# CIRCULATING OMENTIN-1
# AND CHRONIC TEMPOROMANDIBULAR DISORDER PAIN

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**ABSTRACT**

Jennifer B. Harmon: Circulating Omentin-1 and Chronic Temporomandibular Disorder Pain
(Under the direction of Anne E. Sanders)

**Objective:** Literature implicates circulating inflammatory cytokines in pain and TMD. One anti-inflammatory adipokine, omentin-1, has decreased expression in inflammatory conditions. This study tested the hypothesis that circulating levels of omentin-1 were lower in individuals with TMD than healthy controls. **Methods:** A case-control design of chronic TMD cases (n=90) and TMD-free controls (n=54) were selected from the study named OPPERA. Omentin-1 levels were measured in blood plasma samples using an enzyme-linked immunosorbent assay (ELISA). Logistic regression estimated odds ratios (OR) and 95% confidence limits (CL) for the association between omentin-1 and TMD. **Results:** Mean omentin-1 concentration was lower in TMD cases (413.5 μg/ml) than controls (464.8 μg/ml), but the difference was not statistically significant. Odds of TMD decreased 36% per standard deviation increase in circulating omentin-1 (adjusted OR=0.64, 95% CL: 0.43, 0.96. P=0.031). **Conclusion:** Decreased omentin-1 in TMD cases supports the view that TMD pain is mediated by anti-inflammatory pathways.

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| BMI | Body mass index |
| CL | Confidence limits |
| IBS | Irritable bowl syndrome |
| IC/BPS | Interstitial cystitis/bladder pain syndrome |
| IQR | Interquartile range |
| OPPERA | Orofacial Pain Prospective Evaluation and Risk Assessment |
| OR | Odds ratios |
| TMD | Temporomandibular disorder |
| TMJ | Temporomandibular joint |
| TNF | Tumor necrosis factor |

## INTRODUCTION

Idiopathic pain conditions account for a considerable portion of chronic pain disorders. Prominent among these are temporomandibular disorders (TMD), chronic headaches, irritable bowel syndrome (IBS), interstitial cystitis/bladder pain syndrome (IC/BPS), low back pain, and widespread bodily pain such as fibromyalgia.[1] Because these conditions share etiological factors, individuals with pain commonly experience more than one chronic pain disorder.

TMD is the most common chronic orofacial pain condition.[2,3] According to the 2002 National Health Interview Survey, five percent of adults reported TMD-like pain.[4] The condition is characterized by pain in one or both temporomandibular joints and masticatory muscles, and limitations in jaw function. The pathogenesis of TMD is multifactorial, and risk factors commonly associated with chronic TMD pain include joint and muscle trauma, anatomical and pathophysiological factors, psychosocial factors and genetic factors.[1,5-7]

Much of what is known about risk factors for TMD comes from cross-sectional studies. Unlike those studies, the OPPERA study (Orofacial Pain: Prospective Evaluation and Risk Assessment) used a prospective cohort design. It measured potential risk factors at baseline and followed TMD-free people over time finding that a greater number of comorbid pain conditions, psychological characteristics, clinical orofacial characteristics, sociodemographics characteristics, pain sensitivity, and cardiac autonomic function were factors that predicted first onset TMD incidence.[8] Another promising line of evidence suggests that inflammatory cytokines may contribute to the pathophysiology of TMD,[9] however inflammatory pathways have not yet been explored in OPPERA.

Pain disorders frequently coexists with inflammation and altered cytokine levels. Cytokines are intracellular regulatory proteins secreted by specific cells of the immune system.[10] These proteins, especially proinflammatory cytokines, have been found in both chronic and acute pain conditions.[11] Findings suggest that an increased level of cytokines contribute to the sensation of pain by increasing the

sensitization of nociceptors. Cytokines such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor alpha (TNF-α) are released during an inflammatory episode.

