Association of Hormonal Contraceptive Use with Headache and Temporomandibular Pain: The OPPERA Study

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Aims: To determine the relationship between hormonal contraceptive (HC) use and painful symptoms, particularly those associated with headache and painful temporomandibular disorders (TMD). **Methods:** Data from the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) prospective cohort study were used. During the 2.5-year median follow-up period, quarterly health update (QHU) questionnaires were completed by 1,475 women aged 18 to 44 years who did not have TMD, menopause, hysterectomy, or hormone replacement therapy use at baseline. QHU questionnaires evaluated HC use, symptoms of headache and TMD, and pain of ≥ 1 day duration in 12 body regions. Participants who developed TMD symptoms were examined to classify clinical TMD. Headache symptoms were classified based on the International Classification of Headache Disorders 3 (ICHD-3). Associations between HC use and pain symptoms were analyzed using generalized estimating equations and Cox models. **Results:** HC use, endorsed in 33.7% of QHU questionnaires, was significantly associated with concurrent symptoms of TMD (odds ratio [OR]: 1.20, 95% CI: 1.06 to 1.35) and headache (OR: 1.26, 95% CI: 1.11 to 1.43). HC use was also significantly associated with concurrent pain of ≥ 1 day duration in the head (OR: 1.38, 95% CI: 1.16 to 1.63), face (OR: 1.44, 95% CI: 1.13 to 1.83), and legs (OR: 1.22, 95% CI: 1.01 to 1.47), but not elsewhere. Initiation of HC use was associated with increased odds of subsequent TMD symptoms (OR: 1.37, 95% CI: 1.13 to 1.66) and pain of ≥ 1 day in the head (OR: 1.37, 95% CI: 1.01 to 1.85). Discontinuing HC use was associated with lower odds of subsequent headache (OR: 0.82, 95% CI: 0.67 to 0.99). HC use was not significantly associated with subsequent onset of examiner-classified TMD. **Conclusion:** These findings imply that HC influences craniofacial pain, and that this pain diminishes after cessation of HC use. *J Oral Facial Pain Headache 2021;35:105–112. doi: 10.11607/ofph.2727*

Keywords: *contraception, facial pain, headache, hormones, pain*

Despite the documented public health benefits of hormonal contraception (HC), side effects have been of concern since HC was introduced.[1] Among the side effects from HC, headache is frequently reported.[2,3] This is consistent with evidence that reproductive hormones can be pain-enhancing in women; for instance, both headaches and chronic painful temporomandibular disorders (TMD) are more prevalent among women than among men.[4] However, the studies reporting associations between HC use and headache have significant shortcomings, such as a cross-sectional study design, lack of a control population that is not using HC, and likely recall bias in reporting HC.[1–4] In contrast to the association between HC use and headache, evidence of an association between HC use and painful TMD is equivocal. While some studies have identified a greater risk of TMD among HC users,[5] other studies have not.[6] Such study limitations and inconsistencies confound whether headache or painful TMD are related to HC use.

