Temporomandibular Disorders and Anatomic-Psychologic Score

Garrett Masuda, DDS

A thesis submitted in partial fulfillment for the Degree of Master of Science in Orthodontics.

Oregon Health & Science University
Portland, OR

2024

Temporomandibular Disorders and Anatomic-Psychologic Score

Garrett Masuda, DDS

Master of Science in Orthodontics Research Committee

Laura Iwasaki, DDS, MSc, PhD
Chair
Department of Oral and Craniofacial Sciences

Jeffery Nickel, DMD, MSc, PhD
Graduate Program Director
Division of Orthodontics
Department of Oral and Craniofacial Sciences

Saulo L. Sousa Melo, DDS, MS, PhD
Senior Director of Imaging and Radiation Safety, Division of Oral Diagnostic Sciences
Department of Oral and Craniofacial Sciences

Acknowledgements

Thank you to my family, friends, and my fellow orthodontic residents for your continuous encouragement and support.

Thank you to my thesis committee for your guidance and feedback throughout the research process.

<u>Table of Contents</u>

List of Figures

List of Tables

Temporomandibular Disorders and Anatomic-Psychologic Score

Garrett Masuda, DDS[a]
Laura R. Iwasaki, DDS, MSc, PhD[b]
Jeff C. Nickel, DMD, MSc, PhD[c]
Saulo L. Sousa Melo, DDS, MS,PhD[d]

[a]Graduate Student, Department of Oral and Craniofacial Sciences, Oregon Health & Science University, Portland, OR

[b]Professor, Division of Orthodontics, Chair, Department of Oral and Craniofacial Sciences, Oregon Health & Science University, Portland, OR

[c]Professor Provisional, Graduate Program Director, Division of Orthodontics, Department of Oral and Craniofacial Sciences, Oregon Health & Science University, Portland, OR

[d]Associate Professor, Division of Oral Diagnostic Sciences, Department of Oral and Craniofacial Sciences, Oregon Health & Science University, Portland, OR

Abstract

Title: Temporomandibular Disorders and Anatomic-Psychologic Score

Objectives: Currently, it is not possible to accurately predict the prognosis of temporomandibular disorders (TMDs). The objective of this study was to test two hypotheses concerning predicting longitudinal changes in the temporomandibular joint (TMJ) of human subjects. Hypothesis 1: To test if Anatomic-Psychologic Score (APS), an instrument which utilizes easily measured variables, predicted longitudinal changes in TMJ tissue integrity. Hypothesis 2: To test if Machine Learning Models accurately rank ordered anatomic and psychosocial variables that were associated with longitudinal changes in TMJ tissue integrity.

Methods: According to Institutional Review Board oversight, subjects ≥18 years-of-age were recruited. Baseline and >5-year follow-up data were obtained for Axis I (physical assessment) and Axis II (psychosocial status) of Diagnostic Criteria for Temporomandibular Disorders (DC/TMD). Cone-beam computed tomography (CBCT) and magnetic resonance imaging (MRI) were used to determine whether or not there were changes in TMJ integrity. A calibrated radiologist characterized TMJ integrity, and created 3 diagnostic groups based on if the combined hard and soft tissue diagnoses had no change (Group A), got better (Group B), or got worse (Group C). Baseline variables used in APS were from two domains. Firstly, from the psychosocial domain of DC/TMD Axis II, numeric data was derived from the Patient Health Questionnaire-15 (PHQ-15) and 7-Question Behavior Score (7QBS). Secondly, CBCT images which were used to derive anatomic domain measures of i) sagittal occlusal plane angle and anteroposterior position, ii) mandibular ramus length, and iii) variables associated with the axial plane geometry of the mandibular condyle. This included condyle loading area and aspect ratio, and angle of the condyle relative to the midsagittal plane. Means and standard deviations of APS and its component variables at baseline were calculated. To test Hypothesis 1, ANOVA was used to test for significant differences ($p<0.05$) in APS scores amongst the 3 diagnostic groups. Hypothesis 2 was tested using three machine learning models, which rank ordered variables of importance in predicting TMJ integrity changes, and were evaluated according to accuracy of prediction (>0.90), and sensitivity and specificity (0.70 – 0.90).

Results: 31 subjects (18 females and 13 males) met the inclusion criteria and right and left condyles were included for each subject resulting in a total of 62 TMJs. MRI and CBCT TMD diagnoses by the radiologist showed that 36 TMJs (58%) had no change from T1 to T2, 11 TMJs (18%) got better, 10 TMJs (16%) got worse, and 5 TMJs (8%) had no diagnoses. APS was not significantly different amongst TMJ integrity groups A, B, or C. Gradient Boosting Machine modeling had a 74% predictive accuracy (sensitivity = 0.66, specificity = 0.81) of TMJ integrity change and had condylar area as the variable of highest importance. Classification Tree modeling had a 61% predictive accuracy (sensitivity = 0.53, specificity = 0.77) and also had condylar area as the variable of highest importance. Support Vector Machine modeling had a 60% predictive accuracy (sensitivity = 0.45, specificity = 0.70) and had major axis as the variable of highest importance. Classification Tree modeling identified condylar area ≥ 90 mm^2, PHQ-15 < 6, and major axis < 19 mm predicted TMJ integrity changes, and were 83-100% predictive of TMJs that had no change, 54% predictive of TMJs that got better, and 54% predictive of TMJs that got worse. Sample sizes of 88 to 180 TMJs are needed to produce a 95% confidence interval with a width of no more than 0.2 for sensitivity and specificity of 0.7 to 0.9, assuming equal prevalence.

Conclusions: The proposed novel APS equation was not predictive of longitudinal changes in TMJ integrity. Machine learning models reported that condylar area and variables associated

with the geometry of mandibular condylar area (major axis, minor axis, aspect ratio) have high relative importance in the predictive accuracy of TMJ changes.

1. Background

Temporomandibular Disorders Introduction

Temporomandibular disorders (TMDs) encompass more than thirty conditions that can result in recurrent or chronic pain and dysfunction of the temporomandibular joint (TMJ) and jaw muscles (1). TMDs are categorized into three main classes: disorders of the TMJ including the disc, disorders of the masticatory muscles, and headaches associated with TMDs (1). Disorders of the TMJ include joint pain referred to as arthralgia, improper positioning of the disc, and destruction of condylar bone known as degenerative joint disease (DJD) of the TMJ. Disorders of the masticatory muscles include myalgia, pain localized in one area, and myofascial pain with or without referral, pain that spreads beyond its point of origin (1).

Worldwide the prevalence of TMDs is estimated to be between 5% and 12% (2). Within the United States, 11 to 12 million adults reported having pain within the TMJ region (1). Currently, after chronic lower back pain, TMD is the second most common musculoskeletal condition causing pain and disability (3). Unlike other chronic pain conditions, TMDs have higher prevalence rates among younger age populations with symptoms peaking between 20 and 40 years of age (2,4). TMDs also affect women two times more than men and treatment is sought more often in women using oral contraceptives or supplemental estrogen (2).

The exact causes and mechanisms for TMDs are unclear, and symptoms present with no obvious reason for a majority of TMD cases (1). Currently, TMD is thought to be multifactorial in origin with genetics, pain perception, psychological stress, and mechanobehavior playing roles (1,5). Due to no clear causes of TMDs and a wide presentation of symptoms, identifying and treating TMDs pose a challenge.

Diagnosis of TMDs

Since 1992, the most widely utilized diagnostic protocol for TMDs has been the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) (6). The RDC/TMD was created so that clinicians and researchers would have more generalizable and standardized criteria and nomenclature to help better diagnose patients (7). Since its conception, the RDC/TMD has undergone multiple revisions and the diagnostic algorithms for TMDs have been assessed for validity through the Validation Project and assessed for reliability through the TMJ Impact Project (7). The most updated version, the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD), has been proven to be valid in diagnosing the most common pain-related TMDs and for one intra-articular disorder (7). The DC/TMD is a two-axis algorithm based on the biopsychosocial model of pain. Axis I is a physical assessment and Axis II is a psychosocial status assessment (7). Taken together, the two axes provide a physical TMD diagnosis while also identifying relevant patient characteristics that influence TMD expression (7).

Axis I Introduction

Axis I uses history, standardized examinations, and imaging for certain conditions to obtain a physical assessment (7). History is obtained through the Axis I TMD Pain Screener which is a validated self-reporting instrument (7). Standardized examinations include evaluation of jaw movements, palpation of the TMJ and associated muscles, detection of joint noises, and measurements of unassisted or assisted opening (7). For TMJ disc disorders and DJD, magnetic resonance imaging (MRI) and computed tomography imaging, respectively, are needed to confirm diagnoses (7,8)

The Axis I TMD Pain Screener is recommended to be given to all patients in any clinical setting as a positive screening can inform clinicians that further TMD evaluation is required (7).

Axis II Introduction

Axis II which measures psychosocial status is organized into two levels: screening instruments and comprehensive instruments (7). If a patient has a positive Axis I TMD Pain Screener or has had persistent pain for more than 6 months in the TMJ region then Axis II screening instruments are recommended (7). Screening instruments include five self-reporting screeners that assess pain intensity, pain location, pain-related disability, jaw functional limitations, psychological concern, and parafunctional behaviors (7). Positive findings in the screening instruments then indicate that further details are required through the comprehensive instruments (7). Comprehensive instruments include 81 questions that further detail screening instrument assessments as well as assess for depression and anxiety levels (7).

Two examples of comprehensive instruments are the Patient Health Questionnaire-15 (PHQ-15) and the Oral Behaviors Checklist (OBC).

PHQ-15

PHQ-15 is a 15-question self-administered version of the PRIME-MD diagnostic instrument for common mental disorders (9) (Appendix A). It measures the severity of 15 somatic symptoms and each symptom is scored 0: “not bothered at all”, 1: “bothered a little”, or 2: “bothered a lot” (9). Total PHQ-15 scores represent somatic symptom severity with 5, 10, and 15 points representing the cutoff points for low, medium, and high severity (9). PHQ-15 has strong association to symptom-related difficulty and functional status (9).

OBC

The Oral Behavior Checklist (OBC) is a self-reported 21-question validated instrument that assesses the frequency of oral parafunctional behaviors during the preceding month (10) (Appendix B). The OBC quantifies two ‘activities during sleep’ and 19 ‘activities during waking hours’ using five frequency response options (0-4) and the total OBC score is calculated by taking the mean of the questions (10). Oral behaviors have been shown to be a risk factor in the development of TMDs as it has been suggested that they cause overload and microtrauma to the TMJ and associated muscles (10).

Prognosis of TMDs

Currently, predicting the prognosis of TMDs in patients is not possible. Some models to understand the prognosis of TMDs over time have been proposed. One model suggests that TMJ intra-articular disorders progress from a normal joint to disc displacement with reduction (DDwR) to disc displacement without reduction (DDwoR) and then to DJD (11). However, Schiffman et al. reviewed 789 TMJs and diagnostic changes in 401 subjects after an average of 8 years and showed that hard and soft tissue TMJ diagnoses can exhibit progression, no change, or reversal over time (12). In the majority of joints, no change was noted in the hard tissue (71%) and soft tissue (76%) diagnoses (12). Progression and reversal of the severity of joint diagnoses showed similar percentages, with hard tissue progression in 15% and reversal in 14%, and soft tissue progression in 14% and reversal in 10% (12). Further, Schiffman et al. showed that soft tissue TMJ diagnoses had a statistically significant association with the diagnostic changes of hard tissue TMJ diagnoses while the reverse was not statistically significant (12).

Utilizing 614 TMJs from the cohort of TMJs reviewed by Schiffman et al., Chataracherd et al. showed that TMJ intra-articular status (normal joint, DDwR, DDwoR, DJD) had no association with TMJ impact (pain, jaw function, disability) and stated that other models for progression need to be explored (13).

Further research considering a combination of multiple variables is indicated. Given that complex interactions between biology, biomechanics, psychology, and social factors may be involved, a number of candidate variables and the evidence for their importance will be described below (14).