Heightened expression of proinflammatory mediators is characteristic of many pain conditions, implicating a role of inflammation in the pathophysiology of chronic pain. Emerging research suggests that dysregulation of both pro- and anti-inflammatory mechanisms play a role in the induction and maintenance of pain. [12]

Adipokines are a specific type of cytokine that are secreted predominantly by visceral adipose tissue. Several studies have revealed an enhanced expression of pro-inflammatory adipokines in relation to obesity, type 2 diabetes, and cardiovascular disease. [13] Recently, omentin-1, an adipokine that is highly expressed in visceral adipose tissue, has attracted scientific interest because of its anti-inflammatory properties.

Omentin, also known as intelectin, is secreted mainly by cells of visceral adipose tissue [14] and exists in two forms, omentin-1 and omentin-2. Omentin-1, the major circulating form, [15] was first associated with the pathophysiology of obesity-associated disorders and is down regulated in obesity. Therefore, downregulation of omentin-1 may undermine its protective capacity to play an anti-inflammatory action.

Several studies provide evidence of downregulation of omentin-1 in chronic conditions with an inflammatory basis. Shibata et al. for example, observed low levels of ometin-1 in patients with coronary artery disease. [16] Reduced levels of omentin have also been found in people with impaired glucose tolerance [17], suggesting that omentin-1 levels are negatively associated with cardiovascular diseases as well as with obesity-related disorders. Plasma omentin-1 levels are significantly lower in people with obesity-linked metabolic dysfunction such as type 2 diabetes and coronary heart disease. [16,18] Furthermore, reduced levels of omentin-1 are found in the synovial fluid of patients with rheumatoid arthritis. [19] Downregulation of omentin-1 may therefore undermine its protective capacity and contribute to these conditions.

Since decreased omentin-1 is related to obesity, it is intuitive to expect that obesity might be associated with chronic pain. Cross-sectional studies have linked obesity to chronic headaches, abdominal pain, and arthritis. These conditions may also occur in a state of chronic low-grade

inflammation, similar to TMD. Obesity is an expression of systemic inflammation, making plausible an association between obesity and TMD. In fact, in OPPERA, individuals with a higher body mass index (BMI) at baseline were at higher risk of developing first-onset TMD than those with lower BMI.[20] If omentin-1 plays a role in inflammation, and if inflammation is associated with the mechanism of obesity and TMD, then adipokines may play a role in the pathophysiology of TMD.

Since little is known about how anti-inflammatory proteins, specifically omentin-1, are associated with TMD this study sought to examine the role of one such anti-inflammatory cytokine. The aim of this study was to compare levels of circulating omentin-1 in adults with and without chronic temporomandibular disorder. We hypothesized that levels of plasma omentin-1 would be significantly lower in TMD cases than in TMD-free controls.

## REVIEW OF THE LITERATURE

### Pain and Inflammation

Idiopathic pain conditions, meaning that the underlying cause of pain is unknown, account for a considerable portion of chronic pain disorders in the United States. Prominent among these are temporomandibular disorders (TMD), chronic headaches, irritable bowel syndrome (IBS), interstitial cystitis/bladder pain syndrome (IC/BPS), low back pain, and widespread bodily pain such as fibromyalgia.[1] Because these conditions share etiological factors, individuals with pain commonly experience more than one chronic pain disorder.

### Temporomandibular Disorder

TMD is the most common chronic orofacial pain condition.[2,3] According to the 2002 National Health Interview Survey, five percent of adults reported TMD-like pain.[4] The condition is characterized by pain in one or both temporomandibular joints and masticatory muscles, and limitations in jaw function. The pathogenesis of TMD is multifactorial, and risk factors commonly associated with chronic TMD pain include joint and muscle trauma, anatomical and pathophysiological factors, psychosocial factors and genetic factors.[1,5-7]

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**Cytokines**

Pain disorders frequently coexists with inflammation and altered cytokine levels. Cytokines are small intracellular regulatory proteins secreted by specific cells of the immune system. [10] Proinflammatory cytokines such as interleukin-8 (IL-8) promote inflammation, whereas anti-inflammatory cytokines suppress the activity of its counterpart. These proteins, especially proinflammatory cytokines, have been found in both chronic and acute pain conditions. [11] Findings suggest that an increased level of cytokines contribute to the sensation of pain by increasing the sensitization of nociceptors. Cytokines such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor alpha (TNF-α) are released during an inflammatory episode.