Given the substantial overlap in major characteristics of headache and painful TMDs,[7] it would be surprising for HC to contribute selectively to headache symptoms, but not to TMD symptoms. Whether the focus is on headache, TMD, or other pain conditions, more convincing evidence of an association between HC use and a pain condition could
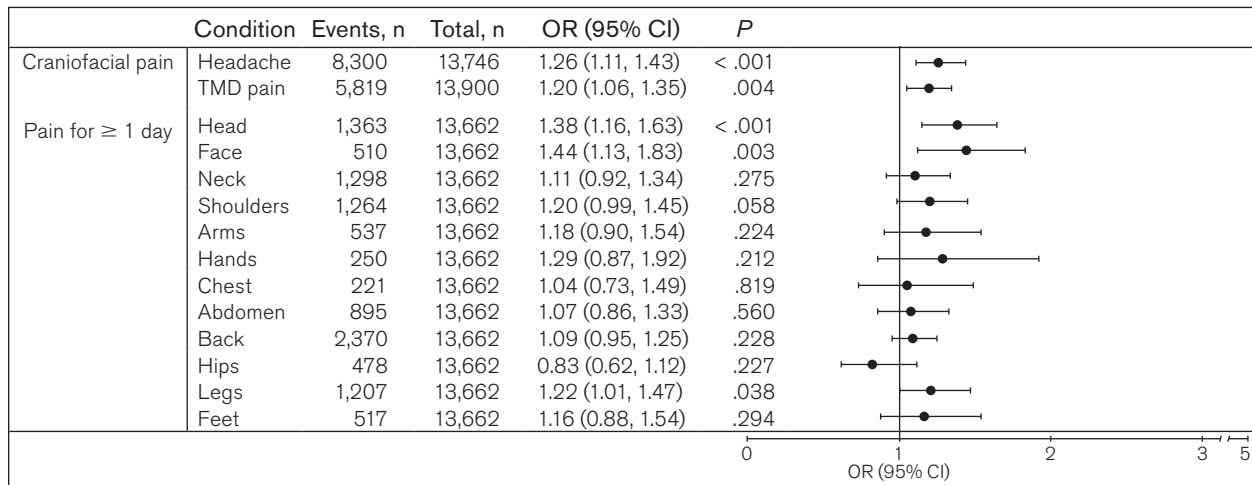
	Condition	Events, n	Total, n	OR (95% CI)	P
Craniofacial pain	Headache	8,300	13,746	1.26 (1.11, 1.43)	< .001
	TMD pain	5,819	13,900	1.20 (1.06, 1.35)	.004
Pain for ≥ 1 day	Head	1,363	13,662	1.38 (1.16, 1.63)	< .001
	Face	510	13,662	1.44 (1.13, 1.83)	.003
	Neck	1,298	13,662	1.11 (0.92, 1.34)	.275
	Shoulders	1,264	13,662	1.20 (0.99, 1.45)	.058
	Arms	537	13,662	1.18 (0.90, 1.54)	.224
	Hands	250	13,662	1.29 (0.87, 1.92)	.212
	Chest	221	13,662	1.04 (0.73, 1.49)	.819
	Abdomen	895	13,662	1.07 (0.86, 1.33)	.560
	Back	2,370	13,662	1.09 (0.95, 1.25)	.228
	Hips	478	13,662	0.83 (0.62, 1.12)	.227
	Legs	1,207	13,662	1.22 (1.01, 1.47)	.038
	Feet	517	13,662	1.16 (0.88, 1.54)	.294

OR (95% CI)

Fig 1 Association between hormonal contraceptive (HC) use and pain for all observations. The associations between HC use and TMD pain, headache, and pain in the head and face regions were significant; the association was not significant for any other body region.

be demonstrated using a prospective cohort study where HC users and non-HC users are compared for their development of pain symptoms over time. Nonetheless, studying the interplay between HC and pain poses other methodologic challenges. For example, HC is commonly prescribed for treatment of common pain disorders, such as dysmenorrhea.[8,9] Thus, observed associations between HC and the subsequent development of pain may be confounded by a previous history of pain and its treatment with HC.

This study aimed to evaluate the association between HC use and symptoms of pain, both in the head and face regions, as well as elsewhere. Data from a prospective cohort study with extensive pain phenotyping were leveraged, allowing for the comparison of differential HC use over time across multiple painful symptoms. Using repeated assessments of HC and pain evaluated in the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) study,[10] the authors tested whether HC use is associated with increased occurrence of headache, facial pain, or other regional painful symptoms and whether initiation or discontinuation of HC use alters the risk of experiencing pain.

Materials and Methods

Study Population

The prospective cohort comprised 3,263 individuals who were TMD-free at enrollment, 1,850 of whom were women. Data for the present study were obtained from 1,576 female participants who did not have TMD when enrolled and who completed a baseline gynecological questionnaire and follow-up questionnaires in the OPPERA prospective cohort study of first-onset TMD. Subjects were recruited at four U.S. study sites

between May 2006 and November 2008.[11] To ensure that subjects were TMD-free at enrollment, subjects were excluded from the prospective cohort if they fulfilled any of the following criteria: reported TMD pain in the month prior to recruitment; five or more headaches per month, on average, reported in the 3 months prior to recruitment; TMD pain symptoms lasting more than 5 days in any one of the 5 months prior to recruitment; or examiner-assessed TMD myalgia or arthralgia, classified using modified Research Diagnostic Criteria (RDC) for TMD.[12] Examinations were performed by a trained, calibrated research clinician at each study site. A detailed description of the study design and methodology, including complete inclusion and exclusion criteria, has previously been reported.[11] The present analysis excluded women based on the following gynecological exclusion criteria: reporting using hormonal therapy for any reason other than contraception or treatment of acne or ovarian cysts; reporting menopause; or reporting having a hysterectomy. Thus the present analysis included 1,475 female participants, as summarized in Appendix Fig 1 (see appendices in the online-only version of this article at www.quintpub.com/journals).