Physical Assessment Variables

As will be postulated in this study, measurements of certain physical TMJ and associated structures may be factors in the prognosis of TMD (13). Certain angular and linear craniomandibular anatomical measurements have been shown to increase TMJ loading, and increased TMJ mechanical work was significantly greater in TMJs with hard tissue and soft tissue diagnoses that progressed to a worse state compared to baselines (5). Some of the candidate measurements are introduced in the sections that follow.

Ramal Length

In a retrospective study using lateral and posteroanterior cephalograms from the American Association of Orthodontists Foundation Legacy Collection and computer-assisted numerical modeling, Desai et al. compared predicted TMJ compressive stresses during incisor biting in 36 dolichofacial subjects and 29 meso-brachyfacial subjects at three time-points, where averages ages were 6 (T1), 12 (T2), and 18 years (T3) (15). Dolichofacial subjects were defined by having Frankfort Horizontal-mandibular plane angles (FHMPA; Figure 1) over 27° and meso-brachyfacial subjects were defined by having FHMPAs less than 27° at T3 (15).

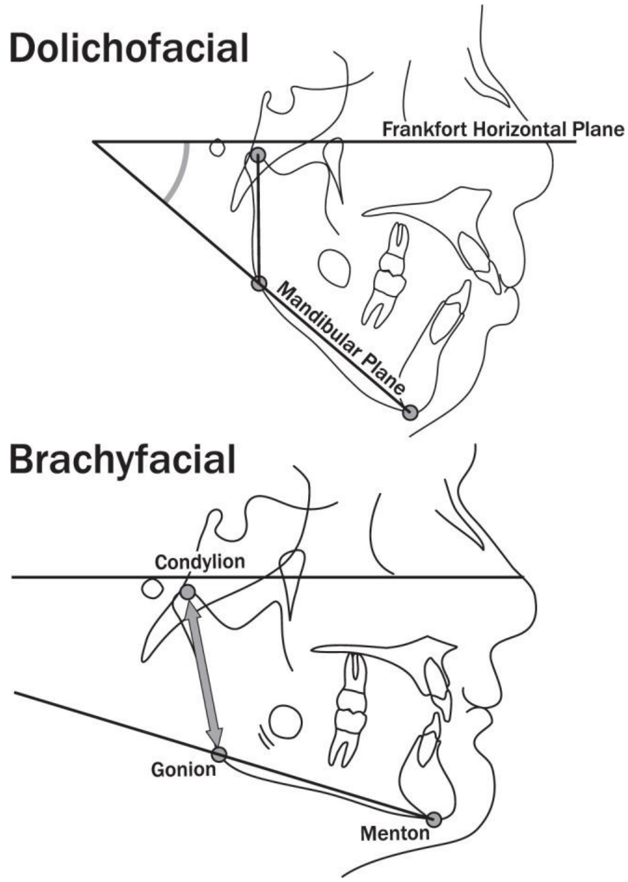

Figure 1 (15): Facial Phenotypes. The Dolichofacial phenotype (top) has a steeper Frankfort Horizontal-mandibular plane angle (FHMPA) and shorter ramal length from condylion to gonion than the Brachyfacial phenotype (bottom).

FHMPAs were significantly larger in dolichofacial compared to meso-brachyfacial subjects at all three time-points and ramal lengths (condylion-gonion, Figure 1) were significantly shorter in dolichofacial compared to meso-brachyfacial subjects at T2 (53.0 ± 3.7 mm versus 55.6 ± 3.3 mm) and T3 (59.3 ± 5.6 mm versus 64.6 ± 4.9 mm) (15). Cephalograms in the two views provided three-dimensional craniomandibular anatomical geometries of each of the subjects at the three time-points that were used in numerical models to predict subject-specific TMJ loads for a range of applied incisor biting angles (15). TMJ compressive stresses (force or load/area) were estimated based on published age-related anteroposterior and mediolateral dimensions of the condyle and published differences in TMJ articular congruency (shape-matching) when the mandibular was in retruded versus protruded (incisor-biting) position (15). For the same biting tasks, predicted TMJ compressive stresses increased over the three time-points and were significantly larger in dolichofacial compared to meso-brachyfacial subjects (15). Notably, higher FHMPA and shorter ramal lengths were correlated with larger TMJ compressive stresses (15).

Riddle et al. also investigated ramal lengths in dolichofacial and brachyfacial subjects by prospectively analyzing TMJ mechanics and behaviors (mechanobehavior) through TMJ energy densities (ED) and duty factors (DF), respectively (16). Energy densities (mJ/mm^3) are measures of mechanical work input per disc tissue volume between mandibular condyle and temporal eminence loading areas (16). Increases in TMJ compressive stresses (MPa) cause an increase in ED which can be measured using dynamic stereometry (16). Duty factors (%), defined as percentage of muscle activity duration/total recording time, are measured from electromyography (16). TMJ ED and DF have been combined as a mechanobehavior score ($MBS = ED^2 \times DF$, $(mJ/mm^3)^2\%$) and Riddle et al. examined 73 facial phenotype subjects (50 females, 23 males) to determine if MBS was correlated with ramal lengths (16). Ramal length (condylion-gonion, mm) was derived from a CBCT or lateral and posteroanterior cephalograms and MBS was calculated from dynamic stereometry and electromyography (16). Average right and left TMJ ED were 0.7-23.1 mJ/mm^3 and average DF were 0.003%-10.8% during the day and 0.012%-9.3% during the night (16). No significant difference between sexes were present for ED and DF (16). MBS based on the averages were 0.5-328.2 mJ/mm^3 (16). Polynomial regression analyses showed that ramal length was non-linearly correlated with MBS (females: $R^2 = 0.57$, males: $R^2 = 0.81$) and that MBS was significantly different between subjects with brachyfacial features and two subgroups of subjects with dolichofacial features (16).

Occlusal Plane Angle and Occlusal Plane Anteroposterior Position

Retrospectively, Glovsky et al. assessed records from 44 orthognathic jaw surgery patients (28 females and 16 males) in which 30 had mandibular advancement and 14 had mandibular setback procedures (17). Pre- and post-surgery CBCT images of the head and jaws were used to obtain craniomandibular anatomy landmarks that were measured in three dimensions to create a geometry file. Numerical modeling was then utilized to examine the effects of the post-surgery versus pre-surgery occlusal plane angle (Frankfort Horizontal-Occlusal Plane (FH-OP)) and anteroposterior mandibular position (Figure 2) changes on mean ipsilateral and contralateral TMJ compressive stress changes during right canine biting (17).

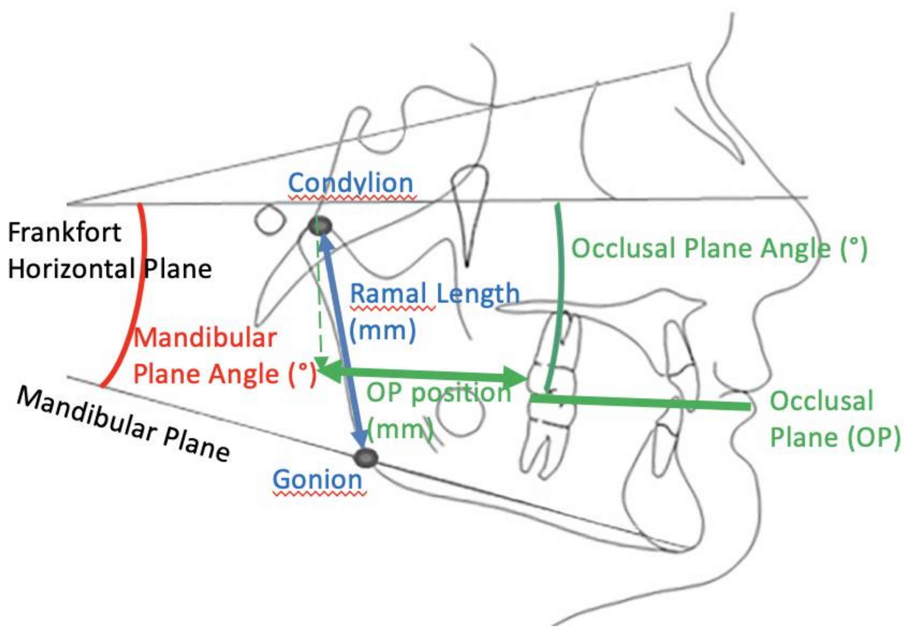

Figure 2: Cephalometric Tracing. Cephalometric angular and linear craniomandibular anatomical measurements from cone-beam computed tomography (CBCT).

The modeling exhibited the largest increases in TMJ compressive stresses post-surgery compared to pre-surgery occurred for females in the mandibular setback with decreased FH-OP angle group (n=6, ipsilateral: +0.005 ± 0.003 MPa, contralateral: +0.007 ± 0.003 MPa) (17). In comparison, TMJ compressive stresses for females showed the largest decreases post-surgery compared to pre-surgery in the mandibular setback with increased FH-OP angle group (n=2, ipsilateral: -0.011 ± 0.006 MPa). For males, TMJ compressive stresses post-surgery compared to pre-surgery showed decreases for the three types of surgeries represented (mandibular advancement and setback with increased FH-OP angle and mandibular setback with decreased FH-OP angle), where the largest decreases were seen in the mandibular setback with decreased FH-OP angle group (n=6, contralateral: -0.008 ± 0.003 MPa) (17).

Condylar Area

Per definition of stress (force/area), a smaller area compared to a larger area with the same unit of force will have a higher amount of stress. In the Glovsky et al. study on 44 orthognathic surgery patients, condylar loading area was also derived using the pre-surgical CBCT images (17). Condylar area (major axis x minor axis, mm^2, Figure 3) was calculated using the maximum lengths of the major axes (largest linear distance between lateral and medial condylar poles) and minor axes (smallest linear distance of the condyle measured perpendicular to the major axis) of the right and left TMJ condyles (17).

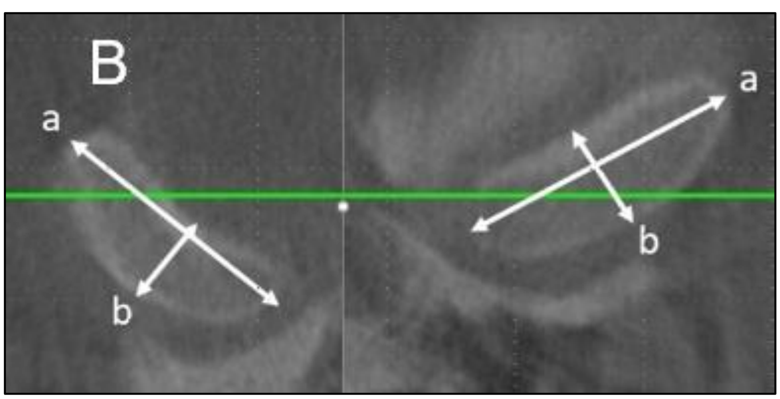

Figure 3: Condylar Area. Product of the major (a) and minor (b) axes of mandibular condyles was used to determined area (mm^2).

The CBCT images demonstrated that males (144 ± 7 mm^2) have significantly greater condylar areas than females (124 ± 5 mm^2) (17). The effects of this condylar size difference between males and females is not fully understood but may be a factor in the increased prevalence of TMDs in females compared to males.

Condylar Angle and Aspect Ratio

The condylar angle has been defined as the angle between the major axis and the x-y plane (midline) measured on the right and left (Figure 4) and the condylar aspect ratio has been defined as the major axis divided by the minor axis (Figure 3).

