenorrhea

Variables	Dysmenorrhea (N (%))			P-value
	No (486)	Mild (574)	Moderate-to-severe (92)	
Smoking now				0.193
No	481 (42.3)	569 (50.0)	88 (7.7)	
Yes	5 (35.7)	5 (35.7)	4 (28.6)	
Used to smoke				0.604
No	471 (42.2)	557 (50.0)	87 (7.8)	
Yes	9 (47.4)	9 (47.4)	1 (5.3)	
Second-hand smoke				<0.001
No	365 (46.5)	363 (46.2)	57 (7.3)	
Yes	121 (33.2)	209 (57.3)	35 (9.6)	
Alcohol drinking within one year				0.110
No	325 (43.6)	366 (49.1)	54 (7.2)	
Yes	160 (39.4)	208 (51.2)	38 (9.4)	
Current alcohol drinking				0.676
No	469 (42.3)	551 (49.7)	88 (7.9)	
Yes	17 (39.5)	22 (51.2)	4 (9.3)	
Vitamin E				0.065
No	392 (41.3)	474 (49.9)	84 (8.8)	
Yes	81 (46.8)	85 (49.1)	7 (4.0)	
Supplementation of fish oil				0.874
No	438 (42.0)	519 (49.8)	85 (8.2)	
Yes	33 (42.9)	38 (49.4)	6 (7.8)	
Leaf vegetables				0.359
＜1 per week	8 (57.1)	6 (42.9)	0 (0)	
1-3 per week	73 (42.4)	81 (47.1)	18 (10.5)	
4-7 per week	264 (40.7)	330 (50.9)	54 (8.3)	
≥ 2 per day	137 (44.1)	154 (49.5)	20 (6.4)	
Fruits				0.262
＜1 per week	8 (32.0)	15 (60.0)	2 (8.0)	
1-3 per week	90 (39.1)	113 (49.1)	27 (11.7)	
4-7 per week	286 (43.4)	331 (50.2)	42 (6.4)	
≥ 2 per day	99 (43.2)	109 (47.6)	21 (9.2)	
Vigorous physical activity				0.460
No	393 (41.6)	475 (50.3)	77(8.1)	
Yes	85 (44.7)	90 (47.4)	15(7.9)	
Moderate physical activity				0.456
No	300 (41.3)	366 (50.3)	61 (8.4)	
Yes	171 (43.4)	193 (49.0)	30 (7.6)	
Walk				0.195
No	24 (57.1)	12 (28.6)	6 (14.3)	
Yes	409 (41.6)	495 (50.4)	78 (7.9)	

P-value was obtained by Kruskal-Wallis test

Soda or energy drink), alcohol drinking during last 12 months, second-hand smoke, supplementation of fish oil, consumption of leaf vegetable, moderate physical activity and walking, tea drinking was associated with a 32% lower prevalence of mild dysmenorrhea. The aOR of mild dysmenorrhea was attenuated by half in women who drank tea for 3-5 cups per day compared with women who did not drink tea, whereas we did not find such relationship in higher tea consumers (≥6 cups/day). We did not find a relationship between number of years of tea drinking and severity of dysmenorrhea among tea drinkers. Consumption of green tea was associated with a lower prevalence of dysmenorrhea, and the relationship was stronger in moderate-to-severe dysmenorrhea than in mild dysmenorrhea, which is shown in Table 5. Consumption of oolong tea was associated with a lower prevalence of dysmenorrhea but the association did not reach statistical significance.

Table 3. Caffeinated beverages according to the severity of dysmenorrhea

Variables	Dysmenorrhea			
	No (486)	Mild (574)	Moderate-to-severe (92)	P-value
Tea				0.216
No	308 (40.8)	384 (50.9)	62 (8.2)	
Yes	178 (44.7)	190 (47.7)	30 (7.5)	
Green tea				0.012
No	347 (40.2)	443 (51.3)	74 (8.6)	
Yes	139 (48.3)	131 (45.5)	18 (6.3)	
Black tea				0.337
No	413 (42.7)	481 (49.7)	74 (7.6)	
Yes	73 (39.7)	93 (50.5)	18 (9.8)	
Oolong tea				0.033
No	434 (41.3)	528 (50.3)	88 (8.4)	
Yes	52 (51.0)	46 (45.1)	4 (3.9)	
Coffee				0.027
No	275 (43.9)	317 (50.6)	34 (5.4)	
Yes	211 (40.1)	257 (48.9)	58 (11.0)	
Soda (Coca-Cola, Pepsi)				0.047
No	335 (43.7)	381 (49.7)	51 (6.6)	
Yes	151 (39.2)	193 (50.1)	41 (10.6)	
Energy beverages				0.050
No	462 (42.7)	539 (49.8)	81 (7.5)	
Yes	24 (34.3)	35 (50.0)	11 (15.7)	