Study Measures
Baseline measures
After enrollment in OPPERA, study participants completed extensive baseline assessments. A gynecological questionnaire was used to ask about contraceptive use, with the options oral contraceptive pills (OCP) or other HC, such as contraceptive rings, patches, transdermal implants, intrauterine implants, injectable, and other hormonal contraceptive formulations. Women also reported whether HC had ever been used to treat pain and the severity of dysmenorrhea. Pain symptoms were reported using the Comprehensive Pain and

Symptom Questionnaire (CPSQ). Participants were first asked whether they had any headaches in the past year and then responded to questions about symptoms of headache experienced in the past year. The headache symptom questionnaire was based on criteria from the International Classification of Headache Disorders, second edition (ICHD-2),[13,14] which was current at the time of CPSQ development. An algorithm for classification was subsequently developed and incorporated the third edition (ICHD-3) beta criteria; the relevant headache criteria in the final version of ICHD-3 did not differ from the beta version.[15] Specifically, these headache types were tension-type (certain, probable), migraine, and mixed-type headaches. A joint measure of "any ICHD-3 headache" was defined by algorithm-based classification of any of these headache types.

Longitudinal measures

Subjects completed quarterly health update questionnaires (QHUs) every 3 months for up to 5 years following enrollment, with 1,576 women completing one or more QHUs after completion of the baseline gynecological questionnaire. QHUs evaluated the presence of pain symptoms and use of HC. In each QHU, female participants were asked if they were currently using HC or hormone replacement therapies. Specific contraceptive formulations were not ascertained. The questionnaire also asked if the subject had experienced aches or pains lasting a day or longer during the preceding 3 months. Those responding affirmatively were then asked to indicate the location of pain by selecting any of 12 different bodily regions in which they had experienced the pain: head, face, neck, shoulders, chest, back, abdomen, arms, hands, hips, legs, and feet.

Craniofacial pain was assessed in the QHU primarily through two items. TMD pain was assessed in QHUs by asking if subjects had experienced "headaches or pain in your face, jaw, temples, in front of the ear, or in the ear" during the preceding 3 months. A separate question asked participants to report if they had experienced headaches of any type during the preceding 3 months. Individuals who reported significant symptoms of TMD were invited to return to the appropriate study site for an RDC/TMD examination to evaluate the presence of first-onset TMD.[16] The TMD examination was conducted if the individual reported (during the 3-month period of the current QHU) *(1)* ≥ 5 consecutive days of symptoms per month for ≥ 2 months, with ≥ 1 day of symptoms in the prior 2 weeks, or *(2)* ≥ 5 consecutive days of symptoms in the preceding month, with ≥ 5 days of symptoms in the preceding 2 weeks.

Longitudinal analyses were limited to 14,097 QHUs completed by 1,475 women (of 1,850 enrolled) after excluding those with no baseline gynecological questionnaire, QHU follow-up data, or gynecological exclusion criteria. During follow-up, 150 developed examiner-determined TMD. On average, each subject completed 10 follow-up questionnaires over the study period, ranging from 1 to 19 questionnaires completed per study participant (SD = 5.2; median = 11). This represented a median follow-up period of 2.5 years.

Ethical Approval

The study protocol was approved by the institutional review boards at all four study sites and the data coordinating center (Battelle Memorial Institute), and all study participants provided informed consent before enrolling in the study.

Statistical Methods
Baseline associations with headache

Using the logit link function, generalized linear models were used to assess the association between HC use (reference group: non-HC use) and binary headache conditions at baseline. All models were adjusted for study site and race using dummy variables, and for age as a continuous variable. Two models were run for each outcome, where the outcomes were presence/absence of headache and particular headache classes. The first model included OCP use as the primary predictor, comparing to non-users of any HCs. The second model included non-OCP HC use as the primary predictor, comparing to non-users of any HCs. All non-OCP HC formulations were grouped together in order to have adequate power, as each of the formulations accounted for less than 1% of the HC users from the entire cohort. Pairwise differences and overall differences were calculated using *t* tests. This was performed for all women in the prospective cohort at baseline meeting the inclusion criteria.

Longitudinal associations with concurrent headache, TMD pain, and regional pain

Generalized estimating equations (GEE) with a logit link function were used to evaluate the association between HC use of any type and, concurrently, presence of headache of any type, TMD pain, and regional pain symptoms during the same quarterly period. The models were adjusted for study site, race, and age. The autoregressive (AR1) correlation structure was used for all models, and all tests were two-tailed. Since HC can be used to treat menstrual pain and other types of pain, this analysis was repeated after excluding 527 women who reported moderate to severe menstrual pain and women who previously used HC to treat pelvic pain, painful periods, or endometriosis at baseline (see Appendix Fig 1).

