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Painful and non-painful comorbidities associated with short- and long-term painful temporomandibular disorders: A cross-sectional study among adolescents from Brazil, Canada, and France

Ana Miriam Velly[1,2,3], Jack Botros[1,2], Michèle Muller Bolla[4,5,6], Khurram Khan[1,2], Oscar Anacleto Teixeira Junior[7], Antonio Sergio Guimarães[7], Mervyn Gornitsky[1,2,3]

[1]Dental Department, Jewish General Hospital, Montreal, QC, Canada

[2]Faculty of Dentistry, McGill University, Montreal, QC, Canada

[3]Lady Davis Institute for Medical Research, Montreal, QC, Canada

[4]Centre Hospitalier Universitaire de Nice, Nice, France

[5]Department of Pediatric Dentistry, Faculty of Dentistry, Côte d'Azur University, France

[6]Laboratory URB2i, University Paris Descartes, Paris, France

[7]Faculdade Sao Leopoldo Mandic, Arceburgo, Brazil

Correspondence

Ana Miriam Velly, Department of Dentistry,

Jewish General Hospital, 3755 Cote Ste

Catherine, Suite A017, Montreal, QC H3T

1E2, Canada.

Email: ana.velly@mcgill.ca

ORCID https://orcid.org/0000-0003-3125-1884

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ABSTRACT

Background: Temporomandibular disorder (TMD) pain is common among adolescents. The association between painful TMD and other comorbidities has been demonstrated. However, the difference between short-term (<6 months) and long-term (≥ 6 months) painful TMD is not yet clear.

Objective: The aim of this study was to assess the association between comorbidities and short- and long-term painful TMD among adolescents.

Methods: In this cross-sectional study, adolescents were recruited from Montreal (Canada), Nice (France), and Arceburgo (Brazil). Self-reported painful TMD, comorbidities, school absence, and analgesic intake were assessed using reliable instruments. Multivariable logistic regression analyses were conducted to assess the study aims.

Results: The prevalence of short- and long-term painful TMD was estimated at 22.29% and 9.93%, respectively. The number of comorbidities was associated with short- (OR = 1.71, 95%CI = 1.53-1.90) and long-term painful TMD (OR = 1.79, 95%CI = 1.55-2.08) compared to the controls. Frequent headaches ($OR_{short\text{-}term}$ = 4.39, 95%CI = 3.23-5.98, $OR_{long\text{-}term}$ = 3.69, 95%CI = 2.45-5.57), and frequent back pain ($OR_{short\text{-}term}$ = 1.46, 95%CI=1.06-2.03, $OR_{long\text{-}term}$ = 1.69, 95%CI = 1.11-2.59) were associated with both pain groups. Frequent neck pain was only associated with short-term painful TMD (OR = 2.23, 95%CI = 1.53-3.26), and frequent stomach pain with long-term painful TMD (OR = 2.01, 95%CI = 1.35-3.26). Allergies were only associated with short-term painful TMD (OR = 1.54, 95%CI = 1.13-2.10). These analyses were adjusted by sex, age, and city.

Conclusion: Short- and long-term painful TMD were associated with comorbidities. Specific comorbidities were related with short- and/or long-term painful TMD.

Keywords: Temporomandibular disorders; pain; orofacial pain; comorbidities; adolescents; epidemiology.

INTRODUCTION

Painful temporomandibular disorder (TMD) is not only prevalent among adults but also among adolescents. The prevalence among adolescents in different countries ranges from 4% to 36.9%.[1-10] Painful TMD has been reported to cause a negative impact on the quality of life among adolescents[11] with an increased rate of school absence and analgesic consumption.[12]

Our previous study, similar to others, demonstrated that painful comorbidities are common among adolescents with painful TMD. Examples of frequent comorbid conditions encountered with painful TMD are headaches,[9, 10, 13-17] neck pain,[10, 17] back pain,[4, 10, 14, 17] and limb pain (arms or legs).[14] LeResche and collaborators in a prospective cohort study found that adolescents reporting painful conditions (back pain, headache, stomach pain) were at a higher risk of developing painful TMD.[18]

The overall aim of the current study was to assess the associations between comorbidities and short- (less than 6 months) and long-term (6 months or more) painful TMD. The specific objectives were to assess if relative to controls, adolescents with short- and long-term painful TMD were more likely to have a higher number of comorbidities; and assess if these associations were modified by specific comorbidity (e.g., headache, allergies).