Heightened expression of proinflammatory mediators is characteristic of many pain conditions, implicating a role of inflammation in the pathophysiology of chronic pain. While proinflammatory cytokines play a role in pain induction, more research is needed to clarify the relationship between cytokines and chronic pain, especially TMD. Emerging research suggests that dysregulation of both pro- and anti-inflammatory mechanisms play a role in the induction and maintenance of pain. [12]

**Adipokines**

Adipose tissue provides nutrient storage for triacyclycerols and houses differentiated cells called adipocytes, its most abundant cell population. Adipokines are a specific type of cytokine that are secreted predominantly by visceral adipose tissue. These proteins function as signaling molecules in many physiological and metabolic processes. Inflammatory processes can be mediated by pro- and anti-inflammatory adipokines. Several studies have revealed an enhanced expression of pro-inflammatory adipokines in relation to obesity, type 2 diabetes, and cardiovascular disease. [13] Recently, omentin-1, an adipokine that is highly expressed in visceral adipose tissue, has attracted scientific interest because of its anti-inflammatory properties.

**Omentin-1: an anti-inflammatory adipokine**

Omentin, also known as intelectin, is a novel adipokine secreted mainly by cells of visceral adipose tissue [14] and exists in two forms, omentin-1 and omentin-2. Omentin-1, the major circulating form in human blood, [15] was first associated with the pathophysiology of obesity-associated disorders and is

down regulated in obesity. Therefore, downregulation of omentin-1 may undermine its protective capacity to play an anti-inflammatory action.

Several studies provide evidence of downregulation of omentin-1 in chronic conditions with an inflammatory basis. Shibata et al. for example, observed low levels of ometin-1 in patients with coronary artery disease. [16] Reduced levels of omentin have also been found in people with impaired glucose tolerance, [17] suggesting that omentin-1 levels are negatively associated with cardiovascular diseases as well as with obesity-related disorders. Plasma omentin-1 levels are significantly lower in people with obesity-linked metabolic dysfunction such as type 2 diabetes and coronary heart disease. [16,18] Furthermore, reduced levels of omentin-1 are found in the synovial fluid of patients with rheumatoid arthritis. [19] Downregulation of omentin-1 may therefore undermine its protective capacity and contribute to these conditions.

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**Purpose**

Since little is known about how anti-inflammatory proteins, specifically omentin-1, are associated with TMD this study sought to examine the role of one such anti-inflammatory cytokine. The aim of this study was to compare levels of circulating omentin-1 in adults with and without chronic temporomandibular disorder. We conducted experiments using cross-sectional data from patients with TMD and those with TMD and other comorbidities to test the following hypothesis: that levels of plasma omentin-1 would be significantly lower in TMD cases than in TMD-free controls.

## INTRODUCTION AND REVIEW OF THE LITERATURE

Idiopathic pain conditions account for a considerable portion of chronic pain disorders. Prominent among these are temporomandibular disorders (TMD), chronic headaches, irritable bowel syndrome (IBS), interstitial cystitis/bladder pain syndrome (IC/BPS), low back pain, and widespread bodily pain such as fibromyalgia.[1] Because these conditions share etiological factors, individuals with pain commonly experience more than one chronic pain disorder.

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## MATERIALS AND METHODS

### Parent Study: OPPERA

The parent study, OPPERA, is an ongoing multisite prospective cohort study of risk factors for the development and persistence of TMD and other idiopathic pain disorders. [6] OPPERA's objectives are to identify physiological, psychological, clinical, and genetic risk factors for the incidence of TMD. [21] At baseline OPPERA enrolled 3,263 participants with no lifetime experience of TMD. Of these, 1,633 were selected at random for a baseline case-control study of chronic TMD. [22] Adults were recruited from communities in: Baltimore, Maryland; Buffalo, New York; Chapel Hill, North Carolina; and Gainesville, Florida. Recruitment took place around these study sites between May 2006 and November 2008 using newspaper and radio station advertisements, university emails, flyers and word of mouth. Eligible adults were aged 18 to 44 years in good health, with no history of facial trauma or surgery, no TMD symptoms or pain, no diagnosis of TMD, and an absence of TMD myalgia and arthralgia upon clinical examination. At baseline, all participants completed questionnaires evaluating behavioral, social, and psychological characteristics related to TMD. An extensive comprehensive clinical examination measured responses to standardized noxious stimuli that measured pain amplification, cardiovascular function, and psychological characteristics. Anthropometric measurements were also determined and a blood draw was performed.