Table 1 Demographic and Clinical Information of the Study Sample

Characteristic		No. (%)
Race	White	822 (55.7)
	African-American	419 (28.4)
	Asian	82 (5.6)
	Hispanic	152 (10.3)
Age at initial visit, y	18–19	193 (13.1)
	20–24	597 (40.5)
	25–29	259 (17.6)
	30–34	140 (9.5)
	35–39	137 (9.3)
	40–44	149 (10.1)
Site	Chapel Hill, NC	431 (29.2)
	Buffalo, NY	374 (25.4)
	Gainesville, FL	414 (28.1)
	Baltimore, MD	256 (17.4)

Longitudinal association with TMD onset

The association between HC use and incidence of examiner-verified TMD was evaluated using a Cox proportional hazards model of time-to-onset of either TMD or censoring (ie, loss to follow-up or study end). Covariates included study site, race, age, and HC use as a time-varying covariate.

Longitudinal associations with initiation and discontinuation of HC use

The temporal sequence of HC use and pain symptoms was investigated to determine whether initiation of HC use was associated with increased risk of pain and whether discontinuation of HC use was associated with decreased risk of pain. In these models, the sample was limited to the 697 (47.3%) women who reported using HC at least once. When analyzing the effects of discontinuing HC use, the sample was restricted to observations where women reported using HC for at least one quarterly questionnaire and then reported not using HC in at least one subsequent questionnaire; only the first period of use (ie, questionnaires reporting use of HC) and subsequent absence of use (ie, later questionnaires reporting no HC use) were included. Conversely, the sample used for those initiating HC use was restricted to women who were not using HC, then began use, excluding any subsequent fluctuations in their use.

A lagged logistic GEE model was used to determine if HC use at a given quarterly period was associated with headache at the subsequent quarterly period. For each quarterly period q, covariates included HC use in period q and presence of headaches in period q (in addition to study site, race, and age). The outcome for each time point was the presence of headaches at period q+1. Data were analyzed with R version 3.5.2.

Results

The 1,576 women with follow-up data completed 14,178 QHUs, and HC use was reported in 4,784 QHUs (33.7% of all questionnaires). At baseline, 326 reported the use of oral contraceptives, and 111 reported the use of other hormonal contraceptives in the gynecological questionnaire. The demographic characteristics of prospective study participants are shown in Table 1.

Baseline Associations with Headache

Oral contraceptive use was associated with greater odds of any ICHD-3 headache (OR: 1.63, 95% CI: 1.07 to 2.48) at baseline (Table 2). The odds of specific headache types (ie, migraine and certain and probable tension-type) were not significantly associated with either type of hormonal contraceptives, but all indicated increased odds with the exception of probable tension-type headache under other HC use. Mixed headaches were not reported concurrently with any HC use by any participant at baseline, and are thus not modeled. Consequently, the types of headache were reduced to simply "headache" for longitudinal analyses.

Longitudinal associations with concurrent headache, TMD pain, and regional pain

HC use was associated with greater odds of self-reported TMD pain (OR: 1.20, 95% CI: 1.06 to 1.35) and greater odds of headache (OR: 1.26, 95% CI: 1.11 to 1.43) (Fig 1). HC use was also associated with greater odds of pain lasting one day or more in the head (OR: 1.38, 95% CI: 1.16 to 1.63), face (OR: 1.44, 95% CI: 1.13 to 1.83), and legs (OR: 1.22, 95% CI: 1.01 to 1.47). There were no significant associations between HC use and pain lasting 1 day or more in other bodily regions. The results remained essentially unchanged after excluding women with moderate to severe menstrual pain or past HC use to treat pain, as summarized in Appendix Table 1.

Longitudinal association with TMD onset

In the Cox model that prospectively evaluated the association between HC use and incidence of clinically verified TMD, HC use was not a statistically significant predictor (hazard ratio [HR]: 1.36, 95% CI: 0.82 to 2.24, *P* = .29).

Longitudinal associations with initiation and discontinuation of HC use

Initiation of HC use was a significant predictor of developing TMD pain symptoms (OR: 1.37, 95% CI: 1.13 to 1.67). Pain in the head region was also significantly associated with initiation of HC use, with an OR of 1.37 (95% CI: 1.01 to 1.85) (Fig 2). Conversely,

Table 2 Association Between Hormonal Contraceptive Use and Headaches for All Observations at Baseline

	Oral contraceptives		Other hormonal contraceptives	
Outcome	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Presence of headaches in the past year	1.50 (0.96, 2.36)	.071	1.15 (0.57, 2.29)	.696
Probable tension-type headache	1.25 (0.90, 1.72)	.170	0.91 (0.52, 1.57)	.732
Tension-type headache	1.44 (0.89, 2.33)	.131	1.19 (0.48, 2.94)	.703
Migraine headache	1.27 (0.92, 1.75)	.140	1.20 (0.68, 2.11)	.517
Any ICHD-3 headache	1.63 (1.07, 2.48)	.021	1.41 (0.72, 2.76)	.310