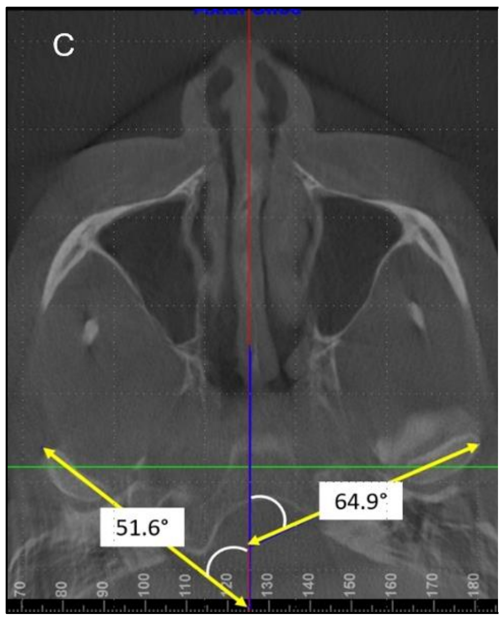

Figure 4: Condylar Angle. Angle (white arc) measured anteromedially between major axis (yellow) and midline (blue) on right and left.

Unpublished data from a follow up of adults with and without TMJ disc displacement were used to assess condylar measurements versus TMJ stress-field velocity in 27 subjects (53 TMJs). TMJ stress-field velocities were calculated using the dynamic stereometry methods described by Gallo et al. in their TMJ energy densities and jaw closing movement study (18).

The 27 subjects had bilateral MRIs of their TMJs recorded and jaw tracking was performed to record the positions of each subject's jaws while biting into an occlusal registration appliance with head reference system and without the appliance while performing jaw movements. Dynamic stereometry was then applied using three-dimensional reconstructions of TMJ structures derived from the MRIs (anatomic data) and the animation of these structures via jaw tracking movements (kinematic data) using the head reference system, which was common to both anatomic and kinematic data sets. Stress-field velocity (mm/s) was one of the component variables derived from the dynamic stereometry and was used in the calculation of energy densities. The data from the 53 TMJs showed that the product of the condylar angle and aspect ratio (see Methods) was inversely and non-linearly related to TMJ stress-field velocity (Figure 3).

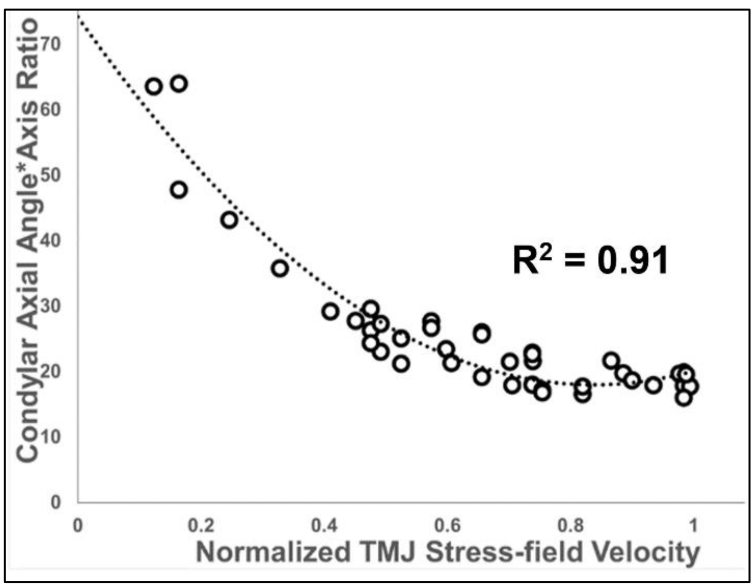

Figure 5: Condylar Angle and Aspect Ratio. Condylar measurements (Condylar Angle X Axis Ratio (also known as Aspect Ratio) versus normalized stress-field velocity in 53 TMJs.

Psychosocial Variables

PHQ-15

PHQ-15 is a 15-question self-administered instrument for common mental disorders that is described in more detail above (9).

7QBS

The 7-Question Behavior Score (7QBS) is a shortened version of the Oral Behavior Checklist (OBC) which assesses the frequency of oral parafunctional behaviors (7). This 7-question self-administered instrument scores the following parafunctional activities from the comprehensive OBC on a 0-4 ordinal scale: “press tongue against teeth”, “hold-jut jaw forward/side”, “clench/waking”, “hold jaw in rigid-tense position”, “press-touch-hold teeth”, “hold-tighten tense muscles”, “clench or grind/sleep” (Appendix C). The sum of the responses yields the total 7QBS.

$(PHQ\text{-}15)^2$ x 7QBS

Jaw-use behaviors and the psychosocial status of individuals may also be factors in the prognosis of TMD. PHQ-15 has been shown to be correlated with mechano-allostatic loads which reflect the masseter muscle activity magnitudes (19). The 7QBS has been shown to aid in differentiation of TMD groups (20). Using unpublished data from the same follow-up study of 27 subjects and 53 TMJs as describe above, masseter duty factors (% time of jaw muscle activity versus total recording time) were tested against Axis II variables and exhibited that the product of $(PHQ\text{-}15)^2$ and 7QBS correlated to day-time masseter duty factors at 2 N or less jaw-loading magnitudes (Figure 6). Therefore, $(PHQ\text{-}15)^2$ x 7QBS may be a marker for masseter muscle activities during awake jaw-loading, and awake jaw-loading involving low magnitudes of masticatory muscle activities has been shown to be associated with the presence of pain in the orofacial region (21).

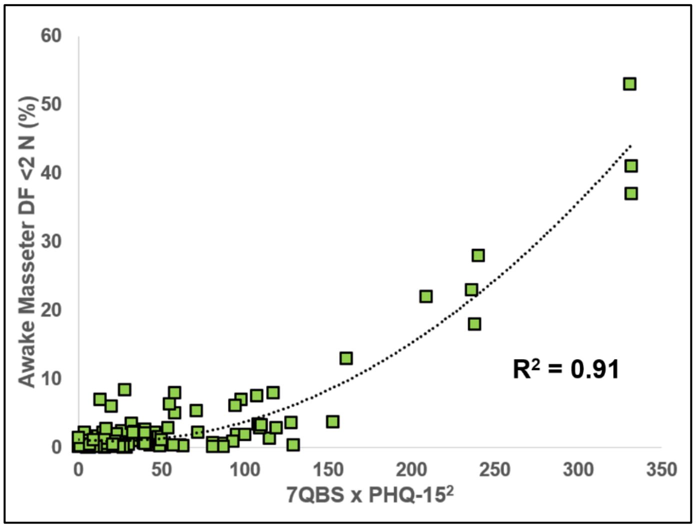

Figure 6: (PHQ-15)^2 x 7QBS. Awake-state masseter duty factor (DF) at ≤2 N loads versus psychosocial variables, 7-Question Behavior Score (7QBS) x [Patient Health Questionnaire-15 (PHQ-15)]^2.

Anatomic-Psychologic Score (APS)

The Anatomic-Psychologic Score (APS) is a novel instrument proposed by this study that utilizes easily measured linear and angular anatomical measurements (described above) from a CBCT image and self-reported psychophysiological data from DC/TMD Axis II questionnaires in order to predict the prognosis of TMDs over time.

2. Significance and Aims

TMDs can significantly impact individuals by inhibiting daily activities, affecting psychosocial functioning, and lowering the quality of life (7). TMDs can also have significant societal impacts. In the past decade, TMD pain management costs have doubled in the United States to an annual cost of $4 billion (3).

Despite a relatively high prevalence rate (5-12%), etiology, prognostic mechanisms, and predictable treatment pathways are unknown (3). As stated by Schiffman et al., “Currently, we cannot predict which individuals will progress, and no treatments, including TMJ surgery, can predictably prevent progression of either soft or hard tissue disorders” (12).

To address the current inability to predict the progress of TMDs, the objective of this study was to test two hypotheses concerning predicting longitudinal changes in the TMJ of human subjects. Hypothesis 1: To test if Anatomic-Psychologic Score (APS), an instrument which utilizes easily measured variables, predicted longitudinal changes in TMJ tissue integrity. Hypothesis 2: To test if Machine Learning Models accurately rank ordered anatomic and psychosocial variables that were associated with longitudinal changes in TMJ tissue integrity.

3. Methods

Subjects

Adult subjects were recruited from the University of Buffalo School of Dental Medicine (UBSDM) from a sample population of 118 subjects who participated in a parent study between November 2011 and May 2017 (baseline) (22). Inclusion criteria for the parent study were: age 18 years or older, with or without TMJ disc displacement as determined by magnetic resonance imaging, and with or without TMD-associated pain. Exclusion criteria for the parent study were: oral tissue inflammation, dental caries, extensive or missing dental restorations, multiple missing teeth, inability to follow study protocols, or past TMJ trauma or musculoskeletal disease. Subjects for the follow-up current study met the inclusion criteria of parent study participants with previous TMJ images ≥3 years old and exclusion criteria of inability to complete the protocols of the current study and females who were pregnant. Institutional Review Board-approved protocols (Appendix D) were used and all subjects gave written informed consent to participate. Axis I baseline and follow-up data included a CBCT of craniofacial structures and an MRI of the TMJ. Axis II baseline and follow-up data included PHQ-15 and 7QBS instruments.

APS Equation

In search for a clinical tool to help improve assessment and risk stratification of TMD diagnoses, the following equation was proposed, based off of CBCT measurements and Axis II instruments:

$$APS = \left[\frac{1}{(Condylar\ Angle\ x\ Aspect\ Ratio)}\right] x\ \left[\frac{Occlusal\ Plane\ Angle\ x\ Position}{Ramal\ Length\ x\ Condylar\ Area}\right] x\ [(PHQ15)^2\ x\ 7QBS]$$

MRI and CBCT TMD Diagnoses

A calibrated radiologist was blinded to Axis I clinical exam data and Axis II data. The calibrated radiologist interpreted baseline and follow-up MRI and CBCT images using the image analysis criteria set forth by the RDC/TMD Validation Project to characterize if the hard tissue diagnosis, soft tissue diagnosis, and overall TMJ integrity diagnosis (hard tissue + soft tissue diagnosis) A. had no change, B. got better, or C. got worse (8).

Physical Assessment Measurements

Time 1 (T1, baseline) CBCT image data sets (DICOMM files) for each subject were uploaded into commercially-available imaging software (Dolphin™, Dolphin Imaging & Management Solutions, Chatsworth CA) by two calibrated investigators who were blinded to TMD diagnoses and Axis II data. The three-dimensional (3D) head image, reconstructed from the CBCT image data set of each subject, was oriented via the software to have anatomy in an x-y-z orthogonal axis system (Figure 7). In the 3D viewer mode, the xy plane was oriented first, parallel to the Occlusal Plane, defined as the best-fit plane through the buccal cusps of maxillary first molars and premolars on the left and right sides (Figure 7A-B). Next the xz plane, defined as the best-fit plane through the right and left condylions (most anterior and superior bony surface point of the mandibular condyle) was oriented using the inferior (Figure 7C), right, and left views of the three-dimensional head image (23). The yz plane was then placed through the best-fit facial midline in the frontal view (Figure 7D) that roughly passed through nasion (mid-point of junction of the frontal-nasal suture), the anterior nasal spine of the maxillary bone, and menton (most inferior midline point on the mandibular symphysial outline) (23). Finally, all three planes were reconfirmed in all aforementioned views.