### Omentin Ancillary Study

Subjects in this ancillary case-control study were drawn from a second case-control OPPERA study of chronic pain. Examiner-classified chronic TMD cases (n = 90) had experienced TMD symptoms for at least 6 months. Controls (n = 55) were a random sample of enrollees in the prospective cohort study who were examiner-verified to not have TMD. Exclusion criteria were the same as the OPPERA study-wide exclusion criteria: currently in orthodontic treatment, heart disease or heart failure, kidney failure or renal dialysis, uncontrolled diabetes, pregnant or nursing, uncontrolled respiratory disease, uncontrolled hypertension, hyperthyroidism, drug or alcohol abuse, epilepsy, chemotherapy or radiation therapy, and psychiatric disorders that have required hospitalization.

**TMD Classification**

All OPPERA participants underwent a clinical examination based on the Research Diagnostic Criteria for TMD [23] performed by trained and calibrated examiners. TMD case status was confirmed based on: 1) pain experienced for at least 5 days per month in masticatory structures; and 2) confirmation of TMD arthralgia (pain of either temporomandibular joint during jaw movement or digital palpation) and/or myalgia (pain during jaw movement in at least 3 of the 8 muscle groups based on evaluation of temporalis, masseter, lateral pterygoid, and submandibular muscles).

**Coexisting Pain Conditions**

At baseline, other pain conditions such as headache, chronic back pain, and IBS were evaluated using the Comprehensive Pain and Symptom Questionnaire (CPSQ). Participants were asked whether they had any headaches in the past year (yes/no). Those answering affirmatively were then asked to differentiate their headaches into stress or tension type, migraine, hunger headache, or sinus headache. To measure headache severity and headache types, participants were asked questions for initial characterization. Questions regarding pains other than the face, current back pain, and number of back pain episodes in the past 12 months were also asked. Participants answered four questions about abdominal pain using the Rome III IBS classification for irritable bowel syndrome. [24] Information was also collected on IBS symptoms over the referent period of the last 3 months.

**Body Mass Index**

Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared ($kg/m^2$) and categorized using standard World Health Organization categories of: underweight and normal combined (<25.00); overweight (25.00–29.99); and obese (≥30.0).

**Blood Plasma Collection and Storage**

A 20-mL sample of peripheral blood was obtained by venipuncture from OPPERA study participants at enrollment for further DNA investigation and genotyping. [22] Blood samples were centrifuged for at least 12 minutes and plasma was quickly frozen and stored at -80°C in 5-mL EDTA tubes containing polyethylene vacutainers.

**Omentin-1 Assessment**

Plasma omentin-1 levels were assessed using an enzyme linked immunosorbent assay (BioVendor Research and Diagnostic Products; Asheville, NC) according to kit instructions. All plasma samples were diluted at 40x.

**Statistical Power and Sample Size**

The sample size calculation was guided by estimates of serum omentin-1 levels for obstructive sleep apnea (OSA) cases and healthy controls reported by Wang et al.[25] where the median (IQR) serum omentin-1 level for cases was 11.29 ng/mL (0.02—15.13) and for controls was 22.62 ng/mL (18.71–27.21); a two-fold effect. To permit a less extreme effect size, we specified a two-sample means test setting the mean for controls as 22.0 ng/mL and allowing the means for cases to be 10.0, 12.0, 14.0 or 16. Assuming equal size groups, an alpha of 0.05, power of 0.8, a pooled standard deviation of 13.0 and, the minimum number of subjects required for the case and control groups combined was 40, 56, 86 and 150 respectively. We conservatively chose a sample size of 150 (n=75 subjects per group), allowing for a difference between cases and controls of 6 ng/ml.