METHODS

Study design and study population

This cross-sectional study was approved by the Jewish General Hospital Research Ethics Committee and the English School Board in Montreal (Canada), the CHUN (*Centre hospitalier universitaire de Nice)* Delegation of Clinical Research and Innovation and the

rectorate of the Nice Academy (France), and the *Comitê de Ética e Pesquisa do Centro de Pós-Graduação São Leopoldo Mandic Campinas-SP/Brasil (Brasil).*

This study enrolled adolescents 14-17 years old in three cities: Montreal (Canada), Nice (France), and Arceburgo (Brazil). Due to feasibility constraints and to comply with the local ethics committee in each country, the data collection methodology varied slightly among locations. In Montreal and Nice, adolescents were recruited from randomly selected schools. In Montreal, adolescents 14-17 years old in the selected classes were provided a thorough explanation of the study and were invited to participate voluntarily. In Nice, adolescents in these classes were given a letter to be delivered to their parents or legal guardians. The letter comprised a full clarification of the study as well as an informed consent form to authorize the adolescent's participation. To be included in the study, the consent form had to be signed by the parents or legal guardians and the adolescent. In Arceburgo, adolescents were identified by the data health system. A letter and a consent form were then sent to their parents or legal guardians inviting them to participate in the study. Recruitment was completed by an agent from the Community Health Agency (ACS). In all locations, adolescents were excluded if they refused to participate or if they fell outside the age range previously indicated. The study methodology has been thoroughly described in our previous publication.[10]

A total of 1432 adolescents were enrolled in our first TMD study.[10] Out of the total, 14 (all from Arceburgo) did not complete the question assessing how long they had painful TMD. Further, 18 answered that they do not have pain but experienced short- or long-term pain. From the 18, 3 were from Arceburgo, 8 from Montreal and 7 from Nice. None of these 32 subjects were included in this study.

Assessment

Temporomandibular Disorder screening

Two questions were used to assess whether the adolescent had painful TMD: (i) *Do you have pain in the temple, face, jaw joint or jaws once a week or more often*? and (ii) *Do you have pain when you open your mouth wide or chew once a week or more often*? Participants who answered "yes" to one or both of the questions were included in the TMD group, while those who answered "no" to both of them were included in the control group. These two questions are valid to identify painful TMD with sensitivity [0.98 (95% CI 0.90-1.0)] and specificity [0.90 (95% CI 0.81 - 0.95)], where RDC/TMD was used as a gold standard.[19, 20] The test-retest reliability of the questions was 0.83 (Kappa). The internal consistency of the English, French, and Portuguese TMD screening questions was found to have acceptable Cronbach's alpha coefficients: 0.70, 0.73, and 0.65, respectively.

Short-term and long-term Painful TMD classification

We asked the question *Did your pain start within the past 6 months?* Participants who reported painful TMD for less than 6 months were classified as short-term painful TMD and those who reported painful TMD for 6 months or more were classified as long-term painful TMD.

When this study was conducted, the International Association for the Study of Pain (IASP) Task Force on Taxonomy recommended to use a threshold of 6 months for research to select the "chronic cases".[21] However, as in 2019 the IASP defined chronic pain as more than 3 months, we decided to classify the group as short- and long-term painful TMD.[22]

Comorbidities

The occurrence of the painful comorbidities (i.e., headache, neck, back and stomach pain) was scored on a five-point scale: never; one to three times a month; once a week; several times a week; and daily. The same scale was used by Nilsson *et al.*[17] to assess the frequency of headaches.

Non-painful comorbidities were assessed by asking the participants whether they had asthma or allergies ("yes" or "no"). The internal consistency for the English, French, and Portuguese versions of these questions was acceptable (Cronbach's alpha: 0.74, 0.69, and 0.67, respectively).

Analgesic consumption and school absences

Analgesic consumption was measured using a six-point scale: daily; three to four times a week; one to two times a week; every month; almost never; or never. [3] The participants were asked about the number of days in the previous month they were absent from school due to pain in the temples, face, jaws or jaw joints.[19]

Statistical analysis

Chi-square and ANOVA were used to test statistical differences between adolescents with short-, long-term painful and without painful TMD.

