Migraine and TMD Comorbidity in Adolescents

Sumeia G.Werfalli

A thesis

submitted in partial fulfillment of the

requirements for the degree of

Master of Science in Dentistry

University of Washington

2013

Committee:

Linda LeResche

Edmond Truelove

Lloyd Mancl

Program authorized to offer degree:

Oral Medicine

Contents

Abstract

Aim: To assess prevalence, cumulative incidence and risk factors for migraine and comorbid severe headache and facial pain among a population of adolescents.

Materials and methods: This is a secondary analysis of a larger study that included a cross-sectional survey of adolescents aged 11-17 with longitudinal follow up of the cohort of participants who were 11 years old. Questions about pain complaints and risk factors were asked through telephone interviews at baseline and a 36-month follow up as well as through mailed questionnaires every three months. Facial pain was assessed through self-report and the RDC/TMD examination was used to assign TMD diagnoses. Severe headache was assessed via self-report. Diagnostic criteria for migraine were based on the International Headache Society classification.

Results: A total of 3,100 adolescents from the cross-sectional survey were included in the analysis. A cohort of 1,817 adolescents was included in the analyses of the cohort. Approximately equal numbers of males and females were enrolled. Migraine prevalence decreased from 11% at baseline to 6.3% at age 14 years old. The cumulative incidence of both severe headache and facial pain decreased as age increased from 11 to 14 years old. At baseline the cumulative incidence of severe headache among those participants reporting a history of facial pain was 55.7% versus 30.5% among those reporting no history of facial pain (odds ratio, 2.86; 95% CI, 2.21-3.70). The cumulative incidence of severe headache among those participants reporting a history of facial pain was 41.9% versus 24.5% among those reporting no history of facial pain (odds ratio, 2.00; 95% CI, 1.54-2.59).

Other pain complaints (OR=3.2), physical activity (OR=1.86), depression (OR=1.96) and somatization (OR=4.4) were associated with migraine diagnosis at baseline. Other pain complaints (OR=4.42), depression (OR=2.79) and somatization (OR= 2.56), were associated with facial pain-severe headache comorbidity at baseline. Female gender (OR =1.83), physical activity (OR = 2.52), other pain complaints (OR = 1.18), depression (OR = 3.06) and somatization (OR = 2.18) were associated with migraine diagnosis at 36 months. Other pain complaints (odds ratio (OR) = 8.39) and somatization (OR = 3.33) were associated with comorbid severe headache and facial pain at 36 months.

Conclusion: Severe headache and facial pain are comorbid in adolescents. Several risk factors are common between migraine and comorbid severe headache and migraine. Better diagnosis and prognostic outcomes can be achieved by addressing such risk factors and by managing both conditions.

Acknowledgements

A special gratitude I give to my supervisor Dr. Linda LeResche, for the useful comments, remarks and engagement through the learning process of this master thesis. Furthermore I would like to express my sincere gratitude to the rest of my thesis committee, Dr. Lloyd Mancl and Dr. Edmond Truelove, for their encouragement and valuable comments.

Special thanks to Dr. Richard Lipton for providing me with the migraine diagnosis algorithm, as well as for his help and support.

Also, I would like to thank Drs. Mark Drangsholt and Marijoyce Leynes for their continuous support and guidance.

Finally, I would like to thank my beloved husband and my wonderful mother who have supported me throughout the entire process.

Introduction

Although less prevalent than tension type headache, migraine headaches are more severe and are associated with high levels of disability (Fuh et al. 2010). Migraine is one of the 20 most disabling diseases according to the World Health Organization (Leonardi et al. 2005). Migraine causes financial burdens, and in the U.S. is estimated to cost employers 13 billion dollars per year. Moreover, the estimated over-the-counter sales of pain medication are 3.2 billion dollars; one third of these over-the-counter analgesics are consumed for headaches (Insinga, Ng-Mak and Hanson 2011). While migraine alone can be severe and disabling, its management may be complicated by the presence of other comorbid conditions, especially other pain conditions. Further understanding of comorbid pain conditions can significantly improve the quality of medical care, as they may confound diagnosis, provide special therapeutic challenges and influence prognosis.

Temporomandibular disorders (TMD) are musculoskeletal pain conditions that affect the temporomandibular joint (TMJ) and muscles of mastication. TMD is a common pain condition that affects approximately 10% of the adult U.S. population (Carlsson 1999; Von Korff et al. 1988). Prevalence rates of TMD range from 2% to 7% during the adolescent period (List et al. 1999, Nilsson, List and Drangsholt 2007). TMD pain has a substantial impact on the quality of life of adolescents. Common complaints among adolescents affected by this concern are increased analgesic consumption, absence from school, and abnormal jaw function (Nilsson, Drangsholt and List 2009).

Migraine and TMD are often comorbid (Plesh, Adams and Gansky 2011). In adults, TMJ pain is more common and more severe in people with headache compared to those without headache (Melo et al. 2012). If TMD and migraine frequently coexist in adults, a common pathogenesis, a causal association, or common risk factors for both conditions would be expected. Exploration of these factors at an early phase of life may provide valuable diagnostic information for clinicians and researchers that could ultimately help improve the quality of life, productivity and prognosis of adolescents affected by both problems.

The purpose of this study was to investigate the prevalence, incidence and risk factors for migraine among a population of adolescents, as well as the co-occurrence of severe headache and facial pain and risk factors associated with such co-occurrence.

Background and significance

Migraine

Migraine is a common chronic headache disorder with episodic attacks (Haut, Bigal and Lipton 2006). It is characterized by a unilateral location of pain of pulsating quality and moderate to severe intensity that is usually caused or aggravated by routine physical activity. Common clinical symptoms of migraine are recurrent headaches, and gastrointestinal and autonomic nervous system symptoms (Silberstein 2004). Aura, a phenomena characterized by neurological and visual symptoms, is experienced in up to one third of patients with migraine before or during the headache attack. Migraine is classified as a primary headache with an unknown etiology. The two major classifications of this condition are migraine without aura and migraine with aura (Headache Classification Subcommittee of the International Headache Society 2004).

The cumulative lifetime prevalence of migraine is about 43% in women and 18% in men (Stewart et al. 2008). The prevalence pattern of migraine shows a bell-shaped age distribution in both sexes. The prevalence of this disorder initially increases with age and becomes more common in girls than boys around puberty. By their late teens, females are twice as likely as males to have this problem. Migraine's prevalence peaks in both sexes during middle age (age 25 to 55 years) and decreases in older age groups (Lipton and Bigal 2005; Strine, Chapman and Balluz 2006).

The pathophysiology of migraine is complex. Both central and peripheral mechanisms involving activation and sensitization of the trigeminovascular pain pathway are implicated in this process (Moskowitz 1984; Pietrobon and Striessnig 2003; Olesen et al. 2009). It has been suggested that the initiation of migraine attacks primarily occurs in the central nervous system (CNS), most likely through multiple genetic changes in ion channels that make the individual more sensitive to environmental factors. Such alterations may result in a wave of cortical spreading depression caused by neuronal depolarization followed by a suppression of neuronal activity with corresponding blood flow changes once the migraine attack is initiated (Edvinsson, Villalon and MaassenVanDenBrink 2012).