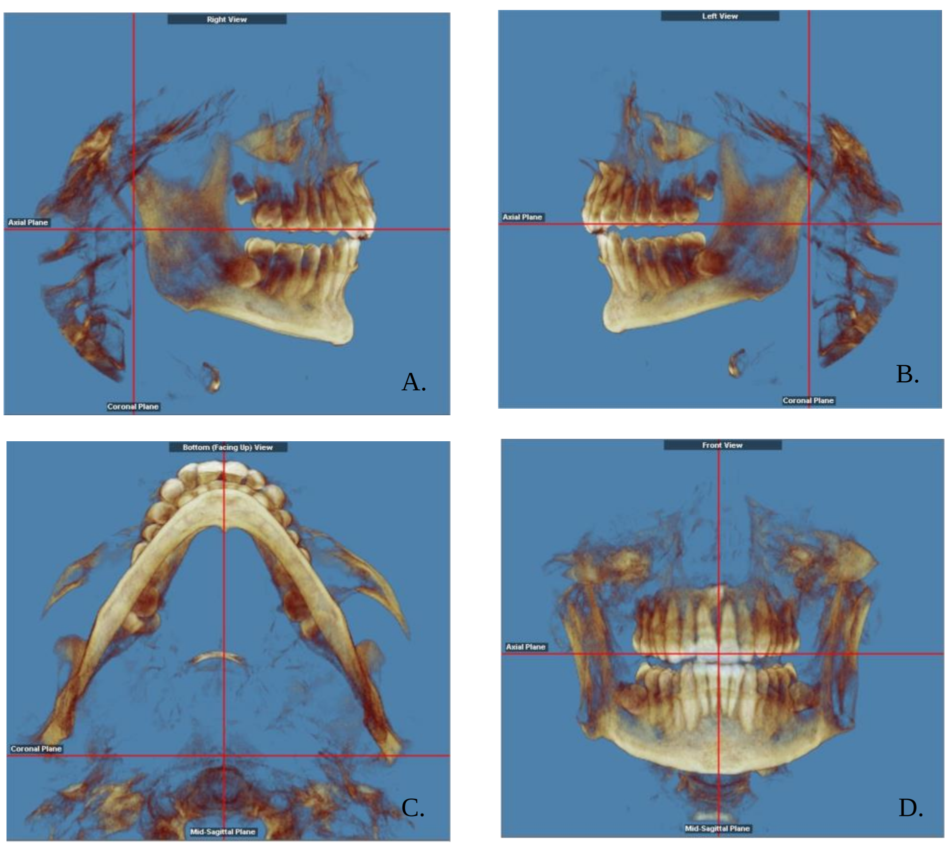

Figure 7: Three-Dimensional Head Image Orientation. A. Right lateral view with xy plane (Axial Plane) and xz plane (Coronal Plane). B. Left lateral view. C. Inferior axial

view with xz plane and yz plane (Mid-Sagittal Plane). D. Frontal view with xy plane and yz plane.

Once three-dimensional orientation was established, the following angular and linear measurements were identified and measured on right and left sides (Figures 2-4). Screen captures of each digital measurement were taken and used for recording.

Occlusal Plane Angle (°): angle between Occlusal Plane and Frankfort-Horizontal Plane, which intersects porion and orbitale, defined as:

-Porion: most superior and superficial bony surface point of the external auditory meatus (24)

-Orbitale: most inferior bony surface point of the orbit (23)

To measure occlusal plane angle, right and left lateral cephalograms were extrapolated from the three-dimensional oriented CBCT. Using the software's "Annotations" tool, a four-point angle of orbitale, porion, a distal point on occlusal plane, and a mesial point on occlusal plane were used on the right and the left cephalograms to obtain the two occlusal plane angles (Figure 8).

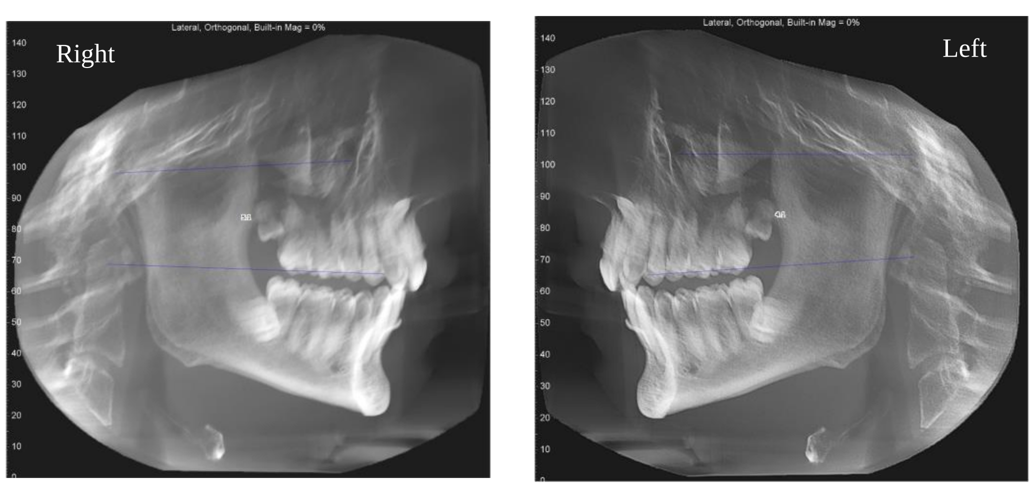

Figure 8: Occlusal Plane Angle. Right and left lateral cephalograms with four-point angle measurements through orbitale, porion, a distal point on occlusal plane, and a mesial point on occlusal plane.

<u>Occlusal Plane Anteroposterior Position (mm):</u> linear distance from distal contact of the maxillary first molar along Occlusal Plane to a point perpendicular to condylion

This linear measurement was obtained in the software's 3D CBCT viewer where the "Digitize/Measurement" 2D line tool can be used on right and left lateral oriented views. A straight line was placed from the distal contact of the maxillary first molar perpendicular to the xz plane that intersected condylion and measured using the software (Figure 9).

<u>Ramal Length (mm):</u> linear distance between condylion and gonion

-Gonion: midpoint of the angle of the mandible (23)

Using the right and left lateral oriented views in the 3D viewer, the Digitize/Measurement 2D line tool was used to measure the ramal lengths (Figure 9).

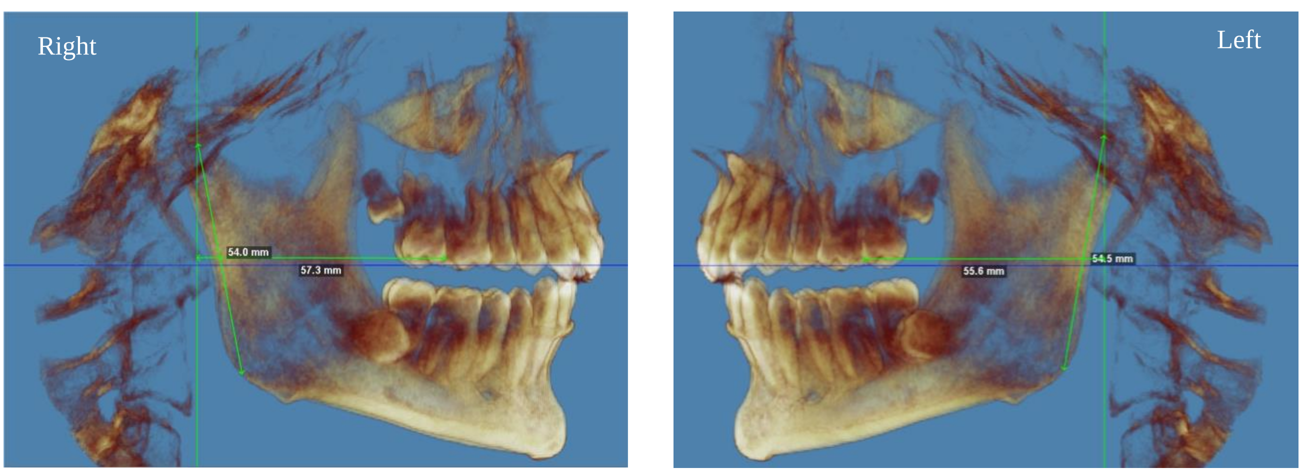

Figure 9: Occlusal Plane Anteroposterior Position and Ramal Length. Right and left three-dimensional oriented views with 2D line measurements of occlusal plane anterior posterior position and ramal length.

Condylar Area (mm^2): Major Axis x Minor Axis

-Major Axis: largest linear distance between medial and lateral condylar poles

-Minor Axis: smallest linear distance measured perpendicular to the major axis

In the 3D viewer, the axial slice view showing the greatest major axis on the right and left sides, independently, was used in conjunction with the Digitize/Measurement 2D line tool to first measure the major axis and then to make a perpendicular line measurement for the minor axis (Figure 10).

Condylar Angle (°): angle between the major axis and yz plane

In the same axial slice used to identify the right and left major axes and minor axes, the Digitize/Measurement 2D angle tool was used to measure the anteromedial angle between the oriented mid-sagittal plane (yz plane) and the major axis on right and left sides (Figure 10).

Aspect Ratio: Major Axis / Minor Axis

Measurements of major axis divided by minor axis for each condyle was used to calculate the aspect ratio (Figure 10).

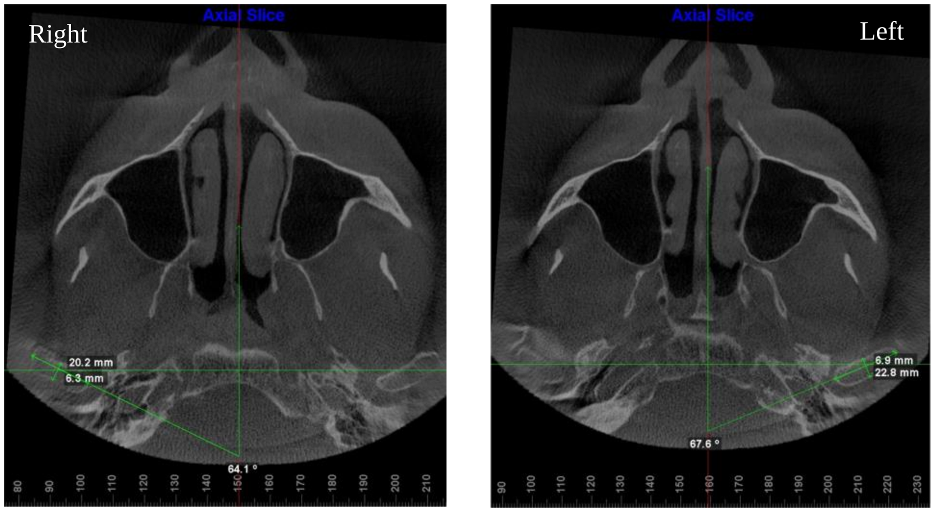

Figure 10: Major Axis, Minor Axis, and Condylar Angle. Right and left axial slices chosen based off the largest linear distance between medial and lateral condylar poles of each condylar head (major axis), showing minor axis, which was shortest condylar width perpendicular to the major axis, and the condylar angle, which was the anteromedial angle between the major axis and midsagittal plane.

Reliability Tests

After T1 subject CBCT measurements were obtained, two weeks later, 10 randomly selected T1 subjects' CBCTs were re-oriented and re-measured independently by the two calibrated investigators. Intraclass correlation coefficient (ICC) estimates and their 95% confident intervals were calculated based on an absolute-agreement, 2 way mixed-effects model.

Psychosocial Measurements

T1 PHQ-15 and 7QBS scores were extracted from the UBSDM subjects' dataset and added to a data sheet by recording as total scores between 0-30 and 0-28, respectively, for each subject.

Data and Statistical Analyses

Means and standard deviations of APS and component variables at T1 were calculated for the overall sample. For physical assessment variables, each TMJ (right and left) was measured while psychosocial variables for a subject were used for their right and left TMJs. APS was tested against T1-T2 overall TMJ integrity groups using analysis of variance (ANOVA). Significance was defined by $p<0.05$. Overall TMJ integrity groups, Group A (no change), Group B (got better), or Group C (got worse), were defined as the combined diagnosis of hard and soft tissue integrity diagnoses. If both hard and soft tissue diagnoses had no change then Group A (no change) was denoted and if both hard and soft tissue diagnoses got worse then Group C (got worse) was assigned. If one of the hard or soft tissue diagnoses got better or got worse in combination with a no change diagnosis for the other tissue type, then the got better or got worse diagnosis took precedent and the TMJ was assigned Group B (got better) or Group C (got worse), respectively. If one of the hard or soft tissue diagnoses got better and the other got worse, then Group C (got worse) was assigned.