P-value was obtained by Kruskal-Wallis test

Table 4. Relationship of tea drinking and dysmenorrhea

Variable	Crude model (cOR)			Adjusted model (aOR) [a]	
	No (486)	Mild (574)	Moderate-to-severe (92)	Mild (574)	Moderate-to-severe (92)
Tea					
No	1	1	1	1	1
Yes	1	0.86(0.66-1.10)	0.84(0.52-1.34)	0.68(0.50-0.93)	0.59(0.32-1.04)
Number of cups/day					
0 per day	1	1	1	1	1
1-2 cups/day	1	0.97(0.71-1.33)	1.06(0.61-1.84)	0.80(0.55-1.17)	0.71(0.36-1.41)
3-5 cups/day	1	0.66(0.44-0.98)	0.57(0.25-1.31)	0.49(0.31-0.79)	0.39(0.15-1.00)
≥ 6 cups/day	1	0.80(0.43-1.50)	0.71(0.21-2.45)	0.75(0.37-1.53)	0.77(0.21-2.86)
Number of years of tea drinking					
< 1 year	1	1	1	1	1
1-5 years	1	0.64(0.36-1.13)	1.41(0.44-4.50)	0.53(0.26-1.07)	2.13(0.40-11.2)
≥ 6 years	1	0.61(0.33-1.14)	0.71(0.18-2.73)	0.54(0.24-1.25)	1.67(0.25-11.2)

[a] model 1 was a crude multinomial logistic regression which was used for each outcome

[b] model 2 was an adjusted multinomial logistic regression model for each outcome, and was adjusted for age, BMI, personal income, ever pregnant, caffeinated beverages drinking, alcohol drinking now and during last one year, second-hand smoke, supplementation of fish oil, consumption of leaf vegetables, moderate- and walk-intensity physical activity.

Table 5. Odds ratios for dysmenorrhea according to consumption of type of tea beverage/caffeinated beverage

Variable	Crude model (cOR)			Adjusted model (aOR)	
	No (486)	mild (574)	Moderate-to-severe (92)	Mild (574)	Moderate-to-severe (92)
[a] **Model 1**					
Green tea	1	0.74(0.56-0.97)	0.61(0.35-1.05)	0.63(0.44-0.90)	0.42(0.20-0.85)
Black tea	1	1.09(0.78-1.53)	1.38(0.78-2.44)	1.27(0.81-2.00)	1.96(0.94-4.10)
Oolong tea	1	0.73(0.48-1.10)	0.38(0.13-1.08)	0.60(0.35-1.03)	0.34(0.11-1.09)
[b] **Model 2**					
Coffee	1	1.06(0.83-1.35)	2.22(1.40-3.52)	1.08(0.80-1.44)	2.11(1.22-3.62)
Soda	1	1.12(0.87-1.45)	1.78(1.13-2.81)	1.05(0.76-1.44)	1.20(0.69-2.10)
Energy beverages	1	1.25(0.73-2.13)	2.61(1.23-5.54)	0.91(0.50-1.69)	1.65(0.66-4.15)

[a] model 1 was a multinomial logistic regression model which was used for each type of tea beverage separately, and was further adjusted for other types of tea beverages, age, BMI, personal income, ever pregnant, caffeinated beverages drinking, alcohol drinking now and during last one year, second-hand smoke, supplementation of fish oil, consumption of leaf vegetables, moderate- and walk-intensity physical activity

[b] model 2 was a multinomial logistic regression model which was used for each caffeinated beverage separately, and was further adjusted for other caffeinated beverages, age, BMI, personal income, ever pregnant, second-hand smoke, walk-intensity physical activity and tea drinking

As for the relationship between each caffeine-contained beverage (coffee, Soda and energy drink) and severity of dysmenorrhea (Table 5), women with moderate-to-severe dysmenorrhea were twice more likely to be coffee drinkers than women without dysmenorrhea. However, after adjusting for potential confounders, consumption of neither soda nor energy beverages was associated with prevalence of moderate-to-severe dysmenorrhea.