Univariate and multivariable unconditional nominal logistic regression analyses were used to assess the association between painful TMD (dependent variable) and the following independent variables: (i) the number of comorbidities; and (ii) specific comorbidities. The multivariable logistic models also included sex, age, and city. The logistic regression analysis was stratified by sex. The odds ratio (OR) and their 95% confidence intervals (CI) were

estimated. Statistical software package SAS (version 9.4) was used to perform the analyses with the significance level for type I error set at 0.05.

RESULTS

Description of the sample

This study enrolled 1400 adolescents: short- (n = 312, 22.29%) and long-term self-reported painful TMD (n = 139, 9.93%), and controls (n = 949, 67.79%). Table 1 shows the characteristics of the groups. This sample includes 506 adolescents from Arceburgo, 304 from Montreal, and 590 from Nice. We did not find a significant difference on the distribution of short-and long-term between cities (P = .18). Most of the short- and long-term painful TMD groups include girls (P < .0001), and the mean age of the participants was similar between the three groups (P = .70). Adolescents with short- and long-term painful TMD missed school more frequently than controls (P < .0001), as well as long-term painful TMD compared to short-term (P = .0015). Likewise, more adolescents with short- and long-term painful TMD reported consuming analgesics than the controls (P < .0001).

Number of comorbidities

In comparison to controls, adolescents with either short- or long-term painful TMD were more likely to present a higher number of comorbidities, regardless of their age, sex, and city (Table 2). A low and nonsignificant OR was found between the odds of short- and long-term painful TMD and number of comorbidities ($OR_{long/short}$ =1.05; 95%CI: 0.90-1.23).

Girls ($OR_{short/controls}$=1.60; 95%CI: 1.41-1.83; $OR_{long/controls}$=1.59; 95%CI: 1.33-1.90) and boys ($OR_{short/controls}$ =1.91; 95%CI: 1.57-2.32; $OR_{long/controls}$=2.20; 95%CI: 1.69-2.88) with painful TMD were more likely to present a greater number of comorbidities than controls, regardless

of their age and city. Nonsignificant ORs were found between the odds of short- and long-term painful TMD and number of comorbidities among girls ($OR_{short/long}$ =0.99; 95%CI: 0.82-1.20) and boys ($OR_{short/long}$ =1.15; 95%CI: 0.85-1.56).

The number of comorbidities was associated with short- and long-term painful TMD among adolescents from Arceburgo ($OR_{short/controls}$ = 1.78, 95%CI = 1.48-2.13; $OR_{long-term}$ = 1.77, 95%CI =1.42-2.20), Montreal ($OR_{short/controls}$ =1.59, 95%CI = 1.23-2.05; $OR_{long-term}$ = 2.95, 95%CI = 1.86-4.69) and Nice ($OR_{short/controls}$= 1.69, 95%CI = 1.44-1.97; $OR_{long-term}$ = 1.54, 95%CI = 1.22-1.93). The odds of a large number of comorbidities were not significantly different between adolescents with short- and long-term painful TMD from Arceburgo ($OR_{short/long}$= 1.00, 95%CI = 0.78-1.27) and Nice ($OR_{short/long}$= 0.91, 95%CI = 0.71-1.17). However, adolescents with long-term painful TMD from Montreal were almost twice as likely to have more comorbidities than the short-term ones ($OR_{short/long}$= 1.86, 95%CI = 1.14-3.04). These multivariable models were adjusted by age and sex.

Specific painful and non-painful comorbidities

Figure 1 illustrates the distribution of comorbidities between groups. The most common comorbidities among short- and longer-term painful TMD group were headaches, back pain, and allergy.

Table 3 shows the crude and the multivariable analyses assessing the association with each comorbidity. Adolescents with short- and long-term painful TMD were four times as likely to report frequent headaches, and almost twice as likely to report frequent back pain, compared to controls. Adolescents with long-term painful TMD were two times as likely to present frequent stomach pain compared to controls, contrary to adolescents with short-term painful TMD where a weak and nonsignificant association was found. Frequent neck

pain and allergy were both only associated with short-term painful TMD. Asthma was neither associated with short- nor long-term painful TMD. Frequent stomach pain was the only comorbidity to be found significantly more common among long- than short-term TMD (OR = 1.82, 95%CI: 1.14-2.90). These multivariable models were adjusted by age, sex, and city.