TMD

Temporomandibular disorders (TMD) is a collective term embracing a number of clinical problems that involve the masticatory muscles, the temporomandibular joint or both, as well as associated structures (American Academy of Orofacial Pain 1996). Common signs and symptoms of TMD are clicking noises in the temporomandibular joint (TMJ), limited jaw opening capacity, deviations in the movement patterns of the mandible and pain in the masticatory muscles or TMJ. Pain is the most common complaint among TMD patients seen by dentists (Dworkin, LeResche and Von Korff 1990).

Temporomandibular disorders are classified according to the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD); this classification is considered the gold standard tool for research purposes. RDC/TMD is a dual-axis classification system that includes a physical diagnosis of TMD as: 1) Myofascial pain (with or without limited opening), 2) Disc Displacements (with or without reduction and with or without limited opening), and 3) Arthralgia, Arthritis or Arthrosis on the first axis. An evaluation of TMD-related parafunctional habits, psychological distress, and psychosocial dysfunction is included on the second axis (Dworkin and LeResche 1992). Wahlund, List and Dworkin (1998) noted the good reliability of the RDC/TMD as a method for assessment of TMD in children and adolescents. The RDC/TMD diagnostic criteria are in the process of revision into DC/TMD criteria which would be more appropriate for clinical implementation (Ohrbach et al. 2010).

The prevalence of TMD increases with age for both genders during adolescence, and the increase is higher in girls than in boys (Nilsson et al 2005). In addition, girls tend to report a more persistent type of pain (Nilsson et al 2011). Some studies suggest that, similar to migraine, the prevalence of TMD declines after middle age (Von Korff et al. 1988).

The pathophysiology of TMD pain is not fully understood. Peripheral mechanisms as well as altered central nervous system pain processing, are thought to contribute to TMD pain (Cairns 2010). In general, multiple factors have been suggested to play a role in TMD etiology (Greene 1995). Proposed risk factors include female gender, pubertal development, negative somatic and psychological symptom scores, as well as the number of other pain complaints (LeResche et al. 2005a).

Comorbidity of Migraine and TMD

Severe headaches or migraines are often associated with other comorbid conditions (Plesh, Adams and Gansky 2012a, Eminson et al. 1996). The presence of comorbid pain conditions plays a role in migraine onset, progression and response to therapies. One study reported that about half of adults with TMD pain have severe headache/migraines (Plesh, Adams and Gansky 2011b). Another study suggests that the observed association between TMD and migraine is only partially explained by shared genetic factors between both conditions (Plesh et al. 2012b), thus a strong role is left for environmental or non-genetic factors shared between both conditions. So far, the co-occurrence of TMD and migraine has been evaluated only in an adult population (Ciancaglini and Radaelli 2001; Scher, Midgette and Lipton 2008).

Female reproductive hormones have been suggested to play a role in trigeminal nerve-mediated pain disorders (Tashiro et al. 2007). LeResche et al. (2005a) found that headache and TMD pain increased with pubertal development in girls. In addition, changes in related pain symptoms are reported during pregnancy (LeResche et al. 2005b), and menstruation (Wober et al. 2007). The higher prevalence rates of these pain conditions in females and the relation of their occurrence to women's hormonal status make reproductive hormones one of the most convincing factors associated with the occurrence of these pain problems.

Chronic pain and psychological distress interact in complex ways. A higher risk of developing psychological problems has been noted among children and adolescents who suffer chronic pain conditions (Siegel and Ehrlich 1989). Stress has been identified as a risk factor for migraine as well as for TMD (Hedborg, Anderberg and Muhr 2011); (Rugh and Solberg 1976); (Dworkin 1994; List, Wahlund and Larsson 2001). Moreover, Grossi et al. (2001) found that depression interferes with achieving a favorable treatment outcome for TMD.

Another suggested common risk factor for TMD and migraine is smoking. Studies have reached opposing conclusions about the relationship between smoking and these two pain conditions. Some studies note a significantly increased risk of 11–15% for migraine among smokers (Aamodt et al. 2006, Le et al. 2011). However, others did not find an association between cigarette smoking and the risk of migraine (Takeshima et al. 2004; Rasmussen 1993). Smoking has been found to be associated with a higher risk for TMD pain (Sanders et al. 2012), as well as increased TMD pain intensity

(Melis et al. 2010). However, not having a history of smoking predicted an onset of facial pain in adolescents (LeResche et al. 2007).

The relationship observed between body weight and pain conditions varies among different studies. A significantly higher rate of an elevated BMI is observed among adolescents with chronic pain compared with a normative sample (Wilson, Samuelson and Palermo 2010). Similarly, a positive association between obesity and migraine was reported by several authors (Bigal, Liberman and Lipton 2006; Bigal et al. 2007). However, other authors did not find a similar relationship (Le et al. 2011). One study noted that facial pain prevalence was lower in obese children compared to children of normal weight (LeResche et al. 2007).

Previous studies also show conflicting results regarding the relationship between physical activity and headache. Analysis of a randomized controlled clinical trial found that brief daily exercise is associated with a decreased headache frequency (Andersen et al. 2011). Likewise, decreased physical activity is associated with higher migraine prevalence rates (Molarius, Tegelberg and Ohrvik 2008). However, others have noted an increased risk of migraine in women with heavy physical work (Le et al. 2011). In another study no association was found between work with high physical demands and migraine (Zivadinov et al. 2003). To our knowledge no studies exist regarding the relationship of physical activity and TMD.

Several studies have found an associated between race or ethnicity and different kinds of pain complaints. White females have higher prevalence rate of TMD and headaches/migraine than Hispanic and black females at early ages and then lower rates at older ages. Males also showed similar patterns as females but with less variation (Plesh, Adams and Gansky 2011a). Other studies have shown that migraine prevalence is higher in Caucasians than in other races throughout the life cycle (Steiner et al. 2003, Breslau and Rasmussen 2001).

The presence of other pains elsewhere in the body was found to be a predictor of onset and maintenance of TMD pain in adults (Rammelsberg et al. 2003; Von Korff et al. 1988). A prospective cohort study found that baseline presence of multiple pain conditions elsewhere in the body was a risk factor for onset of TMD pain in the next three years (Von Korff, LeResche and Dworkin 1993).

Aim of this study

This study assessed prevalence, incidence and risk factors for migraine among a population of adolescents between the ages 11 and 17.

Specifically, this study assessed:

- Prevalence of migraine in a cross sectional sample and a cohort sample, using a reliable and valid algorithm-based diagnosis.
- The association of migraine and TMD at ages 11 and 14 years.
- Cumulative incidence of facial pain by age 11 and by age 14.
- Cumulative incidence of severe headache by age 11 and by age 14.
- In adolescents with migraine but not facial pain at baseline, the association of migraine with incidence of facial pain.
- In adolescents with facial pain but not migraine at baseline, the association of facial pain with migraine incidence.
- The relationship of TMD characteristics (signs and symptoms) and migraine
- Exploration of potential factors associated with co-occurrence of severe headache and facial pain including: gender, race, stage of pubertal development, Body Mass Index (BMI), and smoking, physical activity, the presence of other pain conditions, depression and somatization.