Machine learning models: Gradient Boosting Machine (GBM), Support Vector Machine (SVM), and Classification Trees, were used to rank variables by average relative importance (%) in predicting the overall TMJ integrity change from T1 to T2. Average relative importance was calculated as the percentage with respect to the maximum importance variable for each model. Overall TMJ integrity change was, as above, defined as the combined diagnosis of hard and soft tissue integrity changes. 3-fold cross-validations for parameter tuning were used on GBM and SVM modeling and 5-fold cross-validation was used on Classification Tree modeling. Confusion matrices for visualization of model performance in terms of actual versus predicted T1-T2 TMJ integrity change were used to show results from all the machine learning models. Reported overall accuracies, sensitivities, and specificities were calculated based off of correctly predicted classification of overall TMJ integrity groups.

Power computation and sample size calculations for the number of TMJs were performed to produce a 95% confidence interval and to meet requirements for the precision of sensitivity and specificity.

4. Results

Intra-Rater and Inter-Rater Reliability Analysis

Tests of intra-rater reliability for Rater 1 and Rater 2 showed good to excellent reliability, where ICCs for all physical assessment measurements were above 0.76 (Table 1). Inter-rater reliability between Rater 1 and Rater 2 also showed good to excellent reliability, where ICCs for all measurements were above 0.73 (Table 1).

Measurement	*Rater 1 ICC*	*Rater 2 ICC*	*Rater 1 vs Rater 2 ICC*
Occlusal Plane Angle (°)	0.84	0.99	0.77
Occlusal Plane Anterior Posterior Position (mm)	0.94	0.88	0.90
Ramal Length (mm)	0.93	0.85	0.79
Condylar Area (mm^2)	0.92	0.90	0.74
Condylar Angle (°)	0.93	0.96	0.80
Major Axis (mm)	0.99	0.98	0.94
Minor Axis (mm)	0.78	0.93	0.73
Condylar Aspect Ratio	0.76	0.94	0.75

Table 1: Intra-Rater and Inter-Rater Reliability Analyses. Intraclass Correlation Coefficients (ICCs) for Rater 1, Rater 2, and Rater 1 vs Rater 2 for physical assessment measurements.

Sample Description

At the time of data analysis, 31 subjects (18 females, 13 males) from the parent study met the inclusion criteria and had Axis I and Axis II baseline (T1) data and follow-up (T2) data. Right and left TMJs were included for each subject resulting in a total of 62 TMJs (36 female, 26 male). Ages at the baseline timepoint ranged from 23.4-63.5 years (with average ± standard deviation (SD) of 39.1 ± 12.3 years) and ages at the follow-up timepoint ranged from 31.3-69.9 years (46.4 ± 12.7 years). The number of years between baseline data and follow-up data ranged from 3.3-15.8 years (7.2 ± 2.3 years).

For T1 physical assessment and psychosocial measurements, occlusal plane angle ranged from 0.5-13.1° (5.5 ± 3.2°), occlusal plane anteroposterior position ranged from 35.6-60.9 mm (48.9 ± 5.4 mm), ramal length ranged from 43.5-67.0 mm (56.7 ± 5.1 mm), condylar area ranged from 48.4-194.0 mm^2 (108.0 ± 30.0 mm^2), condylar angle ranged from 51.2-93.9° (68.4 ± 8.0°), major axis ranged from 13.1-24.0 mm (18.7 ± 2.7 mm), minor axis ranged from 3.0-8.5 mm (5.8 ± 1.4 mm), condylar aspect ratio ranged from 1.6-6.9 (3.5 ± 1.1), $(PHQ\text{-}15)^2$ ranged from 1-290 (56 ± 67), and 7QBS ranged from 1-25 (8 ± 7) (Table 2).

	Measurement	*Mean (SD)*	*Median [Min, Max]*
Physical Assessment	Occlusal Plane Angle (°)	5.5 (3.2)	5.3 [0.5, 13.1]
	Occlusal Plane Anterior Posterior Position (mm)	48.9 (5.4)	48.5 [35.6, 60.9]
	Ramal Length (mm)	56.7 (5.1)	58.0 [43.5, 67.0]
	Condylar Area (mm^2)	108.0 (30.0)	108.0 [48.4, 194.0]
	Condylar Angle (°)	68.4 (8.0)	67.7 [51.2, 93.9]
	Major Axis	18.7 (2.7)	18.9 [13.1, 24.0]
	Minor Axis	5.8 (1.4)	5.9 [3.0, 8.5]
	Condylar Aspect Ratio	3.5 (1.1)	3.4 [1.6, 6.9]
Psychosocial	$(PHQ\text{-}15)^2$	56 (67)	26 [1, 290]
	7QBS	8 (7)	7 [1, 25]

Table 2: Physical Assessment and Psychosocial Measurements at T1. SD indicates standard deviation; Min, minimum; Max, maximum.

MRI and CBCT TMD diagnoses by the radiologist showed that overall, 36 TMJs (58.1%) had no change from T1 to T2 (Group A), 11 TMJs (17.7%) got better (Group B), 10 TMJs (16.1%) got worse (Group C), and 5 TMJs (8.1%) had no diagnoses (Table 3).

Status change from T1 to T2	*Change in TMJ Integrity: Number of TMJs (Percentage)*		
	Overall	*Soft Tissue*	*Hard Tissue*
No change	36 (58%)	44 (71%)	48 (77%)
Got Better	11 (18%)	6 (10%)	6 (10%)
Got Worse	10 (16%)	8 (13%)	3 (5%)
Missing Diagnosis	5 (8%)	4 (6%)	5 (8%)

Table 3: Change in TMJ Integrity: Overall, Soft and Hard Tissues. Status change of 62 TMJs from baseline (T1) to follow-up (T2), overall and in terms of hard and soft tissue integrity changes.

APS Data

For T1-T2 overall TMJ integrity Group A (no change), the range for APS values was 1.39e-5 – 0.41 and the average APS was 0.07 ± 0.10. For Group (got better), the range for APS values was 4.31e-3 – 1.48 and the average APS was 0.31 ± 0.45. For Group C (got worse), the range for APS values was 2.79e-5 – 2.47 and the average APS was 0.28 ± 0.77 (Table 4). APS showed no statistically significant differences between overall TMJ integrity groups (Figure 11).

APS	*Mean (SD)*	*Median [Min, Max]*
Group A (no change) (N=36)	0.07 (0.10)	0.02 [1.39e-5, 0.41]
Group B (got better) (N=11)	0.31 (0.45)	0.15 [4.31e-3, 1.48]
Group C (got worse) (N=10)	0.28 (0.77)	0.04 [2.79e-5, 2.47]

Table 4: APS Values for Overall T1-T2 TMJ Integrity Groups. SD indicates standard deviation; Min, minimum; Max, maximum.

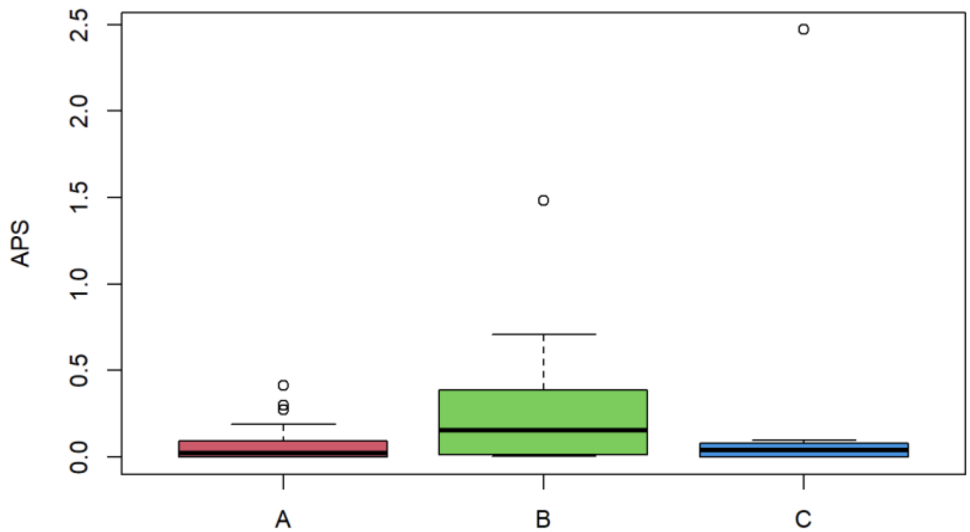

Figure 11: Box Plot of APS versus Overall T1-T2 TMJ Integrity Groups. 'A' represents the no change group in overall TMJ integrity, 'B' the got better group, and 'C' the got worse group. No statistically significant difference for APS values between overall TMJ integrity groups was present.

Variables of Importance

APS, in addition to individual physical assessment and psychosocial measurements were used in the machine learning models below.

Gradient Boosting Machine

GBM modeling had a sensitivity and specificity of 0.83 and 0.57 for the Group A (no change), 0.64 and 0.98 for Group B (got better), and 0.50 and 0.89 for Group C (got worse) (Table 5). GBM modeling had an accuracy of 0.74 in predicting overall TMJ integrity change

(Table 6). The top five variables of importance identified by GBM modeling were condylar area, minor axis, APS, condylar aspect ratio, and ramal length (Figure 12).

GBM	*A. No Change*	*B. Got Better*	*C. Got Worse*
Sensitivity	0.83	0.64	0.50
Specificity	0.57	0.98	0.89

Table 5: Gradient Boosting Machine Sensitivity and Specificity.

		Actual		
		Group A: No Change	*Group B: Got Better*	*Group C: Got Worse*
Predicted	*A. No Change*	30	4	5
	B. Got Better	1	7	0
	C. Got Worse	5	0	5

Table 6: Gradient Boosting Machine Confusion Matrix. For Group A (no change), 30 TMJs were correctly predicted to have no change while 9 TMJs were incorrectly predicted to have changes when no change occurred. For Group B (got better), 7 TMJs were correctly predicted and 1 TMJ was incorrectly predicted. For Group C (got worse), 5 TMJs were correctly predicted and 5 TMJs were incorrectly predicted.

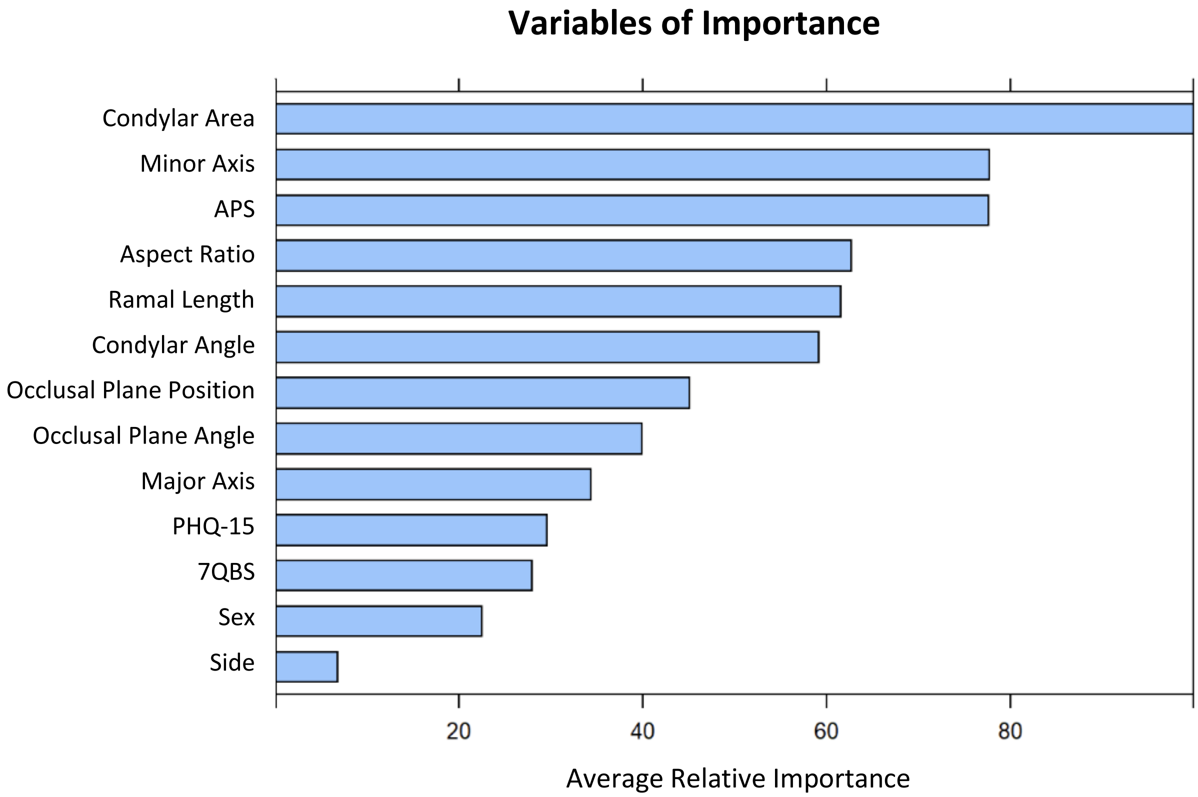

Figure 12: Gradient Boosting Machine Variables of Importance. Condylar area was the most important variable while side (right or left) was the least important variable in this machine learning model. Average relative importance in GBM modeling was calculated as the percentage with respect to condylar area (maximum importance variable).