**Statistical Analysis**

Statistical analyses were conducted using STATA (StataCorp., College Station, TX, USA, Release 13.1). The dependent variable was TMD case status and the exposure was plasma omentin-1 levels. Omentin-1 values were standardized as z-scores to aid in interpretation of statistical estimates. Box-and-whisker plots (median, min-max) reported omentin-1 levels in controls, subjects with only TMD and subjects with TMD plus another pain condition. Binary logistic regression was used to calculate the odds ratio values (ORs) and 95% confidence intervals (CIs) for TMD. Finally, multivariate analysis adjusted for potential confounding covariates of study site, age, sex, and BMI.

**IRB**

Institutional review boards at all four study sites approved study procedures for OPPERA, and participants provided informed consent. This study was approved by the Biomedical Institutional Review Board of the University of North Carolina at Chapel Hill (UNC).

## RESULTS

One study participant was omitted from analysis due to an inadequate amount of blood plasma needed to measure omentin-1 levels. The final sample comprised 106 females and 38 males (Table 1). In unadjusted analysis, mean omentin levels were lower in TMD cases than controls, but failed to reach statistical significance (P=0.072, Table 2). There were no significant differences in sex, age, and BMI between cases and controls. Following adjustment for study site, age, sex, and BMI (Table 3) odds of TMD were 36% lower per standard deviation increase in circulating omentin-1 (OR=0.64, 95% CL: 0.43, 0.96, P=0.031). Odds of TMD were 2.7-fold higher in women than men. As compared to cases with ≥ 1 comorbid pain conditions (n = 72) and pain free participants (n = 54), median plasma omentin-1 levels were lower in cases with TMD only (n = 18) (Fig. 1).

## DISCUSSION

In this case-control study, ancillary to OPPERA, omentin-1 levels were lower in TMD cases than controls after adjustment for potential confounding. The fact that omentin-1 was measured in plasma, indicates that heightened inflammation in TMD is not confined to the temporomandibular tissues.

In *in vitro* studies, omentin-1 inhibited TNFα-induced vascular inflammation in human endothelial cells.[26] In another study, omentin-1 played a similar anti-inflammatory role by preventing the TNFα-induced inflammatory responses in vascular smooth muscle cells.[27] Kim and colleagues further showed that TNF-α, along with several interleukin cytokines, were detected in the synovial fluid of TMD cases as compared to healthy controls.[28] These studies suggest that omentin, in addition to its systemic effect, inhibits a specific inflammatory cytokine that is present in the joint of TMD cases.

Our finding of decreased omentin-1 levels in cases is similar to results from other studies. A recent study revealed that omentin-1 levels were significantly lower in patients with inflammatory bowel disease.[29] In another study, decreased secretion of omentin-1 in the synovial fluid of painful knee osteoarthritis was much lower than omentin-1 levels in the serum of these patients (2.49 vs. 23.76 μg/L).[30]

Lower omentin-1 concentration was found in blood plasma (taken via venipuncture) for those subjects with TMD only. Potential confounding effects of other cytokines may provide the answer as to why omentin-1 levels of the TMD plus another pain group were more similar to the control group. The findings from Slade and colleagues regarding levels of MCP-1 are similar to the findings in our study in that levels of the cytokines are TMD specific.[9] Even though our study did not find a statistically significant difference of omentin-1 levels between the control group and group with TMD plus another pain condition, omentin levels tended to be lower. Similarly in Slade et al., MCP-1 cytokine levels were only significantly associated with TMD in the absence of widespread pain.

There is a growing interest in identifying potential diagnostic biomarkers for pain in patients with TMD. For example, Slade and colleagues found that cytokine profiles differed among cases stratified on the basis of comorbid widespread palpation tenderness.[9] Elevated levels of various circulating inflammatory markers such as cytokine IL-8 were associated with TMD and widespread pain; whereas MCP-1 levels were associated with TMD only in the absence of widespread pain.

Recently, the relationship between proinflammatory cytokines and temporomandibular joint (TMJ) inflammation has been examined.[9,31] The release of TNF-α along with interleukins occurs in conjunction with TMJ inflammation.[31] These proinflammatory cytokines play a role in articular cartilage remodeling and deterioration as seen in osteoarthritis. Changes in the cartilage become noticeable via swelling and redness due to the nociceptors of the TMJ being stimulated by these inflammatory mediators. Moreover, Slade et al.[9] showed that in TMD cases and widespread pain, levels of the anti-inflammatory IL-1RA were lower.