Additionally, girls and boys with short- and long-term painful TMD were more likely to present headaches than controls. Adolescents with short-term painful TMD from either sex were also more likely to have neck pain. Long-term painful TMD was associated with frequent back pain among boys, and with stomach pain among girls and boys. Allergies were only associated with short-term painful TMD among boys (Figure 2).

The Venn diagram shows the overlap between painful comorbidities (Figure 3). All painful comorbidities were reported by 21 (3.52%) of the controls, 18 (22.50%) with short-term, and 17 (34.0%) of the adolescents with long-term painful TMD. In comparison to controls, adolescents with short- and long-term painful TMD were 6.72 times (95%CI = 3.28-13.36) and 12.20 times (95%CI = 5.58-25.82) as likely to report all painful comorbidities, respectively. This analysis was adjusted by age, sex and city.

Discussion

Despite the rich evidence in favor of association between comorbidities and painful TMD in adolescents, the relationship between comorbidities and short- and long-term painful TMD is still lacking. To our knowledge, so far this is the first study that investigated the relationship between painful and non-painful comorbidities with short- and long-term painful TMD among adolescents.

Cohort studies put in evidence that painful comorbidities are associated with TMD risk,[18, 23-25] as well as with its persistence.[26-29] Comorbidity is defined as "any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study".[30] Our study found that comorbidities were associated with short- and long-term painful TMD. However, we did not find a significant difference between the odds of the number of comorbidities between short- and long-term painful TMD. This finding is in disagreement with a previous study where coexisting pain beyond orofacial areas (e.g., neck pain, back pain, irritable bowel syndrome) was more common among adult patients with chronic painful TMD than the acute group.[31] It is possible that the marginally similar magnitude of the ORs for short- and long-term painful TMD is due to the inclusion of adolescents with painful TMD for more than 3 months in the short-term painful TMD group, thus adding chronic painful TMD to this group.

This disagreement may also be due to a specific comorbidity since we found that short- and long-term painful TMD were associated with particular comorbidities. Headaches and back pain were associated with short- and long-term painful TMD, contrary to neck pain and stomach pain that were associated only with short- and long-term painful TMD, respectively. It was interesting to find that back pain was associated with long-term painful TMD only among boys, suggesting that health lifestyle covariates (e.g., physical activity, healthy eating) are potential effect modifiers.

Among adults, allergy was associated with TMD[32] or with temporomandibular joint (TMJ) osteoarthritis/osteoarthrosis.[33] In our study, allergy was only associated with short-term painful TMD, specifically among boys. Thus, our findings suggest that allergic hypersensitivity could be implicated in the mechanism of short-term painful TMD.

In the present study, asthma was not associated with short- and long-term painful TMD either. In previous studies among adults, some found a higher odds of TMD among patients with asthma,[34] which disagrees with another study that did not find an association between temporomandibular joint osteoarthritis/osteoarthrosis and asthma.[33]

Mechanisms related to a dysregulation of pain modulatory systems involving the central and peripheral nerves and the immune systems[35, 36] could explain the association between headache, back pain, and stomach pain, and long-term painful TMD. We cannot exclude the hypothesis that particularly with short-term painful TMD, headache, neck and back pain could be due to a traumatic event.

The limitations of this study should be noted. First, due to the cross-sectional design of the study, temporality is an issue; we do not know if the comorbidities preceded the onset of the painful TMD. Second, even if we used validated and reliable questionnaires for TMD screening and assessment of comorbidities, there is a possibility of information bias. However, headache,[17, 37] back pain,[17, 37] neck pain, [17]and stomach pain[37] were also common painful comorbidities among adolescents, suggesting that the chance of overreporting comorbidities is low. Third, a 6-month threshold was used to define long-term painful TMD according to the former classification of chronic pain by the IASP at the time the data were collected.[21] Nevertheless, the time threshold of chronic pain has been changed to 3 months in the recent classification.[22] This may have led to the inclusion of some chronic cases in the short-term painful TMD group. Fourth, the sample size in Montreal was relatively small due to the inability of the schools there to accommodate our research. Fifth, some potential confounders were not assessed, such as psychological factors, socio-economic status, and health lifestyle. Sixth, we do not have sufficient power for comparing short- to long-term painful TMD. Considering the percentage of comorbidities among short- and long-term TMD

(Figure 1), the sample size required would be 11,000, 3200, 3268, 678 and 3171 per group to assess the association between asthma, allergy, back pain, neck pain, and headache, between short- and long-term painful TMD. In this sample size calculation, it was considered 80% of power and alpha equal to 5%. Seventh, it was not possible to stratify the analysis by city.