There was a significant association between oral contraceptive use and reported headache; all headache subtypes reported consistent effects for the association with oral contraceptives.
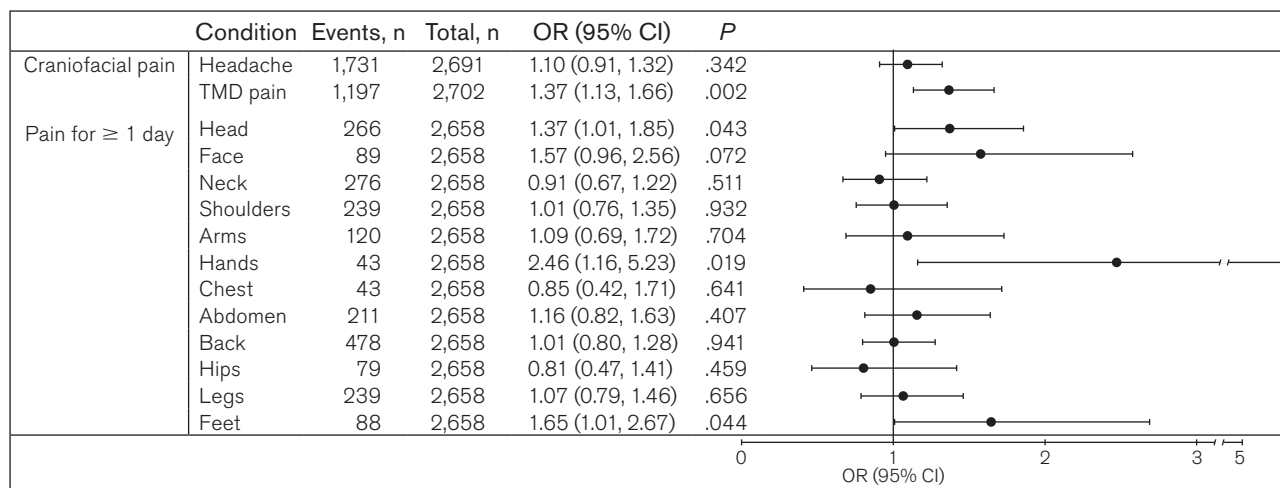
	Condition	Events, n	Total, n	OR (95% CI)	P
Craniofacial pain	Headache	1,731	2,691	1.10 (0.91, 1.32)	.342
	TMD pain	1,197	2,702	1.37 (1.13, 1.66)	.002
Pain for ≥ 1 day	Head	266	2,658	1.37 (1.01, 1.85)	.043
	Face	89	2,658	1.57 (0.96, 2.56)	.072
	Neck	276	2,658	0.91 (0.67, 1.22)	.511
	Shoulders	239	2,658	1.01 (0.76, 1.35)	.932
	Arms	120	2,658	1.09 (0.69, 1.72)	.704
	Hands	43	2,658	2.46 (1.16, 5.23)	.019
	Chest	43	2,658	0.85 (0.42, 1.71)	.641
	Abdomen	211	2,658	1.16 (0.82, 1.63)	.407
	Back	478	2,658	1.01 (0.80, 1.28)	.941
	Hips	79	2,658	0.81 (0.47, 1.41)	.459
	Legs	239	2,658	1.07 (0.79, 1.46)	.656
	Feet	88	2,658	1.65 (1.01, 2.67)	.044

OR (95% CI)