Hypotheses

1) Adolescents will exhibit a significant relationship between severe headache and facial pain, similar to what has been found in adults.
2) The relationship between migraine and facial pain will be bidirectional.
3) The risk of *migraine as well as comorbid severe headache and facial pain* will be increased among adolescents who:
    a) Are overweight vs. normal weight.
    b) Are physically inactive vs. physically active.
    c) Are in later stages of pubertal development.

d) Have other pain complaints.
e) Have high depressive and somatization scores.
f) Are white (compared to other races).

Material and methods

Study subjects

This study is a secondary data analysis of a larger study (LeResche et al. 2005a) that included a cross sectional and a cohort component. Initially, a sample of 3,101 adolescents was surveyed. Almost 2,000 (n=1996) of them were 11-year olds, and 1,105 were aged 12 to 17 years of age. There were approximately equal numbers of boys and girls of each age.

Inclusion criteria

1. Boy or girl aged 11-17 years old.
2. Enrolled in Group Health Cooperative in Washington State.
3. Both child and parent or guardian sufficiently fluent in English to provide informed assent/consent.

Exclusion criteria

1. Children who would turn 18 in two months or less.
2. Children who had a sibling participating in this study.

Data collection

Selected children aged 11-17 years old and their parents were initially contacted by mail. Households not refusing initial contact were telephoned by a female survey interviewer who explained the study procedures in detail. After an informed consent was provided by the parent and an informed assent from the adolescent, participants received a baseline telephone interview. This phase of the study is referred to as the cross-sectional study.

A cohort was developed of all the 11-year olds who completed the baseline survey. These subjects were followed through use of a brief questionnaire mailed every three months for three years. At 18 months participants received an expanded questionnaire. The participants were interviewed by telephone follow-up three years after the baseline interview (at age 14-years old).

A TMD examination was performed for adolescents in the cross sectional study or cohort study after first report of facial pain in their questionnaires. In addition, an age- and gender-matched control group of adolescents who did not report TMD pain also received TMD examinations at baseline. All procedures were approved by the Group Health Institutional Review Board.

Definition of dependent variables (migraine, TMD)

Migraine

1. At baseline and 3-year follow-up: Migraine diagnosis was determined according to an algorithm based on the International Headache Society Classification (Headache Classification Subcommittee of the International Headache Society 2004). This algorithm has been validated against a clinical diagnosis. A diagnosis of migraine was given to the subject if he/she had two or more of the following symptoms with their most severe headache type in the last three months:
    - I. Moderate or severe pain (operationalized as 4 or more on a 0-10 scale).
    - II. Pain is made worse by usual activity more than rarely (on a scale of never, rarely, less than half the time, more than half the time).
    - III. Pain is unilateral more than rarely.
    - IV. Pain is pulsating, pounding more than rarely.

In addition, subjects needed to report <u>either</u> nausea or vomiting more than rarely, or both photophobia <u>and</u> phonophobia more than rarely.

2. Severe headache: diagnosis was assigned for all adolescents who answered with a "yes" response to the following question: *Have you ever had a problem with severe headaches or migraines?*

TMD

1. Facial pain:

   A facial pain diagnosis was assigned for all adolescents who answered "yes" to the following question: *"Have you ever had a problem with facial ache or pain in any of the following places: the jaw muscles, the joint in front of the ear, or inside the ear,* *other than an ear infection?"* (Adolescents were specifically instructed to report facial pain that lasted a whole day or more, or that you had several times in a year. They were also asked to not report little aches and pains that didn't last very long.)

2. RDC/TMD diagnosis:
   A RDC/TMD diagnosis was given to adolescents who had facial pain and met the RDC/TMD examination criteria for one or more Axis I conditions. Specifically those diagnosed with a "TMD pain diagnosis" included those with myofascial pain with or without limited opening (group 1a or 1b of RDC/TMD axis I); and/or arthralgia or arthritis (group 3a, b of RDC/TMD axis I) (Dworkin and LeResche 1992).

Co-morbidity

Comorbid cases were identified by a "yes" response to both of the following questions:

- *Have you ever had a problem with severe headaches or migraines?*
- *Have you ever had a problem with facial ache or pain in any of the following places: the jaw muscles, the joint in front of the ear, or inside the ear, other than an ear infection?*

Definition of independent (risk factor) variables

Data regarding biologic and psychosocial risk factors for pain in adolescents were obtained from a Group Health database and from the baseline interview.

Risk factors that were explored are:

1. Gender
2. Stage of pubertal development
3. BMI
4. Depression and somatization
5. Smoking
6. Race
7. Other pain conditions (i.e. back pain and/or stomach pain)

Demographic factors Age and gender were obtained from the Group Health database, and race was obtained from the baseline interview.

Assessment of risk factors

1. Body Mass Index (BMI) was assessed by asking questions about adolescent's height and weight. After these measurements are converted to body mass index (BMI) percentiles for age and gender using the 2000 CDC Growth Chart Standards, subjects at or above the 95th percentile are classified as obese; those at or above the 85th percentile but below the 95th are classified as overweight, and subjects with a BMI below the 85th percentile are considered to be of normal weight.
2. Smoking questions asked to assess duration, quantity and frequency of smoking are:
   a) Have you ever smoked a cigarette?
   b) Have you ever tried or experimented with cigarette smoking, even a few puffs?
   c) Have you smoked at least 100 cigarettes in your life; that's about 5 packs of cigarettes?

   According to the response to the last question (c), adolescents were classified as either ever smoked (if smoked at least 100 cigarettes), or never smoked (if smoked less than 100 cigarettes).

3. Level of physical activity was assessed by the following question:

In the last year did you do any physical activity that made you sweat or perspire heavily? / How many times per week?

Adolescents were considered physically active if they reported two or more times of activity per week.

4. Other pain problems were assessed by asking subjects if they had ever experienced back pain, and if they had ever experienced stomach pain (not including menstrual pain). Subjects were asked to report only pain that had lasted a whole day or more, or that had occurred several times in a year.
5. Stage of pubertal development was assessed using the Pubertal Development Scale (PDS). This scale is a self-report measure that has been validated against a clinical examination for Tanner stages. It assesses development based on five characteristics for each sex. Questions for both sexes asked about their stage of development for growth in height, body hair, and skin changes. Questions specific for boys were about deepening of the voice and the growth

of facial hair. For girls, questions were about breast development, and whether or not their menstrual periods had begun.

Subjects are asked to respond to each item on a 4-point ordinal scale (no development=1, development barely begun=2, development definitely underway=3, development already completed=4). PDS score was calculated from an algorithm based on these items (Petersen A.C, personal communication, 1998). A score of 1 would mean that development has not begun on any of the items, and a score of 4 means that development is complete for all the items.

6. Depressive and somatization symptoms were assessed using a subset scale of the SCL-90 (LeResche et al. 2005a). Significant depressive or somatic symptoms were defined as scoring higher than the 90th percentile score for that scale in the entire sample of subjects in the cross-sectional survey.