Support Vector Machine

SVM modeling had a sensitivity and specificity of 0.78 and 0.29 for Group A (no change), 0.36 and 0.93 for Group B (got better), and 0.20 and 0.89 for Group C (got worse) (Table 7). SVM modeling had an accuracy of 0.60 in predicting overall TMJ integrity change (Table 8). The top five variables of importance identified by SVM modeling were major axis, sex, 7QBS, condylar area, and minor axis (Figure 13).

SVM	*A. No Change*	*B. Got Better*	*C. Got Worse*
Sensitivity	0.78	0.36	0.20
Specificity	0.29	0.93	0.89

Table 7: Support Vector Machine Sensitivity and Specificity.

		Actual		
		Group A: No Change	*Group B: Got Better*	*Group C: Got Worse*
Predicted	*A. No Change*	28	7	8
	B. Got Better	3	4	0
	C. Got Worse	5	0	2

Table 8: Support Vector Machine Confusion Matrix. For Group A (no change), 28 TMJs were correctly predicted to have no change and 15 TMJs were incorrectly predicted to have changes when no change occurred. For Group B (got better), 4 TMJs were correctly predicted and 3 TMJs were incorrectly predicted. For Group C (got worse), 2 TMJs were correctly predicted and 5 TMJs were incorrectly predicted.

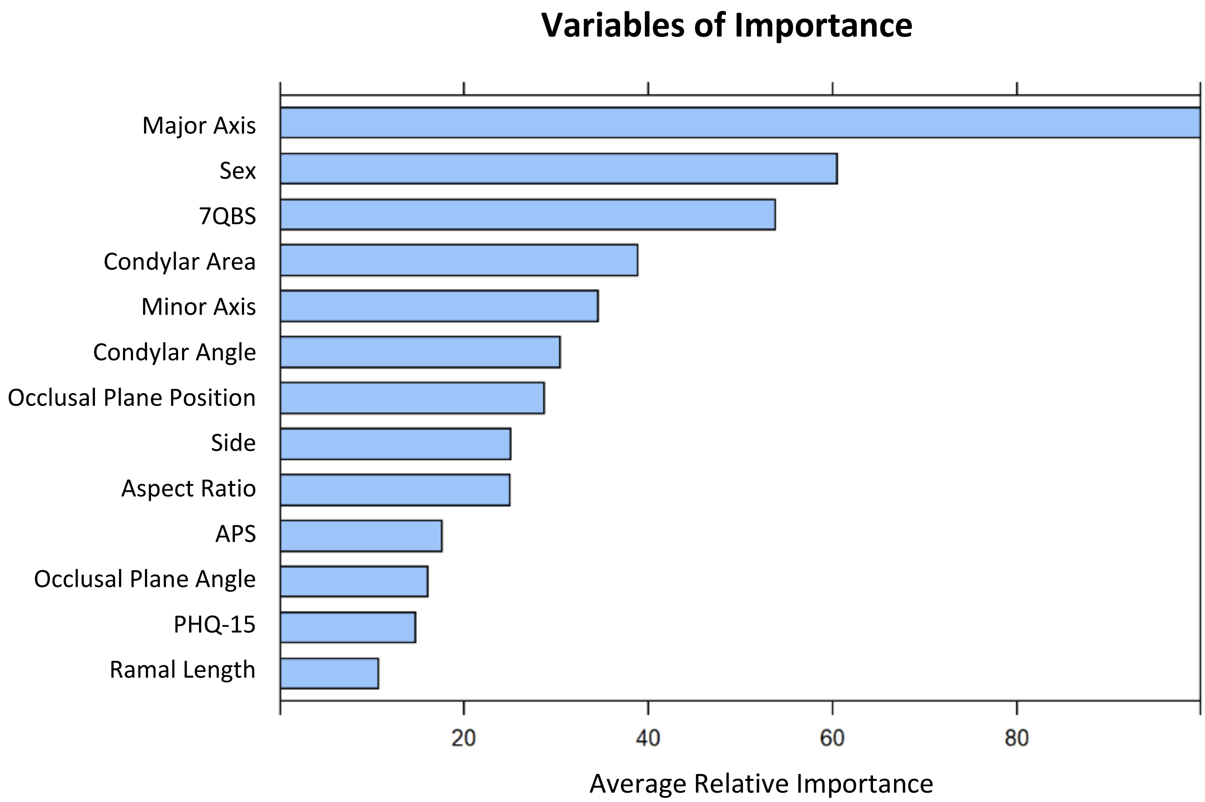

Figure 13: Support Vector Machine Variables of Importance. Major axis was the most important variable while ramal length was the least important variable in this machine learning model. Average relative importance in SVM modeling was calculated as the percentage with respect to major axis (maximum importance variable).

Classification Tree

The Classification Tree modeling had a sensitivity and specificity of 0.72 and 0.62 for Group A (no change), 0.27 and 0.87 for Group B (got better), and 0.60 and 0.83 for Group C (got worse) (Table 9). The Classification Tree modeling had an accuracy of 0.61 in predicting overall TMJ integrity change (Table 10). The top five variables of importance identified by the Classification Tree modeling were condylar area, minor axis, aspect ratio, ramal length, and condylar angle (Figure 14).

Classification Tree	*A. No Change*	*B. Got Better*	*C. Got Worse*
Sensitivity	0.72	0.27	0.60
Specificity	0.62	0.87	0.83

Table 9: Classification Tree Sensitivity and Specificity.

		Actual		
		Group A: No Change	*Group B: Got Better*	*Group C: Got Worse*
Predicted	*A. No Change*	26	6	2
	B. Got Better	4	3	2
	C. Got Worse	6	2	6

Table 10: Classification Tree Confusion Matrix. For Group A (no change), 26 TMJs were correctly predicted to have no change and 8 TMJs were incorrectly predicted to have changes when no change occurred. For Group B (got better), 3 TMJs were correctly predicted and 6 TMJs were incorrectly predicted. For Group C (got worse), 6 TMJs were correctly predicted and 8 TMJs were incorrectly predicted.

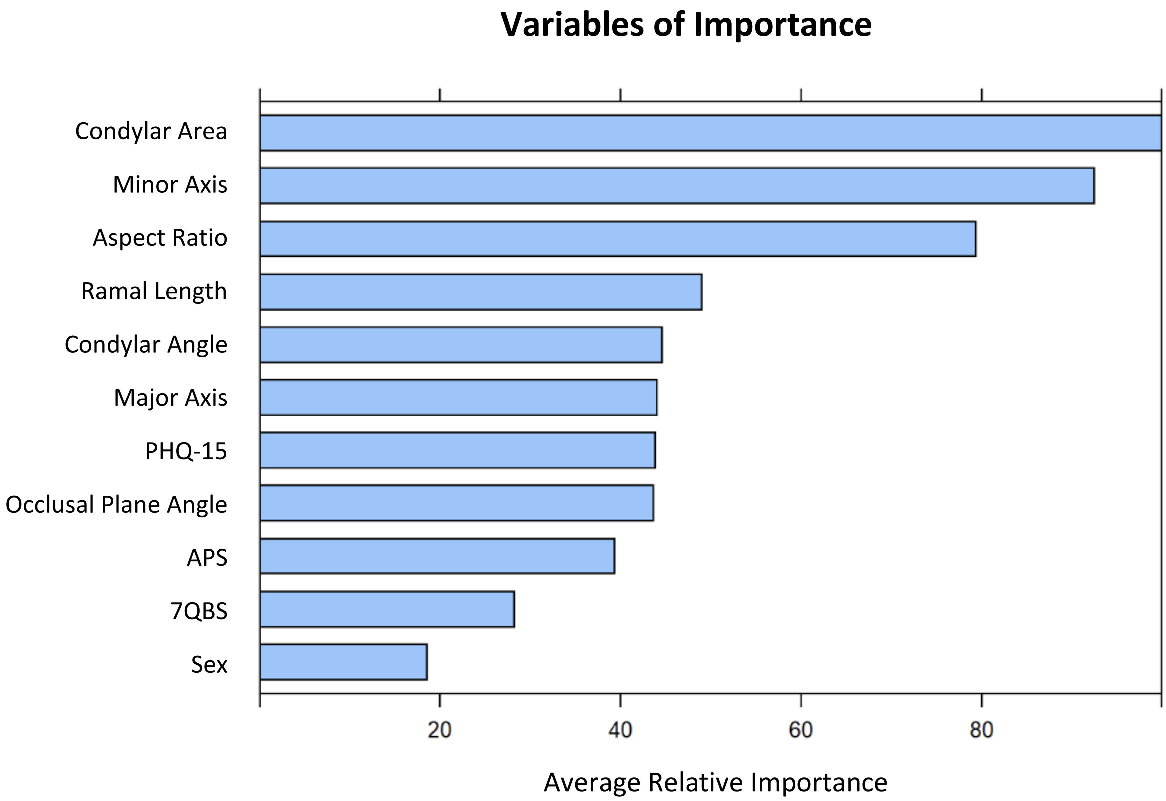

Figure 14: Classification Tree Variables of Importance. Condylar area was the most important variable while sex was the least important variable in this machine learning model. Average relative importance in Classification Tree modeling was calculated as the percentage with respect to condylar area (maximum importance variable).

The conditions where condylar area was ≥ 90 mm^2, PHQ-15 was < 6, and major axis was < 19 mm were identified via Classification Tree modeling as strong predictors of TMJ integrity change (Figure 15). That is, the Classification Tree modeling showed that for Group A (no change), if T1 condylar area was greater than or equal to 90 mm^2 and PHQ-15 was less than 6 then there was a 100% predictive success of correctly classifying the no change group. Also, for Group A (no change), there was an 83% predictive success if condylar area was greater than or equal to 90 mm^2, PHQ-15 was not less than 6, and major axis was less than 19 mm. For Group B (got better), if condylar area was greater than or equal to 90 mm^2, PHQ-15 was not less than 6, and major axis was not less than 19mm then there is a 54% predictive success of correctly classifying the got better group. For Group C (got worse), if condylar area was not greater than or equal to 90 mm^2 then there was a 54% predictive success of correctly classifying the got worse group.