Fig 2 Association between initiating hormonal contraceptive (HC) use and pain. Initiating HC use was associated with significantly greater TMD pain and pain in the head and face.
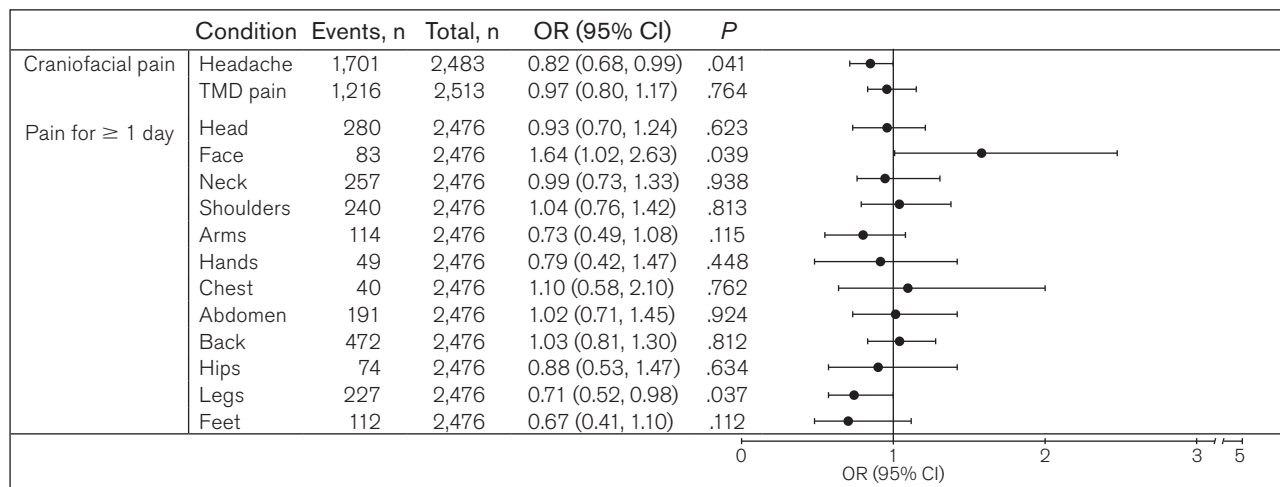
	Condition	Events, n	Total, n	OR (95% CI)	P
Craniofacial pain	Headache	1,701	2,483	0.82 (0.68, 0.99)	.041
	TMD pain	1,216	2,513	0.97 (0.80, 1.17)	.764
Pain for ≥ 1 day	Head	280	2,476	0.93 (0.70, 1.24)	.623
	Face	83	2,476	1.64 (1.02, 2.63)	.039
	Neck	257	2,476	0.99 (0.73, 1.33)	.938
	Shoulders	240	2,476	1.04 (0.76, 1.42)	.813
	Arms	114	2,476	0.73 (0.49, 1.08)	.115
	Hands	49	2,476	0.79 (0.42, 1.47)	.448
	Chest	40	2,476	1.10 (0.58, 2.10)	.762
	Abdomen	191	2,476	1.02 (0.71, 1.45)	.924
	Back	472	2,476	1.03 (0.81, 1.30)	.812
	Hips	74	2,476	0.88 (0.53, 1.47)	.634
	Legs	227	2,476	0.71 (0.52, 0.98)	.037
	Feet	112	2,476	0.67 (0.41, 1.10)	.112

OR (95% CI)

Fig 3 Association between discontinuing hormonal contraceptive (HC) use and pain. Discontinuing HC use was associated with significantly lower odds of headache.

discontinuation of HC use was associated with lower risk of headache (OR: 0.82, 95% CI: 0.67 to 0.99) (Fig 3). Also, HC use at a given time point was associated with increased risk of headaches, as assessed 3 months later (OR: 1.23, 95% CI: 1.08 to 1.40). The initiation or discontinuation of HC use was not otherwise significantly associated with reported pain.

Discussion

The results of this study show that HC use is associated with headache, TMD pain, and facial pain symptoms. Furthermore, analysis of the temporal sequence between HC initiation and onset of headache, or HC cessation and remission of headache, provided evidence for a causal relationship. HC use was more strongly associated with head and face pain than with pain in other body regions, and there was virtually no association with abdominal pain, making it unlikely that the association can be explained by the fact that HC is used to treat menstrual pain (primarily in the abdominal region). Furthermore, the finding that the associations between HC use and both facial pain and headache were at least as strong after excluding participants with a history of dysmenorrhea or who had used HC to treat pain suggests it is unlikely that the association can be explained by confounding by indication. It is noteworthy that HC use at a given time point was associated with headache and TMD pain 3 months in the future, and initiating HC use was associated with greater risk of facial pain. These results satisfy several of Hill's criteria for causation,[17] indicating that the association may be causal.

These findings strengthen the evidence from previous cross-sectional and retrospective studies showing that female reproductive hormones are associated with headaches and other forms of orofacial pain.[18] The results are also consistent with systematic and narrative reviews of clinical trials reporting an association between HC use and headaches[2,3] and with a pair of case-control studies using automated pharmacy records reporting an association between HC use and painful TMD.[5] The current study addresses three shortcomings of these previous studies. First, cross-sectional studies have significant limitations, primarily because it is not possible to establish a temporal sequence between exposure to HC and subsequent development of pain. The prospective study design allowed for the establishment of a temporal sequence between exposure to HC and subsequent change in pain symptoms. Second, steps were taken to control for confounding by indication[19] by excluding women with a history of menstrual pain or use of HC to treat gynecological pain. HC is commonly used to treat painful conditions such as dysmenorrhea,[9] and women with dysmenorrhea have greater risk of migraines and other types of chronic headaches.[20] Thus, it is possible that the observed association between HC use and headaches is confounded by the fact that HC is used to treat dysmenorrhea and other painful conditions that are comorbid with headaches. Third, this study had a large sample size, and subjects were recruited from the community. The latter feature reduces the likelihood of selection bias, which is a long-recognized problem[21] in studies that select subjects from among patients seeking health care. In contrast, the OPPERA cohort studied here is racially, socioeconomically, and geographically diverse, so the results should be generalizable to other populations.