DISCUSSION

The present study found that more than half of Chinese reproductive age women (57.8%) had some degree of dysmenorrhea. Exposure to second-hand smoke or consumption of coffee were positively associated with moderate-to-severe dysmenorrhea. After adjustment for the potential confounders, consumptions of green tea and possibly oolong tea were associated with lower prevalence of dysmenorrhea.

The prevalence of dysmenorrhea in our population was consistent with previous studies. It was reported that at least 50% of women around the world[17] and 56.4% of university students in China suffered from dysmenorrhea.[5] However, the prevalence of severe dysmenorrhea in this study was slightly lower than the previous study (3.5% vs 6.5%, respectively),[5] which may be explained by the age difference between the study populations (29.4 ± 3.2 years in the current study versus 20.3 ± 1.3 in Zhou's study[5]). Previous literature indicated that menstrual pain was alleviated to some degree with advancing age.[12, 18, 19]

The relationships between dysmenorrhea and menstrual characteristics (such as onset of menarche, regular menses, bleeding duration) are still uncertain.[20] Some studies reported that older age at menarche was associated with a decreased risk of dysmenorrhea,[18, 21] while others showed no association.[12, 22] Unsal et al. found that menstrual irregularity was one of risk factors for dysmenorrhea [OR=1.90 (1.22-32.95)].[12] As for blood flow, some studies showed that reduced menstrual flow may be a sign of uterine constriction and it was associated with cramp pain[1, 23] while others showed that the severity of dysmenorrhea increased with increasing volume of blood flow.[5, 24] Our study was consistent with the latter finding, that is,

women with heavy blood flow were more likely to have dysmenorrhea. However, we did not find any other relationship between menstrual health and dysmenorrhea. Interestingly, our result showed that pregnancy history was inversely associated with dysmenorrhea, in line with previous studies.[12, 18]

Our results showed a tendency towards dysmenorrhea relief when women drank tea in daily life. Those who consumed 3-5 cups/day of tea were 51% less likely to report having mild dysmenorrhea than non-drinkers. The observation of no relationship between high tea drinking (≥6 cups/day) and dysmenorrhea may be true or due to chance; only 45 participants stated tea consumption of ≥6 cups/day. In contrast, a small cross-sectional study with randomly selected 440 female university students in Ethiopia suggested that people drinking tea for more than 4 glasses/day had 19 times higher prevalence of dysmenorrhea than non-drinkers, the corresponding aOR was 18.94 (2.19-163.73).[13] However, the very wide confidence interval indicates that the conclusion is uncertain.

Among three types of tea, our study showed that consumption of green tea may be beneficial for relief of dysmenorrhea while consumption of black tea was not. The latter finding is consistent with the results from a Turkey study - a cross-sectional study with 729 reproductive-age women, which found no association between tea consumption and dysmenorrhea,[12] as the traditional tea in Turkey is black tea. Consumption of oolong tea had a boardline association with a lower prevalence of dysmenorrhea, which may be ascribed to a small sample size. Our study may be underpowered to detect the desired difference between oolong tea drinkers and non-drinkers.

To explore whether caffeine in tea was responsible to the relief of dysmenorrhea, we examined the association between consumption of caffeinated beverages, especially coffee, and dysmenorrhea. Unlike tea, consumption of coffee was positively related to the severity of dysmenorrhea in this study after adjustment of potential confounders. Previous studies showed that the risk of dysmenorrhea was twice as high in high caffeine consumers (≥300 mg/day) compared with low/moderate caffeine consumers (<300 mg/day) [OR=1.97 (1.09-3.59)][25] and

in coffee consumers [OR=2.08 (1.34-3.24)].[12] The mechanism through which caffeine could aggravate cramp-like pain is uncertain and further studies are warranted. One possible mechanism is the vasoconstricting action of caffeine.[26] A study in pregnant women indicates that caffeine stimulates uterine muscle and, consequently, causes increased uterine contraction.[27] Uterine hypercontraction reduces blood flow and results in pain.[1]