The strengths of this study include: First, we used validated and reliable questionnaires to assess TMD.[1] Second, 949 controls, 312 short-term painful TMD and 139 long-term painful TMD adolescents were enrolled in this study providing sufficient power (>80%) for the primary analysis assessing the association between comorbidities and short- and long-term painful TMD, relative to controls. Third, we investigated the difference between short- and long-term painful TMD regarding each separate comorbidity and not only the number of comorbidities.

Future studies should look for the difference between acute and chronic painful TMD at the 3-month threshold to investigate the potential risk factors for the transition from acute to chronic painful TMD among adolescents.

In summary, we have revealed that the number of comorbidities was associated with short- and long-term painful TMD, regardless of age, sex, and city of the participants. Relative to controls, specific comorbidities were associated differently with short- and/or long-term painful TMD suggesting the involvement of distinct mechanisms. Our results highlight the importance of identifying specific comorbidities.

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CONFLICT OF INTEREST

The authors declared no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors participated in the design of the study. AMV obtained funding from RSBO. MMB, OATJ, ASG obtained support from France and Brazil. AMV, KK, MMB, OATJ acquired the data. AMV and JB carried out the statistical analysis and wrote the manuscript. All authors revised and approved the manuscript.

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Table and Figures legends

Table 1: Characteristics of the study participants

Table 2: Logistic regression analyses assessing the association between number of comorbidities and short and long-term painful TMD

Table 3: Logistic regression analyses assessing the association between each comorbidity and short and long-term painful TMD

Figure 1. Distribution of various comorbidities among control, short-term and long-term painful TMD groups

Figure 2. Logistic regression analyses assessing the association between each comorbidity and short and long-term painful TMD stratified by gender.

Figure 3. Venn diagram showing the relationship between painful comorbidities

Table 1: Characteristics of the study participants				
Sample characteristics	Category	No pain (n = 949)	Short-term painful TMD (< 6m) (n = 312)	Long-term painful TMD (≥ 6m) (n = 139)
Sex, n (%)*	Male	461 (48.58)	75 (24.04)	38 (27.34)
	Female	488 (51.42)	237 (75.96)	101 (72.66)
Age	Mean (SD)	15.36 (0.90)	15.39 (0.92)	15.41 (0.90)
City, n (%)*	Arceburgo	318 (33.51)	122 (39.10)	66 (47.48)
	Montreal	231 (24.34)	50 (16.03)	23 (16.55)
	Nice	400 (42.15)	140 (44.87)	50 (35.97)
School absence, n (%)*,**	Yes	9 (0.96)	48 (15.43)	39 (28.26)
	No	930 (99.04)	263 (84.57)	99 (71.74)
Analgesic intake, n (%) *	Yes	8 (0.85)	36 (11.54)	20 (14.39)
	No	936 (99.15)	276 (88.46)	119 (85.61)
Note: * between groups $P<0.05$, **between painful TMD groups $P<0.05$, missing data < 0.01%				

Table 2: Logistic regression analyses assessing the association between number of comorbidities and short and long-term painful TMD					
Comorbidities & demographics	Groups	Crude (n = 1400)		Adjusted[a] (n = 1400)	
		OR	95% CI	OR	95% CI
Number of comorbidities (1-6)	Controls	1	reference	1	reference
	Short-term painful TMD (< 6m)	1.74*	1.58-1.93	1.71*	1.53-1.90
	Long-term painful TMD (≥ 6m)	1.82*	1.57-2.10	1.79*	1.55-2.08
Note: * P < 0.05 [a]Multivariable models adjusted by age, sex and city.					