It is interesting to note that while a significant association emerged between HC use and pain lasting 1 day or more in the head and face in parallel with the headache and TMD pain, the longitudinal analysis found no statistically significant association with pain in other bodily regions except the legs. While estrogens can influence pain processing via multiple peripheral and central mechanisms,[4,22] it is less obvious why HC-related pain should be localized to the head. However, preclinical studies demonstrate that estrogens could enhance head and face pain by increasing the excitability of trigeminal afferent fibers, thereby enhancing their responses to noxious stimuli.[23] Specifically, recent evidence suggests that estrogens can potentiate nociceptive responses in part by increasing expression of trigeminal nociceptive mediators, including the transient receptor potential vanilloid 1 (TRPV1) receptor and the anoctamin 1 (ANO1) channel.[24] Also, estradiol enhanced hyperalgesia following TMJ inflammation by upregulating voltage-gated sodium channel 1.7 in the trigeminal ganglion.[25] In addition to these effects on afferent excitability, estradiol has been shown to alter responses of trigeminal brainstem neurons to sensory inputs, suggesting a central site for estrogenic modulation of nociception.[26] Evidence from human studies has suggested further that estrogen may also act to modulate pain, demonstrated particularly for facial pain.[27] While these results from human and preclinical research studies suggest potential mechanisms whereby estrogen could enhance the risk of head and face pain, the effects of estrogen on craniofacial pain are complex. Future research is needed to determine the extent to which the aforementioned and other potential mechanisms contribute to the findings observed in this study.

The present study has several limitations. Although it includes a control group who did not use HC, it was an observational study with no random allocation of HC, so the possibility of confounding of the association between HC use and development of pain cannot be ruled out. This prospective design also may be capturing effects related to the onset of new symptoms, which may differ from ongoing pain. Also, the study did not record the type of HC that participants used, so it cannot be determined if some types of HC are more (or less) strongly associated with facial pain and headache. It would be very useful to be able to distinguish differences between estrogen and progesterone-based formulations. Headache classification was based on headache symptom data collected

by self-report rather than by direct interview. While the algorithm was based on ICHD-3 (beta), symptom reports regarding headache that potentially overlap between migraine and chronic tension-type headache benefit from interview, and daily headache diary data are needed for the most reliable classification.

These results have several clinical implications. Evidence was not found that HC use causes examiner-classified TMD; however, an association with recent facial pain was observed. Furthermore, a statistically significant association between HC use and recent headache was observed. There is evidence to suggest that discontinuation of HC use will reduce headache symptoms, indicating that any headaches occurring as a result of HC use should be treatable by simply discontinuing the use of HC. Obviously, discontinuation of HC use is not always a viable solution given the high risk of unintended pregnancy. Previous research indicates that use of HC containing only progesterone, as opposed to combined oral contraceptives containing both progesterone and estrogen, is not significantly associated with headaches[28] and that switching from HC containing estrogen to progesterone-only HC reduces headache symptoms.[29] These results suggest that HC that does not contain estrogen may be a better option for women who report headache symptoms during HC use. Further research is warranted to understand the mechanisms behind the association between HC use and craniofacial pain and to determine if use of specific HC formulations can reduce the risk of these painful symptoms.

Conclusions

HC use has been previously linked to painful conditions. In this study, HC was significantly associated with TMD symptoms and headache, as well as with pain $\geq$ 1 day duration in the head and face. Initiation of HC use was associated with increased odds of face and head pain, while discontinuation of HC use was associated with decreased odds of subsequent headache. HC use was not associated with subsequent TMD diagnosis. These findings suggest that pain resulting from HC use affects the craniofacial region.

Clinical Research
- An analysis of the association between HC use and painful conditions using a prospective cohort study was carried out.
- HC use was associated with greater occurrence of pain in the craniofacial region but inconsistently elsewhere in the body.
- HC use exhibited a temporal relationship with craniofacial pain, consistent with a causal effect.

- Further investigation to identify associations with specific HC formulations and to identify those at greater risk of pain would permit more informed clinical decision-making.