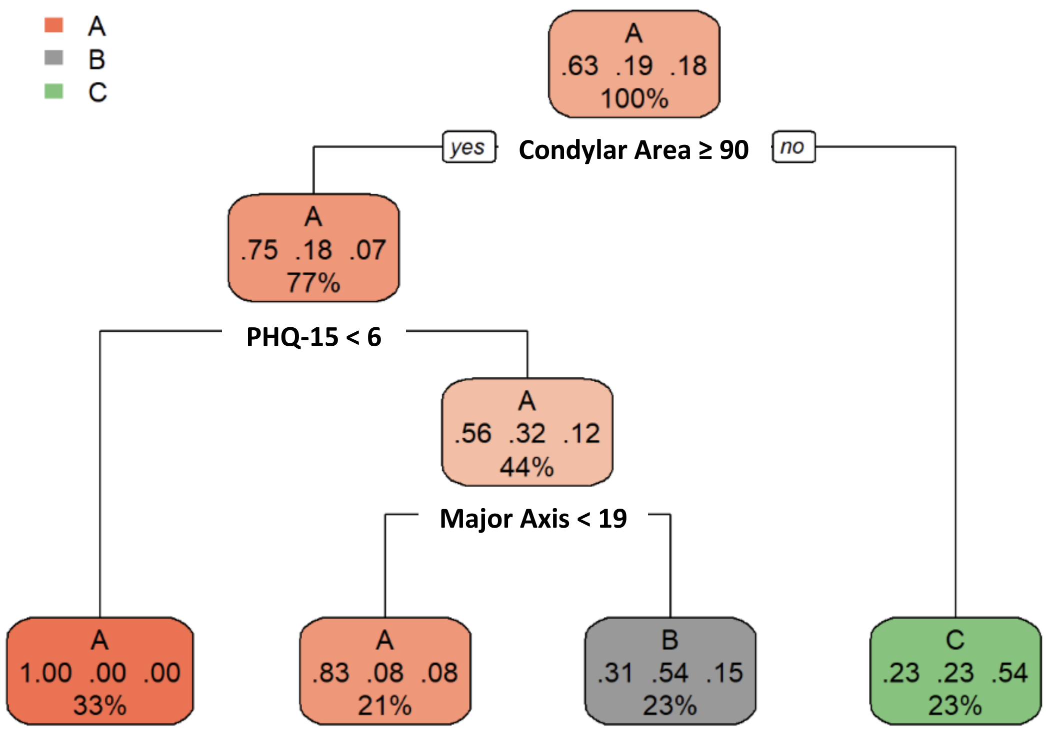

Figure 15: Classification Tree. 'A' represents the no change group in TMJ integrity, 'B' the got better group, and 'C' the got worse group. The 2nd row per tile indicates the fractions of TMJs that were predicted to the no change group (left), got better group (middle), and got worse group (right) in comparison to the actual groups which are denoted on the 1st row per tile. The 3rd row per tile indicates the percentage of overall

TMJs at each node of the tree. Darker shades of red for Group A (no change) represent higher predictive success.

Power Analysis

Sample sizes of 88 to 180 TMJs will be needed to produce a 95% confidence interval with a width of no more than 0.2 for sensitivity and specificity of 0.7 to 0.9, assuming equal prevalence.

5. Discussion

This study demonstrated that the proposed novel APS equation was not predictive of TMJ integrity change. However, this study further exhibited that specific physical assessment and psychosocial variables were correlated with changes in TMJ integrity.

The relative importance of APS physical assessment variables in this study support previous findings that differences in the magnitude of work imposed on TMJ structures may lead to differential mechanical tissue fatigue in TMD groups (25). Iwasaki et al. and Gallo et al. have shown, respectively, that magnitudes of compressive stresses increase with decreased condylar loading area while shear stresses increase with larger condylar aspect ratios (25, 26). The current study's GBM and the Classification Tree models showed that condylar area (major axis x minor axis) had the highest relative importance of tested variables in TMJ changes. The two models also showed that minor axis had the second highest importance while SVM modeling showed that major axis had the highest importance for TMJ changes. Condylar aspect ratio (major axis / minor axis) was in the top four of importance in GBM and the Classification Tree models. Because these variables can affect compressive and shear stress magnitudes during TMJ function, their overall relative importance across all of the machine learning models in this study is further evidence for their importance to TMJ mechanical fatigue and longitudinal changes in TMJ structures.

Previous studies showed that higher magnitudes of TMJ compressive stress were also influenced by shorter ramal lengths and decreases in occlusal plane anteroposterior position with a counterclockwise mandibular rotation (15, 16, 17). In this study's modeling, the correlation of ramal length with compressive stress appears to be supported as GBM and the Classification Tree models had ramal length in the top five variables of importance. However, SVM modeling found that ramal length was the least predictive. For occlusal plane anteroposterior position, GBM and SVM modeling indicated moderate importance while Classification Tree modeling showed no importance of this variable in predictive integrity change. Based on these data, and Glovsky et al.'s study that had occlusal plane anteroposterior position linked with FH-OP angle, further research is needed to figure out if occlusal plane anteroposterior position is independently correlated with TMJ compressive stresses and integrity changes (17).

Mechanical tissue fatigue is also influenced by the frequency of work imposed on the TMJ cartilages. It has been previously suggested that more frequent loading of articular tissues can fatigue the disk and contribute to myofascial pain (28). The unpublished data, previously described, from the follow-up study of 27 subjects and 53 TMJs showed that the product of $(PHQ\text{-}15)^2$ and 7QBS correlated to day-time masseter duty factors. In this study, the product of $(PHQ\text{-}15)^2$ and 7QBS was not a variable of importance in predicting TMJ changes. Further, the psychosocial variables of PHQ-15 and 7QBS all ranked low in relative importance across all three machine learning models except for 7QBS which ranked 3rd highest (average relative importance = 53% with respect to maximum importance variable) in SVM modeling. This study's modeling implies that 7QBS independently may be a better indicator of frequency of applied loading and that the previously suggested weighted product of psychosocial variables does not hold notable prognostic capability. However, in the Classification Tree modeling, PHQ-15 correlated well in TMJ integrity prediction when used in conjunction with the physical assessment variables of condylar area and major axis. PHQ-15 as the second branch of the decision tree allows for 100% predictive accuracy for Group A (no change) if PHQ-15 is less than 6 and leads into differentiating Group A (no change) from Group B (got better). Further investigation into the frequency aspect of mechanical fatigue is required to better determine if there is a relationship with a psychosocial variable independently, with psychosocial variables in different weighted amounts, or with one or more psychosocial variables correlated with physical assessment variables.

Despite an increased prevalence of TMDs in females, sex only had a relatively high importance, ranked 2nd highest (average relative importance = 60% with respect to maximum importance variable), in SVM modeling while GBM (average relative importance = 22% with respect to maximum importance variable) and Classification Tree (average relative importance = 19% with respect to maximum importance variable) models had sex at or near the bottom of variables of importance.

GBM modeling had the highest accuracy of the three machine learning models with a 74% accuracy while the Classification Tree model had 61% accuracy and SVM model had 60% accuracy. With adjustments of tuning parameters for machine learning models, the three models should achieve similar accuracies but GBM modeling had a statistically higher accuracy even with tuning by cross-validation. This may be due to the small sample sizes or suggests that the current data set would be better fit by a different machine learning model.

This study had limitations because there were small sample sizes of TMJs, especially in Group B (got better) and Group C (got worse). This limited the training accuracy of the machine modeling resulting in non-prognostic accuracy for the current data. Additionally, the study was limited to comparing APS and machine modeling variables of importance to overall TMJ integrity change instead of also comparing to hard tissue integrity and soft tissue integrity changes independently. APS may have shown different statistical results when correlated to no change, got better, or got worse groups for hard tissue integrity changes and soft tissue integrity changes analyzed separately. Also, data may have shown a differentiation in variables of importance between hard and soft tissue integrity changes.

Results from the current study indicates that 88 to 180 TMJs are required to have more accurate results with higher sensitivity and specificity from machine learning models. Future follow-up studies with the aforementioned targeted sample size can utilize machine modeling to reverse engineer improved APS equations that may accurately predict TMJ integrity changes. If new equations show no prognostic accuracy then using larger sample sizes in decision tree learning can create Classification Trees that can possibly have a high capability to predict TMJ changes.

6. Conclusion

The proposed novel APS equation was not predictive of longitudinal TMJ integrity. Machine learning models indicated that condylar area and variables associated with condylar area (major axis, minor axis, aspect ratio) have high relative importance in the predictive accuracy of overall TMJ changes over time. GBM modeling had the highest accuracy in predicting TMJ integrity changes at 74%. Classification Tree modeling showed that important variables in determining predictive success were condylar area $\geq 90\ mm^2$, PHQ-15 <6, and major axis < 19 mm. Future studies with larger sample sizes can possibly utilize machine learning to reverse engineer a prognostic APS equation.

7. References

1. TMD (Temporomandibular Disorders) | National Institute of Dental and Craniofacial Research [Internet]. [cited 2023 Sep 2]. Available from: https://www.nidcr.nih.gov/health-info/tmd

2. Prevalence of TMJD and its Signs and Symptoms | National Institute of Dental and Craniofacial Research [Internet]. [cited 2023 Sep 2]. Available from: https://www.nidcr.nih.gov/research/data-statistics/facial-pain/prevalence

3. Facial Pain | National Institute of Dental and Craniofacial Research [Internet]. [cited 2023 Sep 2]. Available from: https://www.nidcr.nih.gov/research/data-statistics/facial-pain

4. Alrizqi AH, Aleissa BM. Prevalence of Temporomandibular Disorders Between 2015-2021: A Literature Review. Cureus. 15(4):e37028.

5. Nickel JC, Iwasaki LR, Gonzalez YM, Gallo LM, Yao H. Mechanobehavior and Ontogenesis of the Temporomandibular Joint. J Dent Res. 2018 Oct;97(11):1185–92.

6. Schiffman EL, Truelove EL, Ohrbach R, Anderson GC, John MT, List T, et al. The Research Diagnostic Criteria for Temporomandibular Disorders. I: overview and methodology for assessment of validity. J Orofac Pain. 2010;24(1):7–24.

7. Schiffman E, Ohrbach R, Truelove E, Look J, Anderson G, Goulet JP, et al. Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Applications: recommendations of the International RDC/TMD Consortium Network* and Orofacial Pain Special Interest Group†. J Oral Facial Pain Headache. 2014;28(1):6–27.

8. Ahmad M, Hollender L, Anderson Q, Kartha K, Ohrbach R, Truelove EL, et al. Research diagnostic criteria for temporomandibular disorders (RDC/TMD): development of image analysis criteria and examiner reliability for image analysis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009 Jun;107(6):844–60.

9. Kroenke K, Spitzer RL, Williams JBW. The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. Psychosom Med. 2002;64(2):258–66.

10. Donnarumma V, Ohrbach R, Simeon V, Lobbezoo F, Piscicelli N, Michelotti A. Association between waking-state oral behaviours, according to the oral behaviors checklist, and TMD subgroups. J Oral Rehabil. 2021 Sep;48(9):996–1003.

11. Wilkes CH. Internal derangements of the temporomandibular joint. Pathological variations. Arch Otolaryngol Head Neck Surg. 1989 Apr;115(4):469–77.

12. Schiffman EL, Ahmad M, Hollender L, Kartha K, Ohrbach R, Truelove EL, et al. Longitudinal Stability of Common TMJ Structural Disorders. J Dent Res. 2017 Mar;96(3):270–6.

13. Chantaracherd P, John MT, Hodges JS, Schiffman EL. Temporomandibular Joint Disorders' Impact on Pain, Function, and Disability. J Dent Res. 2015 Mar;94(3 Suppl):79S-86S.

14. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Care Services; Board on Health Sciences Policy; Committee on Temporomandibular Disorders (TMDs): From Research Discoveries to Clinical Treatment. Temporomandibular Disorders: Priorities for Research and Care [Internet]. Yost O, Liverman CT, English R, Mackey S, Bond EC, editors. Washington (DC): National Academies Press (US); 2020 [cited 2023 Sep 2]. (The National Academies Collection: Reports funded by National Institutes of Health). Available from: http://www.ncbi.nlm.nih.gov/books/NBK555057/

15. Desai RJ, Iwasaki LR, Kim SM, Liu H, Liu Y, Nickel JC. A theoretical analysis of longitudinal temporomandibular joint compressive stresses and mandibular growth. Angle Orthod. 2022 Jan 1;92(1):11–7.