Table 3: Logistic regression analyses assessing the association between each comorbidity and painful TMD groups					
Comorbidities & demographics	Groups	Crude (n = 1400)		Adjusted[a] (n = 1400)	
		OR	95% CI	OR	95% CI
Frequent headachesδ	No Painful TMD	1	Reference	1	reference
	Short-term painful TMD (< 6m)	6.69*	5.06-8.86	4.39*	3.23-5.98
	Long-term painful TMD (≥ 6m)	5.97*	4.10-8.68	3.69*	2.45-5.57
Frequent neck painδ	No Painful TMD	1	reference	1	reference
	Short-term painful TMD (< 6m)	4.15*	3.01-5.73	2.23*	1.53-3.26
	Long-term painful TMD (≥ 6m)	3.28*	2.13-5.05	1.61	0.98-2.64
Frequent back painδ	No Painful TMD	1	reference	1	reference
	Short-term painful TMD (< 6m)	3.22*	2.46-4.21	1.46*	1.06-2.03
	Long-term painful TMD (≥ 6m)	3.51*	2.44-5.06	1.69*	1.11-2.59
Frequent stomach painδ	No Painful TMD	1	reference	1	reference
	Short-term painful TMD (< 6m)	2.33*	1.69-3.20	1.15	0.79-1.67
	Long-term painful TMD (≥ 6m)	3.92*	2.64-5.80	2.01*	1.35-3.26
Allergies (yes vs no)	No Painful TMD	1	reference	1	reference
	Short-term painful TMD (< 6m)	1.71*	1.31-2.22	1.54*	1.13-2.10
	Long-term painful TMD (≥ 6m)	1.53*	1.07-2.21	1.28	0.85-1.92
Asthma (yes vs no)	No Painful TMD	1	reference	1	reference
	Short-term painful TMD (< 6m)	1.30	0.84-2.03	1.13	0.67-1.89
	Long-term painful TMD (≥ 6m)	1.43	0.80-2.57	1.36	0.71-2.60
Note: * P < 0.05, δ ≥ once a week vs < once a week. [a] Multivariable models adjusted by age, sex and city.					

Figure 1. Distribution of various comorbidities among control, short-term and long-term painful TMD groups