Based on the emerging collective evidence for omentin-1 in epidemiologic studies, low levels of omentin exacerbate the putative effects of proinflammatory mediators. Therefore it is conceivable that a decrease in omentin-1 levels may be involved in the pathophysiology of TMD. Further studies are needed to clearly elucidate the plausible mechanism by which omentin-1 may contribute to persistent pain and development of pain. This information could motivate development of effective interventions to increase omentin-1 levels and other anti-inflammatory cytokines in an attempt to decrease inflammation, thereby reducing existing pain or preventing the development of new pain.

**Strengths and Limitations**

The ancillary case-control design, took advantage of the established infrastructure, protocols and rich dataset of the OPPERA parent study. Multiple study sites and community recruitment optimized the diversity and representativeness of the study population to improve the generalizability of the findings.

Potential limitations of this study merit consideration. First, the total number of participants in the ancillary case-control study was small. In addition, factors with the potential to affect inflammation such as alcohol, smoking, and medications were not controlled for during statistical analyses.

## CONCLUSIONS

Circulating levels of omentin-1 were lower in TMD cases than controls, suggesting a potential protective effect of omentin-1 against TMD pain mediated by anti-inflammatory pathways.

## TABLES

Table 1. Characteristics of chronic TMD cases and pain-free controls (column percentages), n=144

| | N | Percent | TMD Case (n=90) | Control (n=54) | P-value |
|---|---|---|---|---|---|
| **Sex** | | | | | |
| Male | 38 | 26.4 | 21.1 | 35.2 | 0.064 |
| Female | 106 | 73.6 | 78.9 | 64.8 | |
| **Age (years)** | | | | | |
| 18–24 | 55 | 38.2 | 32.2 | 48.2 | 0.452 |
| 25–29 | 32 | 22.2 | 24.4 | 18.5 | |
| 30–34 | 20 | 13.9 | 15.6 | 11.1 | |
| 35–39 | 18 | 12.5 | 13.3 | 11.1 | |
| 40–44 | 19 | 13.2 | 14.4 | 11.1 | |
| **Body mass index (kg/m$^2$)** | | | | | |
| Unweight/healthy (<25.00) | 83 | 57.6 | 57.3 | 61.5 | 0.691 |
| Overweight (25.00–29.99) | 34 | 23.6 | 23.6 | 25.0 | |
| Obese (≥30.00) | 24 | 16.7 | 19.1 | 13.5 | |
| Missing | 3 | 2.1 | | | |

Table 2: Mean (std. dev.) circulating omentin-1 concentration (μg/ml)

| | Mean | Std. dev. | P-value |
|---|---|---|---|
| **TMD case status** | | | |
| Case | 413.5 | 145.9 | 0.072 |
| Control | 464.8 | 191.8 | |
| **Sex** | | | |
| Male | 436.8 | 149.3 | 0.861 |
| Female | 431.3 | 172.0 | |
| **Age (years)** | | | |
| 18–24 | 408.4 | 141.4 | 0.174 |
| 25–29 | 452.9 | 181.7 | |
| 30–34 | 496.4 | 224.5 | |
| 35–39 | 383.8 | 106.2 | |
| 40–44 | 448.7 | 167.7 | |
| **Body mass index (kg/m$^2$)** | | | |
| Unweight/healthy (<25.00) | 423.6 | 159.2 | 0.289 |
| Overweight (25.00–29.99) | 469.7 | 194.8 | |
| Obese (≥30.00) | 407.8 | 137.6 | |