Instead, catechins in green tea might partly explain the observed relationship with relieved severity of dysmenorrhea. The extent of the oxidative processing (also called “fermentation”) differs among three types of tea - green tea is minimally processed, while black tea is completed fermented. Hence, catechins are rich in green tea followed by oolong tea, while much lower in black tea, as it is unstable and sensitive to oxidization. A number of animal and *in vitro* studies suggest that green tea extract (catechins) is an effective inhibitor of COX-2 but not COX-1[10, 11] thereby preventing overproduction of uterine prostaglandin levels, a major pathogenesis of primary dysmenorrhea. In addition, catechins inhibit the activity of phospholipase A2, an enzyme involved in the production of arachidonic acid, and consequently decreases the production of additional prostaglandin from arachidonic acid.[28] Given the high catechins content in green tea, it is convincingly expected green tea may be beneficial to relieve menstrual cramp by inhibiting prostaglandin level.

Further studies are needed to specify the role of catechins in dysmenorrhea. Despite the promising effect of tea drinking in dysmenorrhea, tea drinking during menstrual period may also have unwanted side effects. Catechins and tannic acid rich in tea can chelate iron, thus tend to interfere with iron absorption.[29-31] As menstruating women lose iron through bleeding, caution of drinking too much tea during menstruation may be warranted.

Several limitations of our study are worth mentioning. First, as our study collected data from the study population at a single point of time, it may be difficult to establish a causal relationship between tea drinking and dysmenorrhea. Second, this study did not distinguish secondary dysmenorrhea from primary dysmenorrhea. However, secondary dysmenorrhea may share some

of the same pathways of pain as the primary dysmenorrhea, with an evidence of an increased level of prostaglandin in endometriosis and adenomyosis.[32, 33] On the other hand, an animal study has shown that green tea catechins inhibited the development of endometriosis through anti-angiogenic effects.[34] Thus, it is possible that green tea may potentially be beneficial to both primary and secondary dysmenorrhea. Third, we did not include information on oral contraceptive pills use, which may cause potential bias due to residual confounding. However, this study recruited women of reproductive age who were planning to become pregnant. Therefore, the number of participants using oral contraceptive pills was negligible. Fourth, the size of a tea serving and the biochemical quantity in a tea serving vary widely with different methods of preparing tea between individuals in China. We were unable to standardize the size of tea cups. Finally, the information on dysmenorrhea was based on participants' self-report and, as such, it was subject to information bias. However, it is difficult to explain why such a bias only occurred in certain types of tea but not all types.

The strengths of this study are also worth noting. The large sample size made the results more precise. In addition, this study was based on a large cohort, which enables us to involve more potential confounders in the analyses. The study population was women who were planning to be pregnant, so they were more likely to remember their health-related behaviors and characteristics, especially those related to reproduction, such as menstrual characteristics.

In conclusion, our study suggests that drinking green tea was associated with a lower prevalence of dysmenorrhea among reproductive-age women in China. On the other hand, excessive tea drinking may not be advisable, either, as tea may inhibit iron absorption. Given the scarcity of epidemiological evidence of tea drinking and dysmenorrhea, this study gives new insights in the possible role of green tea on the relief of dysmenorrhea. Cohort studies and subsequent randomized controlled trials are needed to confirm this finding, which may have important clinical and publich health significance.

AUTHOR STATEMENT

J.Z, P.Z and Y.T contributed to study conception and design, and contributed to acquisition of data. X.Z, D.C and R.H contributed to analysis and interpretation of data. X.Z and R.Z contributed to drafting article. J.Z, and P.Z contributed to revising the article critically. All authors reviewed the final version of the manuscript and gave final approval of the version to be published.

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DECLARATION OF INTEREST

There is no conflict of interest that could be perceived.

DATA SHARING

Currently, the Shanghai Birth Cohort data are not yet open to public due to the confidentiality agreement. Data used in this analysis and computing programs are available from the corresponding author upon request.

ETHICAL APPROVAL

This study is based on the Shanghai Birth Cohort which was approved by the Institutional Review Board of Xinhua Hospital affiliated to the Shanghai Jiao Tong University School of Medicine, and no additional review was needed for this analysis. All participants signed an informed consent.

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-10
		(b) Indicate number of participants with missing data for each variable of interest	7-10
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.