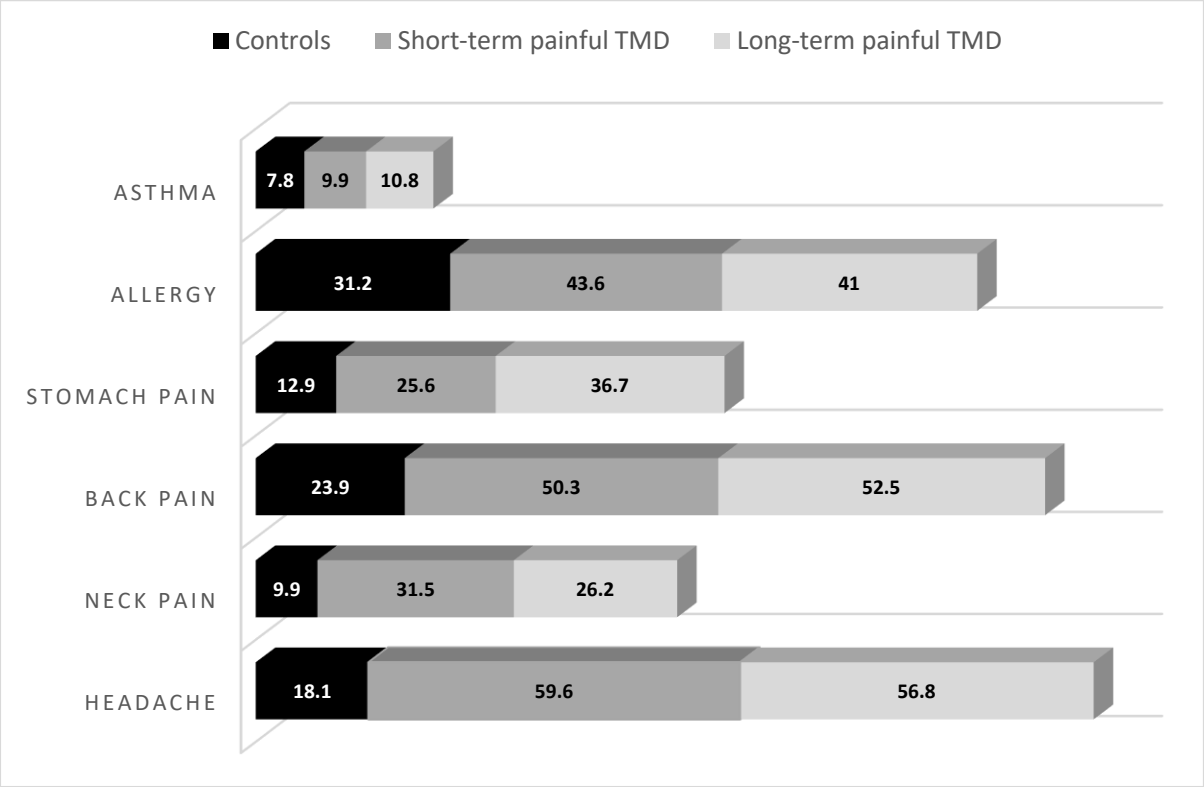
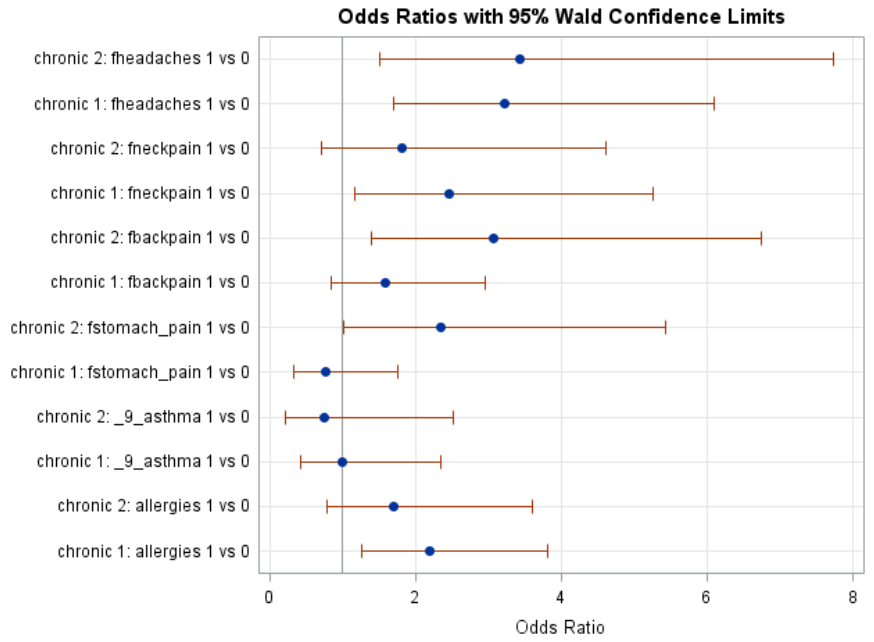
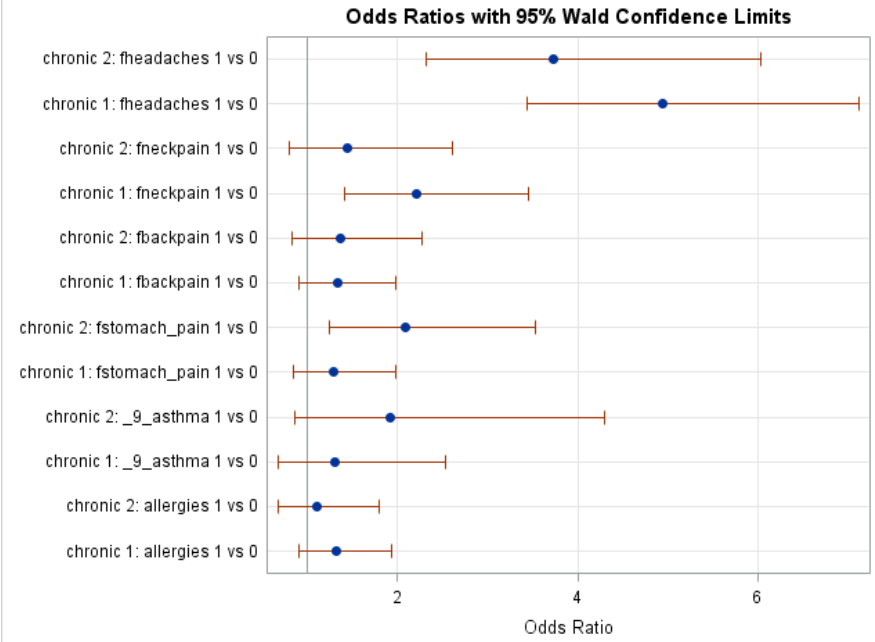


Figure 2. Association between comorbidities and painful TMD across boys and girls.

Among boys



Among girls



Note: chronic 2= long-term painful TMD, chronic 1= short-term painful TMD. Multivariable models also included age and cities.

Figure 3. Venn diagram showing the relationship between painful comorbidities