Data Analysis

Descriptive/ background analyses

Descriptive statistics (percentages) were calculated at baseline and at 3-year follow-up, for all risk factors. Migraine prevalence, by age and gender was calculated from the cross-sectional data as well as at baseline and 3-year follow up.

The primary data analysis included calculation of the cumulative incidence of severe headache and facial pain, the risk of 3-year onset of migraine in adolescents with vs. without facial pain at baseline, the risk of 3-year onset of facial pain in adolescents with vs. without migraine at baseline, and finally the relationship of TMD characteristics (signs and symptoms) and migraine. Odds ratios with 95% confidence intervals were calculated to assess the strengths of these relationships. The secondary data analysis assessed risk factors for migraine as well as comorbid severe headache and facial pain using bivariate and multivariate logistic regression analyses.

Results

A total of 3,100 adolescents from the cross-sectional survey were included in the analysis. A cohort of 1,817 adolescents completed measures both at baseline (age 11 years) and at three-year follow-up (at age 14 years) and were included in the analyses of the cohort. Demographic data for the study participants are shown in Table 1.

Table 1. Descriptive demographic information for cross-sectional and cohort samples

	Cross- sectional survey (ages 11-17)	**Cohort at age 11**	**Cohort at age 14**
Age			
11 - year-olds	64.4%		
12-17 - year-olds	35.6%		
Gender			
Male	50.1%	50.6%	
Female	49.9%	49.4%	
Race			
Native American or Alaskan Native	3.2%	3.7%	
Asian or Pacific Islander	8.9%	8.4%	
Black or African American	10.0%	10.0%	
White	67.2%	64.7%	
Other	10.8%	11.2%	
Smoking	2.8%	0.2%	2.4%
Physically active	67.4%	72.4%	83.2%
BMI			
Normal	80.4%	85.1%	84.4%
Overweight	8.9%	10.3%	10.6%
Obese	4.8%	4.6%	5.0%
PDS			
Stage 1	4.5%	6.1%	0.2%
Stage 2	24.0%	30.6%	3.1%
Stage 3	46.1%	51.0%	27.6%
Stage 4	21.4%	11.4%	56.9%
Other pains	55.9%	53.4%	41.5%
Depression	10.4%	8.6%	6.2%
Somatization	11.0%	11.3%	6.0%

As shown in Table 1, by design approximately two-thirds of the cross sectional sample were 11 year olds, and the remaining adolescents were aged from 12-17 years old. Approximately equal numbers of males and females were enrolled in the cross-sectional survey. This distribution remained stable throughout study period. With regards to race distribution, approximately two thirds of adolescents identified themselves as White, 8.9% were Asian or Pacific Islanders and 10.0% were African American.

The number of adolescents who ever smoked increased as their age increased from 11 years old (0.2%) to 14 years old (2.4%). Because of the very small number of smokers at baseline, smoking was dropped from the risk factor analysis. About three quarters of the subjects in the cross-sectional sample were considered physically active. In the cohort, the percentage physically active increased with age from 72.4% at age 11 years to 83.2% at 14 years old. The majority of adolescents were of normal weight both at 11 and 14 years of age, while the percentage of overweight and obese subjects remained stable from age 11 to 14 years old.

Data on pubertal development (PDS scale scores) at age 11 and 14 years old are also shown in Table 1. The percent of subjects in late and post-pubertal stages increased as age increased and the percent of subjects at early stages decreased. Because of the small numbers of subjects in Stage 1, Stage 1 was combined with Stage 2 in the risk factor analysis. The number of subjects who had no pain complaints (neither back pain nor stomach pain) increased from age 11 to 14 years. That is fewer adolescents reported experiencing pain complaints at age 14 years.

In the cohort sample, the percentage of subjects meeting the cut-off score for depression (top 10% of the cross-sectional sample) decreased somewhat as age increased from 11 to 14 years old. The rate of somatization was almost cut in half, from 11.3% to 6.0%.

Table 2 shows that the percent of the sample meeting criteria for migraine in the prior 3 months at the 3–year follow up point (age 14 years) was lower than at baseline. Also, the prevalence rate for the 14-year-olds in the cohort was somewhat lower than for children of the same age in the cross sectional survey.

Table 2. Migraine (algorithm-based diagnosis) prevalence by age and gender for cross-sectional and cohort samples

Migraine prevalence	**Cross-sectional survey (ages 11-17 years)**	**Cohort at age 11 years**	**Cohort at age 14 years**
	12.4%	11.1%	6.3%
Age			

11- year-olds 12-17- year-olds 14- year-olds	9.0% 10.9% 7.6%	11.1%	 6.3%
Gender Female Male	 217 (56.5%) 167 (43.5%)	 80 (48.7%) 84 (51.2%)	 76 (66%) 39 (34%)

Cumulative incidence is the percent of participants who reported ever having experienced the specific pain condition over the course of their lifetime. Overall, the cumulative incidence of both severe headache and facial pain decreased as age increased from 11 to 14 years old (Table 3).

Table 3. Cumulative incidence of severe headache and facial pain at age 11 and 14 years

	Cohort at age 11 years	Cohort at age 14 years
Severe headache	34.6%	26.6%
Facial pain	16.2%	11.2%

As shown in Table 4, at age 11, the cumulative incidence of severe headache among those participants reporting a history of facial pain was 55.7% versus 30.5% among those reporting no history of facial pain (odds ratio, 2.86; 95% CI, 2.21-3.70).

Table 4. Comorbidity of severe headache and facial pain at age 11 years

	Cumulative facial pain		
Cumulative severe headache	**yes**	**No**	**Total**
Yes	162 (55.7%)	463(30.5%)	625
No	129 (44.3%)	1054 (69.5%)	1183
Total	291	1517	1817

As shown in Table 5, at age 14, the cumulative incidence of severe headache among those participants reporting a history of facial pain was 41.9% versus 24.5% among those reporting no history of facial pain (odds ratio, 2.00; 95% CI, 1.54-2.59).

Table 5. Comorbid severe headache and facial pain at age 14 years

Cumulative severe headache	Cumulative facial pain		
	yes	**no**	**Total**
Yes	85 (41.9%)	396 (24.5%)	481
No	118 (58.1%)	1218 (75.5%)	1336

Total	203	1614	1817

As shown in Table 6, at age 14, the prevalence of migraine among those participants reporting a history of facial pain at baseline (age 11) was 19.7% versus 15.0% among those reporting no history of facial pain (odds ratio, 1.19; 95% CI, 0.58-2.91).

Table 6. Risk of 3-year onset of migraine in adolescents with vs. without a history of facial pain at baseline (given no migraine at baseline)

Facial pain (11-year-olds, cumulative incidence)	Migraine (14-year-olds)		
	yes	No	Total
Yes	54 (19.7%)	220 (80.3%)	274
No	198 (15.0%)	1118 (85.0%)	1316
Total	252	1338	1590

As shown in Table 7, at age 14, the prevalence of facial pain among those participants reporting a history of severe headache at baseline was 8.0% versus 7.1% among those reporting no history of severe headache (odds ratio, 1.14; 95% CI,0.77-1.67).