16. Riddle PC, Nickel JC, Liu Y, Gonzalez YM, Gallo LM, Conley RS, et al. Mechanobehavior and mandibular ramus length in different facial phenotypes. Angle Orthod. 2020 Nov 1;90(6):866–72.

17. Glovsky TE, Iwasaki LR, Wu Y, Liu H, Liu Y, Sousa Melo SL, et al. Orthognathic surgery effects on temporomandibular joint compressive stresses. Orthod Craniofac Res. 2023 Mar 31;

18. Gallo LM, Fankhauser N, Gonzalez YM, Liu H, Liu Y, Nickel JC, et al. Jaw Closing Movement and Sex Differences in Temporomandibular Joint Energy Densities. J Oral Rehabil. 2018 Feb;45(2):97–103.

19. Gonzalez Y. An observational study of mechano-allostatic load and chronic temporomandibular pain in humans. 57:112–22.

20. Lantz-Subtelny B. Evaluation of oral behaviors among subjects with temporomandibular disorders. J Dent Res. 2019;98(A):1456.

21. Khawaja SN, Iwasaki LR, Dunford R, Nickel JC, McCall W, Crow HC, et al. Association of Masseter Muscle Activities during Awake and Sleep Periods with Self-Reported Anxiety, Depression, and Somatic Symptoms. J Dent Health Oral Disord Ther. 2015;2(1):00039.

22. Nickel JC, Gonzalez YM, Liu Y, Liu H, Gallo LM, Iwasaki LR. Mechanics- and Behavior-Related Temporomandibular Joint Differences. J Dent Res. 2024 Oct;103(11):1083–90.

23. Trpkova B, Major P, Prasad N, Nebbe B. Cephalometric landmarks identification and reproducibility: A Meta analysis. Am J Orthod Dentofacial Orthop. 1997 Aug 1;112(2):165–70.

24. Choi JW, Jung SY, Kim HJ, Lee SH. Positional symmetry of porion and external auditory meatus in facial asymmetry. Maxillofac Plast Reconstr Surg. 2015 Dec;37(1):33.

25. Iwasaki LR, Gonzalez YM, Liu Y, Liu H, Markova M, Gallo LM, et al. Mechanobehavioral Scores in Women with and without TMJ Disc Displacement. J Dent Res. 2017 Jul;96(8):895–901.

26. Iwasaki LR, Gonzalez YM, Liu Y, Liu H, Markova M, Gallo LM, et al. TMJ energy densities in healthy men and women. Osteoarthritis Cartilage. 2017 Jun;25(6):846–9.

27. Gallo LM, Nickel JC, Iwasaki LR, Palla S. Stress-field translation in the healthy human temporomandibular joint. J Dent Res. 2000 Oct;79(10):1740–6.

28. Nickel J, Spilker R, Iwasaki L, Gonzalez Y, McCall WD, Ohrbach R, et al. Static and dynamic mechanics of the TMJ: Plowing forces, joint load, and tissue stress. Orthod Craniofac Res. 2009 Aug;12(3):159.

8. Appendices

A. Patient Health Questionnaire-15 (PHQ-15)

Sourced from University at Buffalo (https://ubwp.buffalo.edu/rdc-tmdinternational/wp-content/uploads/sites/58/2017/01/PHQ-15_2013-05-12.pdf)

Patient Health Questionnaire-15: Physical Symptoms

During the last 4 weeks, how much have you have been bothered by any of the following problems? Please place a check mark in the box to indicate your answer.

	Not bothered 0	Bothered a little 1	Bothered a lot 2
1. Stomach pain	☐	☐	☐
2. Back pain	☐	☐	☐
3. Pain in your arms, legs, or joints (knees, hips, etc)	☐	☐	☐
4. Menstrual cramps or other problems with your periods [women only]	☐	☐	☐
5. Headaches	☐	☐	☐
6. Chest pain	☐	☐	☐
7. Dizziness	☐	☐	☐
8. Fainting spells	☐	☐	☐
9. Feeling your heart pound or race	☐	☐	☐
10. Shortness of breath	☐	☐	☐
11. Pain or problems during sexual intercourse	☐	☐	☐
12. Constipation, loose bowels, or diarrhea	☐	☐	☐
13. Nausea, gas, or indigestion	☐	☐	☐
14. Feeling tired or having low energy	☐	☐	☐
15. Trouble sleeping	☐	☐	☐
TOTAL SCORE =			

B. Oral Behaviors Checklist (OBC)

Sourced from University at Buffalo (https://ubwp.buffalo.edu/rdc-tmdinternational/wp-content/uploads/sites/58/2017/01/Oral-Behavior-Checklist_2013-05-12.pdf)

The Oral Behavior Checklist

How often do you do each of the following activities, based on **the last month**? If the frequency of the activity varies, choose the higher option. Please place a (√) response for each item and do not skip any items.

	Activities During Sleep	**None of the time**	**< 1 Night /Month**	**1-3 Nights /Month**	**1-3 Nights /Week**	**4-7 Nights/ Week**
1	Clench or grind teeth **when asleep**, based on any information you may have	☐	☐	☐	☐	☐
2	Sleep in a position that puts pressure on the jaw (for example, on stomach, on the side)	☐	☐	☐	☐	☐
	Activities During Waking Hours	**None of the time**	**A little of the time**	**Some of the time**	**Most of the time**	**All of the time**
3	Grind teeth together **during waking hours**	☐	☐	☐	☐	☐
4	Clench teeth together **during waking hours**	☐	☐	☐	☐	☐
5	Press, touch, or hold teeth together other than while eating (that is, contact between upper and lower teeth)	☐	☐	☐	☐	☐
6	Hold, tighten, or tense muscles without clenching or bringing teeth together	☐	☐	☐	☐	☐
7	Hold or jut jaw forward or to the side	☐	☐	☐	☐	☐
8	Press tongue forcibly against teeth	☐	☐	☐	☐	☐
9	Place tongue between teeth	☐	☐	☐	☐	☐
10	Bite, chew, or play with your tongue, cheeks or lips	☐	☐	☐	☐	☐
11	Hold jaw in rigid or tense position, such as to brace or protect the jaw	☐	☐	☐	☐	☐
12	Hold between the teeth or bite objects such as hair, pipe, pencil, pens, fingers, fingernails, etc	☐	☐	☐	☐	☐
13	Use chewing gum	☐	☐	☐	☐	☐
14	Play musical instrument that involves use of mouth or jaw (for example, woodwind, brass, string instruments)	☐	☐	☐	☐	☐
15	Lean with your hand on the jaw, such as cupping or resting the chin in the hand	☐	☐	☐	☐	☐
16	Chew food on one side only	☐	☐	☐	☐	☐
17	Eating between meals (that is, food that requires chewing)	☐	☐	☐	☐	☐
18	Sustained talking (for example, teaching, sales, customer service)	☐	☐	☐	☐	☐
19	Singing	☐	☐	☐	☐	☐
20	Yawning	☐	☐	☐	☐	☐
21	Hold telephone between your head and shoulders	☐	☐	☐	☐	☐

C. 7-Question Behavior Score (QBS)

The seven questions extracted from the OBC for the 7QBS are indicated by red boxes.

The Oral Behavior Checklist

How often do you do each of the following activities, based on **the last month**? If the frequency of the activity varies, choose the higher option. Please place a (√) response for each item and do not skip any items.

	Activities During Sleep	**None of the time**	**< 1 Night /Month**	**1-3 Nights /Month**	**1-3 Nights /Week**	**4-7 Nights/ Week**
1	Clench or grind teeth **when asleep**, based on any information you may have	☐	☐	☐	☐	☐
2	Sleep in a position that puts pressure on the jaw (for example, on stomach, on the side)	☐	☐	☐	☐	☐
	Activities During Waking Hours	**None of the time**	**A little of the time**	**Some of the time**	**Most of the time**	**All of the time**
3	Grind teeth together **during waking hours**	☐	☐	☐	☐	☐
4	Clench teeth together **during waking hours**	☐	☐	☐	☐	☐
5	Press, touch, or hold teeth together other than while eating (that is, contact between upper and lower teeth)	☐	☐	☐	☐	☐
6	Hold, tighten, or tense muscles without clenching or bringing teeth together	☐	☐	☐	☐	☐
7	Hold or jut jaw forward or to the side	☐	☐	☐	☐	☐
8	Press tongue forcibly against teeth	☐	☐	☐	☐	☐
9	Place tongue between teeth	☐	☐	☐	☐	☐
10	Bite, chew, or play with your tongue, cheeks or lips	☐	☐	☐	☐	☐
11	Hold jaw in rigid or tense position, such as to brace or protect the jaw	☐	☐	☐	☐	☐
12	Hold between the teeth or bite objects such as hair, pipe, pencil, pens, fingers, fingernails, etc	☐	☐	☐	☐	☐
13	Use chewing gum	☐	☐	☐	☐	☐
14	Play musical instrument that involves use of mouth or jaw (for example, woodwind, brass, string instruments)	☐	☐	☐	☐	☐
15	Lean with your hand on the jaw, such as cupping or resting the chin in the hand	☐	☐	☐	☐	☐
16	Chew food on one side only	☐	☐	☐	☐	☐
17	Eating between meals (that is, food that requires chewing)	☐	☐	☐	☐	☐
18	Sustained talking (for example, teaching, sales, customer service)	☐	☐	☐	☐	☐
19	Singing	☐	☐	☐	☐	☐
20	Yawning	☐	☐	☐	☐	☐
21	Hold telephone between your head and shoulders	☐	☐	☐	☐	☐

D. Institutional Review Board Approval Letter

OREGON HEALTH & SCIENCE UNIVERSITY

IRB MEMO

Research Integrity Office
3181 SW Sam Jackson Park Road - L106RI
Portland, OR 97239-3098
(503)494-7887 irb@ohsu.edu

APPROVAL OF SUBMISSION

March 28, 2023

Dear Investigator:

On 3-28-2023, the IRB reviewed the following submission:

IRB ID:	STUDY00018800	MOD or CR ID:	MOD00048255
Type of Review:	Modification / Update		
Title of Study:	Contribution of Mechanobehavioral, Psychosocial, and Physiological Domains in the Progression of Temporomandibular Disorders		
Title of modification	Revised protocol to increase study sample accrual to 35		
Principal Investigator:	Laura Iwasaki		
Funding:	Name: American Association of Orthodontists Foundation, PPQ #: 1014638		
IND, IDE, or HDE:	None		
Documents Reviewed:	• Protocol • Protocol_Prog TMD_no EN_032723_tracked.docx		

The IRB granted final approval on 3/28/2023. The study is approved until 3/1/2024.

Review Category: Expedited-Minor Modification

Copies of all approved documents are available in the study's **Final** Documents (far right column under the documents tab) list in the eIRB. Any additional documents that require an IRB signature (e.g. IIAs and IAAs) will be posted when signed. If this applies to your study, you will receive a notification when these additional signed documents are available.

Ongoing IRB submission requirements:

- Six to ten weeks before the expiration date, you are to submit a continuing review to request continuing approval.
- Any changes to the project must be submitted for IRB approval prior to implementation.
- Reportable New Information must be submitted per OHSU policy.

- You must submit a continuing review to close the study when your research is completed.

Guidelines for Study Conduct

In conducting this study, you are required to follow the guidelines in the document entitled, "Roles and Responsibilities in the Conduct of Research and Administration of Sponsored Projects," as well as all other applicable OHSU IRB Policies and Procedures.

Requirements under HIPAA

If your study involves the collection, use, or disclosure of Protected Health Information (PHI), you must comply with all applicable requirements under HIPAA. See the HIPAA and Research website and the Information Privacy and Security website for more information.

IRB Compliance

The OHSU IRB (FWA00000161; IRB00000471) complies with 45 CFR Part 46, 21 CFR Parts 50 and 56, and other federal and Oregon laws and regulations, as applicable, as well as ICH-GCP codes 3.1-3.4, which outline Responsibilities, Composition, Functions, and Operations, Procedures, and Records of the IRB.

Sincerely,

The OHSU IRB Office