Table 3. Multivariate-adjusted association between standardized omentin-1 concentration and TMD (odds ratio (OR) and 95% confidence limits (CL), n=141

| | Site-adjusted OR (95% CL) | P-value | Multivariate-adjusted OR (95% CL) | P-value |
|---|---|---|---|---|
| **Standardized omentin (z-score)** | 0.70 (0.48, 1.02) | 0.066 | 0.64 (0.43, 0.96) | 0.031 |
| **Sex** | | | | |
| Male | | | Ref | |
| Female | | | 2.74 (1.13, 6.68) | 0.026 |
| **Age (years)** | | | | |
| 18-24 | | | Ref | |
| 25-29 | | | 1.76 (0.63, 4.92) | 0.280 |
| 30-34 | | | 2.94 (0.79, 10.95) | 0.108 |
| 35-39 | | | 1.31 (0.37, 4.67) | 0.681 |
| 40-44 | | | 2.17 (0.59, 7.93) | 0.242 |
| **Body mass index ($kg/m^2$)** | | | | |
| Unweight/healthy (<25.00) | | | Ref | |
| Overweight (25.00–29.99) | | | 1.29 (0.50, 3.33) | 0.603 |
| Obese (≥30.00) | | | 1.51 (0.48, 4.73) | 0.482 |
| Intercept | 0.60 (0.26, 1.40) | 0.239 | 0.17 (0.04, 0.62) | 0.008 |

## FIGURES

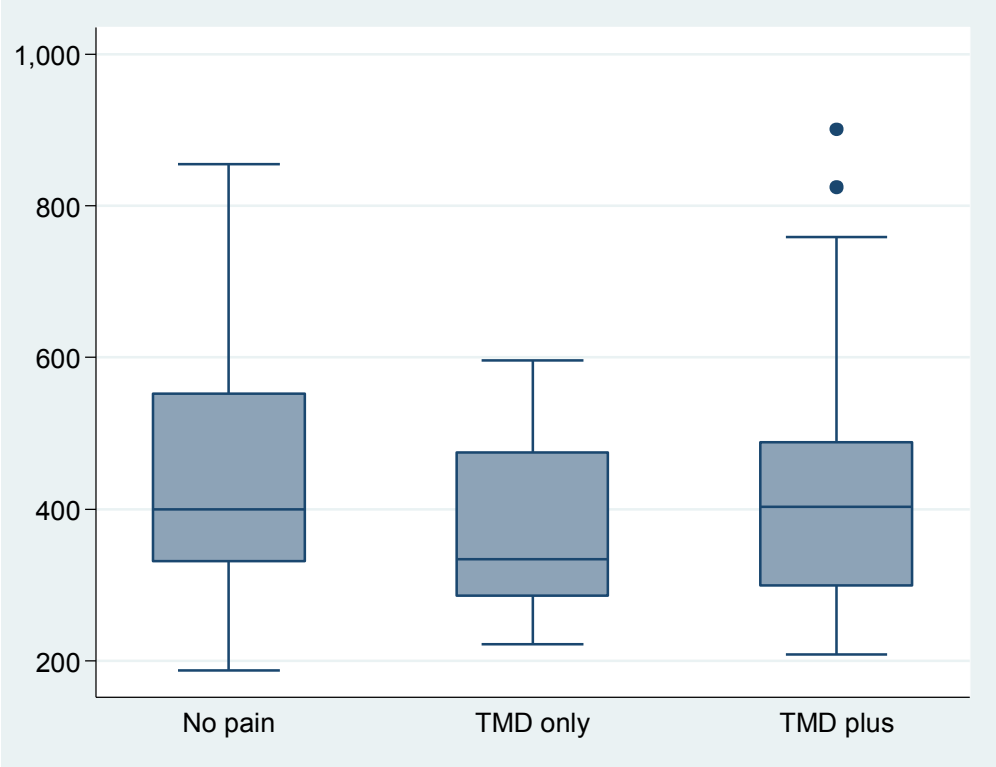


Figure 1. Box and whisker plot depicting plasma omentin-1 concentration (μg/ml) in pain-free controls (No pain, n=54), TMD cases with no other pain conditions (TMD only, n=18) and TMD cases with ≥1 other pain condition (TMD plus, n=72). Other pain conditions are migraine, low back pain or irritable bowel syndrome. The median value is the horizontal line subdividing the box. The length of the box represents the interquartile range (IQR). Whiskers extend to 1.5 IQR of the nearest quartile. Solid circles represent outlying values. Plasma omentin-1 levels are reduced only in TMD patients.

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