Table 7. Risk of 3-year onset of facial pain in adolescents with vs. without a history of severe headache at baseline (given no facial pain at baseline)

Severe headache (11 years old, cumulative incidence)	Facial pain (14-year-olds)		
	No	Yes	Total
No	1066 (92.9%)	81 (7.1%)	1147
Yes	508 (92.0%)	44 (8.0%)	552
Total	1574	125	1699

As shown in Table 8, overall, TMD pain diagnoses were more common among adolescents with migraine compared with migraine-free subjects. The most common TMD pain diagnosis among adolescents with migraine was group I (myofascial pain).

Table 8. RDC/TMD pain diagnoses among adolescents with vs. without migraine at 36 months follow-up

	TMD characteristics				Total
	No TMD pain diagnosis	Group 1 only	Group 3 only	Both groups 1&3	

No migraine at 36 months	275 (74.5%)	37 (10.0%)	24 (6.5%)	33 (8.9%)	369
Migraine at 36 months	7 (43.7%)	5 (31.2%)	1 (6.2%)	3 (18.7%)	16
Total	282	42	25	36	385

Logistic regression was used to determine the association between individual risk factors and the presence of migraine and comorbid severe headache and facial pain) at baseline and at 36 month follow-up. Table 9 shows bivariate and multivariate logistic regression analyses of all proposed risk factors for migraine diagnosis at baseline. Results of multivariate analyses showed that other pain complaints (OR=3.20), physical activity (OR=1.86), depression (OR=1.96) and somatization (OR=4.40) were statistically significantly (p-value< 0.05) associated with migraine diagnosis at baseline.

Table 9. Predictors of migraine diagnosis at baseline:

Predictor	Bivariate		95%CI		Multivariate		95%CI	
	Odds ratio	P-value			Odds ratio	P-value		
Gender (female vs. male)	1.01	0.92	0.73	1.41	1.24	0.31	0.82	1.90
Race		.060				0.22	0.26	
Native American or Alaskan Native vs. other races	1.39	0.46	0.57	3.38	0.85	0.85	0.77	2.40
Asian or Pacific Islander vs. other races	0.57	0.19	0.25	1.31	0.41	0.23	0.07	1.08
Black or African American vs. other races	1.49	0.21	0.79	2.82	1.21	0.21	0.61	2.60
White vs. other races	0.82	0.46	0.49	1.38	0.81	0.80	0.47	1.43
BMI		0.07				0.82		
Normal vs. obese	0.76	0.48	0.35	1.63	0.87	0.74	0.37	2.05
Overweight vs. obese	1.31	0.59	0.55	3.13	1.02	0.97	0.38	2.72
PDS (stages1,2 vs. 3,4)	0.99	0.95	0.70	1.40	1.47	0.08	0.96	2.25
Other pains (yes/no)	4.94	<.001	3.25	7.53	3.20	<.001	2.04	5.05
Physically active vs. physically inactive	2.20	<.001	1.43	3.41	1.86	0.02	1.13	3.08
Depression (yes/no)	5.08	<.001	3.38	7.66	1.96	0.02	1.14	3.38
Somatization (yes/no)	6.36	<.001	4.39	9.27	4.40	<.001	2.75	7.11

Table 10 shows bivariate and multivariate logistic regression analyses of all proposed risk factors for comorbid severe headache and facial pain at baseline. Other pain complaints (OR=4.42), depression (OR=2.79) and somatization (OR= 2.56), were statistically significantly associated with comorbidity at baseline ($p<0.05$).

Table 10. Predictors of comorbid severe headache and facial pain at baseline

Predictor	Bivariate		95%CI		Multivariate		95%CI	
	Odds ratio	P-value			Odds ratio	P-value		
Gender (female vs. male)	1.08	0.65	0.77	1.49	0.78	0.28	0.49	1.22
Race		0.78				0.49		
Native American or Alaskan Native vs. other races	0.99	0.93	0.37	2.50	0.64	0.44	0.21	2.00
Asian or Pacific Islander vs. other races	0.84	0.64	0.41	1.72	0.97	0.94	0.41	2.29
Black or African American vs. other races	0.67	0.27	0.32	1.37	0.46	0.09	0.18	1.14
White vs. other races	0.76	0.28	0.46	1.25	0.75	0.34	0.41	1.35
BMI		0.07				0.89		
Normal vs. obese	0.99	0.98	0.39	2.53	1.02	0.98	0.37	2.78
Overweight vs. obese	1.68	0.33	0.59	4.75	1.18	0.77	0.38	3.65
PDS (stages1,2 vs. 3,4)	0.56	0.01	0.38	0.82	0.63	0.07	0.38	1.05
Other pains (yes/no)	7.35	<.001	4.51	12.0 0	4.42	<.001	2.56	7.62
Physically active vs. physically inactive	1.50	0.07	0.97	2.33	1.34	0.28	0.78	2.29
Depression (yes/no)	5.21	<.001	3.36	8.08	2.79	<.001	1.59	4.92
Somatization (yes/no)	5.35	<.001	3.56	8.04	2.56	<.001	1.52	4.34

Table 11 shows bivariate and multivariate logistic regression analyses of all proposed risk factors for migraine diagnosis at 36 months follow-up. Results of multivariate analyses showed that female gender (OR =1.83), physical activity (OR = 2.52), other pain complaints (OR = 1.18), depression (OR = 3.06) and somatization (OR = 2.18) were statistically significantly associated with migraine diagnosis at 36 months ($p < 0.05$).

Table 11. Predictors of migraine diagnosis at 36 months follow-up

Predictor	Bivariate		95%CI		Multivariate		95%CI	
	Odds ratio	P-value			Odds ratio	P-value		
Gender (female vs. male)	2.09	<.001	1.40	3.11	1.83	0.005	1.20	2.80
Race		0.44				0.33		
Native American or Alaskan Native vs. other races	0.71	0.60	0.10	2.55	0.48	0.29	0.12	1.87
Asian or Pacific Islander vs. other races	0.53	0.21	0.20	1.42	0.50	0.18	0.18	1.38
Black or African American vs. other races	0.54	0.19	0.21	1.36	0.49	0.15	0.19	1.28
White vs. other races	0.94	0.82	0.52	1.68	0.89	0.70	0.48	1.63
BMI		0.44				0.54		
Normal vs. obese	0.89	0.79	0.38	2.10	1.07	0.88	0.43	2.66
Overweight vs. obese	1.28	0.62	0.48	3.39	1.49	0.45	0.53	4.21
PDS (stages1,2 vs. 3,4)	0.49	0.33	0.12	2.03	0.53	0.42	0.12	2.42
Other pains (yes/no)	2.60	<.001	1.76	3.85	1.83	0.004	1.21	2.78
Physically active vs. physically inactive	2.21	0.02	1.14	2.28	2.52	0.01	1.24	5.13
Depression (yes/no)	5.05	<.001	3.11	8.20	3.60	<.001	2.05	6.30
Somatization (yes/no)	3.81	<.001	2.25	6.46	2.18	0.01	1.18	4.04

Table 12 shows bivariate and multivariate logistic regression analyses of all proposed risk factors for comorbid severe headache and facial pain at 36 months. Results of multivariate analyses showed that other pain complaints (odds ratio (OR) = 8.39) and somatization (OR = 3.33) were statistically significantly associated with comorbid severe headache and facial pain at 36 months ($p < 0.05$).