Acknowledgments

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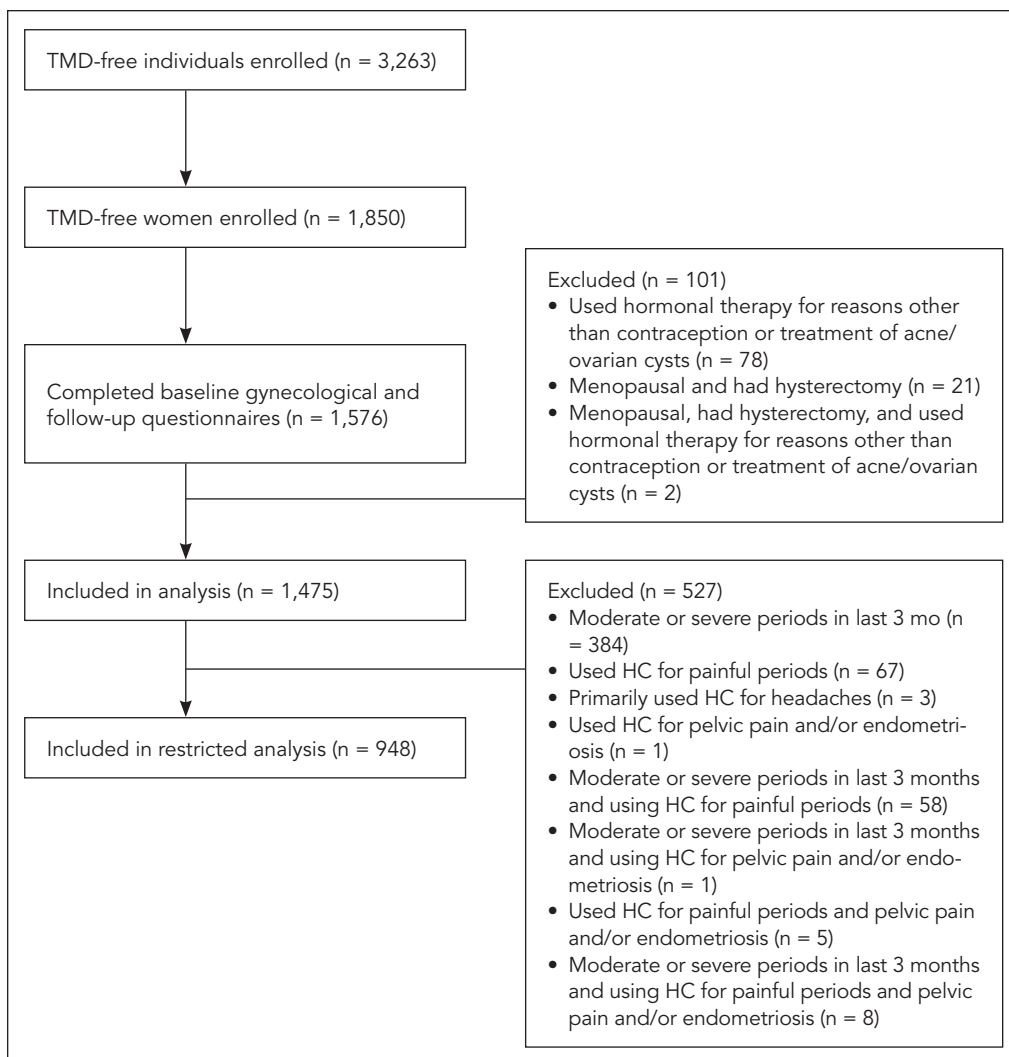
Appendix Fig 1 Flowchart of analytical sample selection from the OPPERA prospective cohort study.

Appendix Table 1 Association Between Hormonal Contraceptive (HC) Use and Pain, Excluding Women with Moderate to Severe Menstrual Pain and Use of HC to Treat Pain

	Condition	Events	Total	Odds ratio (95% CI)	P
Craniofacial pain	Headache	6,056	10,383	1.26 (1.09, 1.46)	.002
	TMD pain	4,295	10,497	1.2 (1.03, 1.38)	.016
Pain for ≥ 1 d	Head	1,020	10,307	1.4 (1.15, 1.72)	.001
	Face	395	10,307	1.55 (1.18, 2.05)	.002
	Neck	896	10,307	1.05 (0.84, 1.3)	.668
	Shoulders	859	10,307	1.2 (0.96, 1.5)	.118
	Arms	378	10,307	1.22 (0.88, 1.69)	.241
	Hands	175	10,307	1.54 (0.92, 2.57)	.097
	Chest	163	10,307	0.98 (0.63, 1.53)	.933
	Abdomen	601	10,307	1.05 (0.8, 1.37)	.721
	Back	1,667	10,307	1.02 (0.86, 1.21)	.803
	Hips	317	10,307	0.90 (0.63, 1.3)	.507
	Legs	835	10,307	1.04 (0.83, 1.29)	.751
	Feet	356	10,307	1.12 (0.8, 1.56)	.508

The associations between HC use and headache, TMD pain, head, and face were significant. The association was not significant for pain in any other bodily region.