Table 12. Predictors of comorbid severe headache and facial pain at 36 months

Predictor	Bivariate		95%CI		Multivariate		95%CI	
	Odds ratio	P-value			Odds ratio	P-value		
Gender (female vs. male)	0.95	0.83	0.62	1.47	0.79	0.33	0.49	1.27
Race		0.60				0.45		
Native American or Alaskan Native vs. other races	0.50	0.37	0.11	2.29	0.33	0.17	0.07	1.61
Asian or Pacific Islander vs. other races	0.58	0.28	0.21	1.56	0.65	0.42	0.23	1.85
Black or African American vs. other races	0.49	0.16	0.18	1.33	0.43	0.11	0.15	1.20
White vs. other races	0.67	0.23	0.36	1.25	0.67	0.23	0.34	1.29
BMI		0.13				0.31		
Normal vs. obese	0.45	0.05	0.22	0.99	0.54	0.14	0.23	1.23
Overweight vs. obese	0.56	0.25	0.22	1.49	0.66	0.44	0.24	1.86
PDS (stages1,2 vs. 3,4)	0.33	0.28	0.05	2.41	0.27	0.22	0.04	2.16
Other pains (yes/no)	10.40	<.001	5.48	19.75	8.390	<.001	4.36	16.10
Physically active vs. physically inactive	1.76	0.12	0.87	3.52	1.68	0.19	0.78	3.63
Depression (yes/no)	2.77	.001	1.48	5.16	1.35	0.42	0.65	2.77
Somatization (yes/no)	5.68	<.001	3.69	9.79	3.33	<.001	1.79	6.19

Discussion

This secondary data analysis of the cross sectional component and a 3-year cohort component of a previous population based study (LeResche et al. 2005a) examined the association between severe headache and facial pain at baseline (age 11) and at follow up (age 14). A significant comorbid relationship was found between severe headache and facial pain both at baseline and follow up. In addition, the presence of a history of facial pain at baseline predicted the onset of migraine by age 14. Also the presence of a history of severe headache at baseline predicted the onset of facial pain report within the next three years. However, neither of these relationships was statistically significant.

In the multivariate analysis, several common risk factors were associated with both migraine and comorbid severe headache and facial pain at baseline and at age 14. First, the presence of other pain complaints was associated with increased risk of migraine diagnosis as well as comorbid severe headache and facial pain at baseline and at age 14. This finding is consistent with several previous studies (Plesh et al. 2012a; Von Korff et al. 1993) . Second, adolescents with higher depression and somatization scores (above the 90% percentile of the entire sample) were at an increased risk of having migraine at both baseline and at follow up. Significant somatization symptoms were also associated with comorbid severe headache and facial pain at age 14 years. Similar effects of depressive and somatic symptoms on the onset of migraine and TMD has been found by other studies (Hedborg et al. 2011; Rugh and Solberg 1976; Dworkin 1994; List et al. 2001).

We also found that subjects who were physically active were significantly more likely to have migraine at baseline and follow-up than physically inactive subjects. The literature on the relationship between physical activity and migraine is mixed. Some studies noted an increased risk of migraine in women with heavy physical work (Le et al. 2011) . However, another study found that decreased physical activity is associated with higher migraine prevalence rates (Molarius et al. 2008). Female gender was a positive predictor of migraine diagnosis within the last 3 months at 3-year follow up but not at baseline. This finding suggests a possible role of female hormones as participants progress through puberty

Our results are similar to those of a previous population based cross sectional study of adults Goncalves et al. (2010), that found an association of TMD and headache including migraine. Another study analyzed self-reported pains in the 2000-2005 US National Health Interview Survey

(Plesh et al. 2012a) and found that among adults with severe headache or migraine pain, 16% had recent TMD pain compared with 3% of those without severe headache or migraine. To our knowledge this is the first study that assess such relationshipsin adolescents.

The percent of the sample meeting criteria for migraine in the prior three months at age 14 years was lower than at 11 years of age. Similarly, the cumulative incidences of severe headache and facial pain also decreased from baseline to follow up. A possible reason for lower cumulative incidence rates of both severe headache and facial pain at age 14 years than at baseline is that adolescents had experienced headache and/or facial pain at an early age but had forgotten about it. There is also a chance of misclassification of headache diagnosis, given that this is a cohort study that relies on self-report for case definition. To examine this issue further, we conducted a secondary analysis of data from the cross sectional study. In these analyses, a similar trend for the cumulative incidence of severe headache and migraine was found, i.e., there was a decrease in percent of subjects who had ever experienced severe headache as well as those who met migraine diagnostic criteria when the 11-year-old sample was compared to the 14-year-old sample. However, the cumulative incidence of facial pain increased from age 11 to 14 years old.

This study has some limitations and a number of strengths. An important strength of this study is that it used a very frequent follow up (every three months) rather than a longer follow-up period used by other pain onset studies. Because such high frequency follow ups might be associated with much higher rates of facial pain report, to ascertain occurrences of new TMD, a TMD exam was done to confirm diagnosis of all self-reported facial pain onset. Thus, we were able to look at differences in TMD diagnoses among those with versus without migraine (Table 8). On the other hand, one limitation of this study is that questions about criteria for migraine diagnosis were only asked at baseline and at 3-year follow up. These questions were not included in the 3-month follow up questionnaires.

Different mechanisms have been hypothesized to explain the coexistence of chronic pain conditions. The most accepted theory is called sensitization, which refers to irreversible changes within the peripheral and central nervous systems particularly in areas mediating nociception, affecting duration, intensity and location of pain (Puretic and Demarin 2012). Sensitization of the trigeminal complex might result in chronic pain conditions that are supplied by the trigeminal nerve such as headaches and TMD. This phenomenon may give rise to classification problems, where there is an overlap between many symptoms of different pain conditions. Such classification issues have been studied (Schiffman et al. 2010; Anderson et al. 2011) and continue to require further research.

Our study has several clinical implications. Given that severe headache and facial pain are comorbid in adolescents, the presence of one condition can remind the clinician to rule out the other one. Moreover, such comorbidity highlights the importance of a comprehensive clinical evaluation especially because comorbid pain complaints are significantly associated with a lower level of perceived general health (Plesh et al. 2012a). In addition, better prognostic outcomes can be achieved by managing both conditions.

The comorbidity of severe headache and facial pain might also be explained by medication overuse. Vasconcellos et al. (1998) studied the occurrence of analgesic rebound headache in children and adolescents. They found that the daily use of analgesics might result in daily or near daily headaches among this age group. These results are similar to previous observations reported in adults (Tepper 2012; Bigal et al. 2004). Further research should be done targeting this significant clinical issue.

Study supervisors

Head of Committee:
Dr. Linda LeResche
ScD
Professor
Department of Oral Medicine
University of Washington

Dr. Edmond Truelove
DDS, MSD
Professor
Department of Oral Medicine
University of Washington

Dr. Lloyd Mancl
PhD
Research Associate Professor
Department of Oral Health Sciences

University of Washington

References

Aamodt, A. H., L. J. Stovner, K. Hagen, G. Brathen & J. Zwart (2006) Headache prevalence related to smoking and alcohol use. The Head-HUNT Study. *Eur J Neurol,* 13**,** 1233-8.

Andersen, L. L., O. S. Mortensen, M. K. Zebis, R. H. Jensen & O. M. Poulsen (2011) Effect of brief daily exercise on headache among adults--secondary analysis of a randomized controlled trial. *Scand J Work Environ Health,* 37**,** 547-50.

Anderson, G. C., M. T. John, R. Ohrbach, D. R. Nixdorf, E. L. Schiffman, E. S. Truelove & T. List (2011) Influence of headache frequency on clinical signs and symptoms of TMD in subjects with temple headache and TMD pain. *Pain,* 152**,** 765-71.

Bigal, M. E., J. N. Liberman & R. B. Lipton (2006) Obesity and migraine: a population study. *Neurology,* 66**,** 545-50.

Bigal, M. E., R. B. Lipton, P. R. Holland & P. J. Goadsby (2007) Obesity, migraine, and chronic migraine: possible mechanisms of interaction. *Neurology,* 68**,** 1851-61.

Bigal, M. E., A. M. Rapoport, F. D. Sheftell, S. J. Tepper & R. B. Lipton (2004) Transformed migraine and medication overuse in a tertiary headache centre--clinical characteristics and treatment outcomes. *Cephalalgia,* 24**,** 483-90.

Breslau, N. & B. K. Rasmussen (2001) The impact of migraine: Epidemiology, risk factors, and co-morbidities. *Neurology,* 56**,** S4-12.

Cairns, B. E. (2010) Pathophysiology of TMD pain--basic mechanisms and their implications for pharmacotherapy. *J Oral Rehabil,* 37**,** 391-410.

Carlsson, G. E. (1999) Epidemiology and treatment need for temporomandibular disorders. *J Orofac Pain,* 13**,** 232-7.

Ciancaglini, R. & G. Radaelli (2001) The relationship between headache and symptoms of temporomandibular disorder in the general population. *J Dent,* 29**,** 93-8.

Dworkin, S. F. (1994) Perspectives on the interaction of biological, psychological and social factors in TMD. *J Am Dent Assoc,* 125**,** 856-63.

Dworkin, S. F. & L. LeResche (1992) Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. *J Craniomandib Disord,* 6**,** 301-55.

Dworkin, S. F., L. LeResche & M. R. Von Korff (1990) Diagnostic studies of temporomandibular disorders: challenges from an epidemiologic perspective. *Anesth Prog,* 37**,** 147-54.

Edvinsson, L., C. M. Villalon & A. MaassenVanDenBrink (2012) Basic mechanisms of migraine and its acute treatment. *Pharmacol Ther,* 136**,** 319-33.

Eminson, M., S. Benjamin, A. Shortall, T. Woods & B. Faragher (1996) Physical symptoms and illness attitudes in adolescents: an epidemiological study. *J Child Psychol Psychiatry,* 37**,** 519-28.

Fuh, J. L., S. J. Wang, S. R. Lu, Y. C. Liao, S. P. Chen & C. Y. Yang (2010) Headache disability among adolescents: a student population-based study. *Headache,* 50**,** 210-8.

Goncalves, D. A., M. E. Bigal, L. C. Jales, C. M. Camparis & J. G. Speciali (2010) Headache and symptoms of temporomandibular disorder: an epidemiological study. *Headache,* 50**,** 231-41.

Greene, C. S. (1995) Etiology of temporomandibular disorders. *Semin Orthod,* 1**,** 222-8.

Grossi, M. L., M. B. Goldberg, D. Locker & H. C. Tenenbaum (2001) Reduced neuropsychologic measures as predictors of treatment outcome in patients with temporomandibular disorders. *J Orofac Pain,* 15**,** 329-39.

Haut, S. R., M. E. Bigal & R. B. Lipton (2006) Chronic disorders with episodic manifestations: focus on epilepsy and migraine. *Lancet Neurol,* 5**,** 148-57.

Headache Classification Subcommittee of the International Headache, S. (2004) The International Classification of Headache Disorders: 2nd edition. *Cephalalgia,* 24 Suppl 1**,** 9-160.

Hedborg, K., U. M. Anderberg & C. Muhr (2011) Stress in migraine: personality-dependent vulnerability, life events, and gender are of significance. *Ups J Med Sci,* 116**,** 187-99.

Insinga, R. P., D. S. Ng-Mak & M. E. Hanson (2011) Costs associated with outpatient, emergency room and inpatient care for migraine in the USA. *Cephalalgia,* 31**,** 1570-5.

Le, H., P. Tfelt-Hansen, A. Skytthe, K. O. Kyvik & J. Olesen (2011) Association between migraine, lifestyle and socioeconomic factors: a population-based cross-sectional study. *J Headache Pain,* 12**,** 157-72.

Leonardi, M., T. J. Steiner, A. T. Scher & R. B. Lipton (2005) The global burden of migraine: measuring disability in headache disorders with WHO's Classification of Functioning, Disability and Health (ICF). *J Headache Pain,* 6**,** 429-40.

LeResche, L., L. A. Mancl, M. T. Drangsholt, G. Huang & M. Von Korff (2007) Predictors of onset of facial pain and temporomandibular disorders in early adolescence. *Pain,* 129**,** 269-78.

LeResche, L., L. A. Mancl, M. T. Drangsholt, K. Saunders & M. V. Korff (2005a) Relationship of pain and symptoms to pubertal development in adolescents. *Pain,* 118**,** 201-9.

LeResche, L., J. J. Sherman, K. Huggins, K. Saunders, L. A. Mancl, G. Lentz & S. F. Dworkin (2005b) Musculoskeletal orofacial pain and other signs and symptoms of temporomandibular disorders during pregnancy: a prospective study. *J Orofac Pain,* 19**,** 193-201.

Lipton, R. B. & M. E. Bigal (2005) Migraine: epidemiology, impact, and risk factors for progression. *Headache,* 45 Suppl 1**,** S3-S13.

List, T., K. Wahlund & B. Larsson (2001) Psychosocial functioning and dental factors in adolescents with temporomandibular disorders: a case-control study. *J Orofac Pain,* 15**,** 218-27.

List, T., K. Wahlund, B. Wenneberg & S. F. Dworkin (1999) TMD in children and adolescents: prevalence of pain, gender differences, and perceived treatment need. *J Orofac Pain,* 13**,** 9-20.

Melis, M., S. L. Lobo, C. Ceneviz, U. N. Ruparelia, K. H. Zawawi, B. P. Chandwani & N. R. Mehta (2010) Effect of cigarette smoking on pain intensity of TMD patients: a pilot study. *Cranio,* 28**,** 187-92.

Melo, C. E., J. L. Oliveira, A. C. Jesus, M. L. Maia, J. C. de Santana, L. S. Andrade, J. D. Quintans, L. J. Quintans-Junior, P. C. Conti & L. R. Bonjardim (2012) Temporomandibular disorders dysfunction in headache patients. *Med Oral Patol Oral Cir Bucal,* 17**,** e1042-6.

Molarius, A., A. Tegelberg & J. Ohrvik (2008) Socio-economic factors, lifestyle, and headache disorders - a population-based study in Sweden. *Headache,* 48**,** 1426-37.

Moskowitz, M. A. (1984) The neurobiology of vascular head pain. *Ann Neurol,* 16**,** 157-68.

Nilsson, I. M., M. Drangsholt & T. List (2009) Impact of temporomandibular disorder pain in adolescents: differences by age and gender. *J Orofac Pain,* 23**,** 115-22.

Nilsson, I. M., T. List & M. Drangsholt (2007) Incidence and temporal patterns of temporomandibular disorder pain among Swedish adolescents. *J Orofac Pain,* 21**,** 127-32.

Ohrbach, R., T. List, J. P. Goulet & P. Svensson (2010) Recommendations from the International Consensus Workshop: convergence on an orofacial pain taxonomy. *J Oral Rehabil,* 37**,** 807-12.

Olesen, J., R. Burstein, M. Ashina & P. Tfelt-Hansen (2009) Origin of pain in migraine: evidence for peripheral sensitisation. *Lancet Neurol,* 8**,** 679-90.

Pietrobon, D. & J. Striessnig (2003) Neurobiology of migraine. *Nat Rev Neurosci,* 4**,** 386-98.

Plesh, O., S. H. Adams & S. A. Gansky (2011a) Racial/Ethnic and gender prevalences in reported common pains in a national sample. *J Orofac Pain,* 25**,** 25-31.

--- (2011b) Temporomandibular joint and muscle disorder-type pain and comorbid pains in a national US sample. *J Orofac Pain,* 25**,** 190-8.

--- (2012a) Self-reported comorbid pains in severe headaches or migraines in a US national sample. *Headache,* 52**,** 946-56.

Plesh, O., C. Noonan, D. S. Buchwald, J. Goldberg & N. Afari (2012b) Temporomandibular disorder-type pain and migraine headache in women: a preliminary twin study. *J Orofac Pain,* 26**,** 91-8.

Puretic, M. B. & V. Demarin (2012) Neuroplasticity mechanisms in the pathophysiology of chronic pain. *Acta Clin Croat,* 51**,** 425-9.

Rammelsberg, P., L. LeResche, S. Dworkin & L. Mancl (2003) Longitudinal outcome of temporomandibular disorders: a 5-year epidemiologic study of muscle disorders defined by research diagnostic criteria for temporomandibular disorders. *J Orofac Pain,* 17**,** 9-20.

Rasmussen, B. K. (1993) Migraine and tension-type headache in a general population: precipitating factors, female hormones, sleep pattern and relation to lifestyle. *Pain,* 53**,** 65-72.

Rugh, J. D. & W. K. Solberg (1976) Psychological implications in temporomandibular pain and dysfunction. *Oral Sci Rev,* 7**,** 3-30.

Sanders, A. E., W. Maixner, A. G. Nackley, L. Diatchenko, K. By, V. E. Miller & G. D. Slade (2012) Excess risk of temporomandibular disorder associated with cigarette smoking in young adults. *J Pain,* 13**,** 21-31.

Scher, A. I., L. A. Midgette & R. B. Lipton (2008) Risk factors for headache chronification. *Headache,* 48**,** 16-25.

Schiffman, E. L., R. Ohrbach, E. L. Truelove, F. Tai, G. C. Anderson, W. Pan, Y. M. Gonzalez, M. T. John, E. Sommers, T. List, A. M. Velly, W. Kang & J. O. Look (2010) The Research Diagnostic Criteria for Temporomandibular Disorders. V: methods used to establish and validate revised Axis I diagnostic algorithms. *J Orofac Pain,* 24**,** 63-78.

Siegel, R. A. & A. Ehrlich (1989) A comparison of personality characteristics, family relationships, and drug-taking behavior in low and high socioeconomic status adolescents who are drug abusers. *Adolescence,* 24**,** 925-36.

Silberstein, S. D. (2004) Migraine. *Lancet,* 363**,** 381-91.

Steiner, T. J., A. I. Scher, W. F. Stewart, K. Kolodner, J. Liberman & R. B. Lipton (2003) The prevalence and disability burden of adult migraine in England and their relationships to age, gender and ethnicity. *Cephalalgia,* 23**,** 519-27.

Stewart, W. F., C. Wood, M. L. Reed, J. Roy, R. B. Lipton & A. A. Group (2008) Cumulative lifetime migraine incidence in women and men. *Cephalalgia,* 28**,** 1170-8.

Strine, T. W., D. P. Chapman & L. S. Balluz (2006) Population-based U.S. study of severe headaches in adults: psychological distress and comorbidities. *Headache,* 46**,** 223-32.

Takeshima, T., K. Ishizaki, Y. Fukuhara, T. Ijiri, M. Kusumi, Y. Wakutani, M. Mori, M. Kawashima, H. Kowa, Y. Adachi, K. Urakami & K. Nakashima (2004) Population-based door-to-door survey of migraine in Japan: the Daisen study. *Headache,* 44**,** 8-19.

Tashiro, A., K. Okamoto, S. B. Milam & D. A. Bereiter (2007) Differential effects of estradiol on encoding properties of TMJ units in laminae I and V at the spinomedullary junction in female rats. *J Neurophysiol,* 98**,** 3242-53.

Tepper, S. J. (2012) Medication-overuse headache. *Continuum (Minneap Minn),* 18**,** 807-22.

Vasconcellos, E., J. E. Pina-Garza, E. J. Millan & J. S. Warner (1998) Analgesic rebound headache in children and adolescents. *J Child Neurol,* 13**,** 443-7.

Von Korff, M., S. F. Dworkin, L. Le Resche & A. Kruger (1988) An epidemiologic comparison of pain complaints. *Pain,* 32**,** 173-83.

Von Korff, M., L. Le Resche & S. F. Dworkin (1993) First onset of common pain symptoms: a prospective study of depression as a risk factor. *Pain,* 55**,** 251-8.

Wahlund, K., T. List & S. F. Dworkin (1998) Temporomandibular disorders in children and adolescents: reliability of a questionnaire, clinical examination, and diagnosis. *J Orofac Pain,* 12**,** 42-51.

Wilson, A. C., B. Samuelson & T. M. Palermo (2010) Obesity in children and adolescents with chronic pain: associations with pain and activity limitations. *Clin J Pain,* 26**,** 705-11.

Wober, C., W. Brannath, K. Schmidt, M. Kapitan, E. Rudel, P. Wessely, C. Wober-Bingol & P. S. Group (2007) Prospective analysis of factors related to migraine attacks: the PAMINA study. *Cephalalgia,* 27**,** 304-14.

Zivadinov, R., K. Willheim, D. Sepic-Grahovac, A. Jurjevic, M. Bucuk, O. Brnabic-Razmilic, G. Relja & M. Zorzon (2003) Migraine and tension-type headache in Croatia: a population-based survey of precipitating factors. *Cephalalgia,* 23**,** 336-43.