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Mandibular morphology in schizophrenia patients compared with non-psychiatric controls using digital panoramic radiography: a retrospective cross-sectional study from Istanbul, Türkiye

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Abstract

Background Schizophrenia is a chronic severe mental disorder characterized by impairment in cognition, emotion, perception, and other aspects of behavior. In light of the association of craniofacial dysmorphology with schizophrenia, mandibular morphology may provide clues about the role of neurodevelopment in the pathophysiology of schizophrenia. This retrospective cross-sectional study aimed to compare the mandibular morphology of patients with schizophrenia with controls using digital panoramic radiography (DPR).

Methods 302 recorded diagnostic panoramic images obtained from 143 schizophrenia patients (98 males, 45 females), and 159 controls (73 males, 86 females), aged 18–45 years, were evaluated. Seven mandibular measurements consisting of ramus height, condylar height, gonial angle, antegonial angle, antegonial notch depth, ramal notch depth and bigonial width were measured from the DPRs in a double-blinded manner. Bivariate comparisons were carried out using the Independent t-test and Mann–Whitney U test. Logistic regression analysis was used for multivariate comparisons.

Results Linear measurements were higher while angular measurements were lower in schizophrenia patients. Regression analyses indicated that female patients had greater ramus height (OR = 1.243; P = 0.001), condylar height (OR = 1.463; P = 0.048) and bigonial width (OR = 1.082; P < 0.001); male patients had greater ramus heights (OR = 1.216; P = 0.001) and bigonial width (OR = 1.076; P < 0.001) as well as lower antegonial angle (OR = 0.908; P = 0.012) compared to their respective controls.

Conclusion Quantitative differences in mandibular morphology in schizophrenia patients versus controls deserve attention and corroborate with the concept of abnormal neurodevelopment in schizophrenia.

Keywords Mandibular morphology, Schizophrenia, Panoramic radiography

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Background

Minor physical anomalies (MPAs) have been considered as biomarkers on the basis of the neurodevelopmental model of schizophrenia [1] with potential pathophysiological significance [2, 3]. A higher rate of MPA in different anatomical regions, particularly the mouth region, has been widely reported in schizophrenia patients compared to controls [2–9]. MPAs are typically found in the craniofacial region rather than other sites in schizophrenia patients [4, 8, 10, 11], but has not been confirmed yet in a meta-analysis [2]. Facial-cerebral morphogenesis is primarily a midline process, and dysmorphology in schizophrenia primarily affects the midline head and face structures [12, 13]. It is therefore reasonable to assume that specific craniofacial MPAs may point to specific brain abnormalities and a higher risk for this disease. The mid-facial region has a high number of cranial neural crest cells during embryogenesis, which could explain the co-occurrence of midfacial MPAs and schizophrenia. Based on the known correlation between the development of the face and the brain, crucial phases of neurodevelopment may be implicated by quantitative craniofacial findings in the pathogenesis of schizophrenia [1, 14, 15].

Lane et al. [5] suggested that schizophrenia patients had a wider skull base compared to controls. McGrath et al. [4] also reported wider skull base widths in schizophrenia patients, as well as wider palates. Additionally, an elongation and overall widening of the face was shown in schizophrenic patients compared to controls in a 3D morphometric study [10]. Subtle facial dysmorphology associated with schizophrenia include an altered proportion along the anterior midline of the middle and lower part of the face, resulting in a pronounced midline craniofacial elongation; a widening of the upper face, mandible, and skull base; and lateral displacement of the cheeks, eyes, and orbits [16, 17]. Using 3D laser surface imaging and geometric morphometrics, an overall wider face and nose, narrower mouth and upward displacement of the chin have been demonstrated in patients with bipolar disorder and schizophrenia [11]. Buretic-Tomljanovic et al. [18] reported that schizophrenia patients had significantly higher upper facial arc, maxillary arc, and mandibular arc values compared to controls. Deutch et al. [19] demonstrated that first-degree biological relatives of patients with schizophrenia and bipolar disorder had significantly more frontonasal and mandibular anomalies compared to controls.

The need for intensive research and understanding of the relationship between specific craniofacial MPAs and the underlying neurodevelopmental disturbances leading to schizophrenia has been highlighted in the literature [14]. Considering that craniofacial morphology may affect mandibular parameters, the possibility of mandibular morphological differences in patients with schizophrenia is conceivable. Therefore, the current retrospective cross-sectional study aimed to compare mandibular morphology between schizophrenia and non-psychiatric control participants using diagnostic digital panoramic radiographs (DPRs).

Methods

Study population

In this retrospective study, radiographs taken for diagnostic purposes from schizophrenia and control patients who presented for routine dental treatment were examined. Informed consent was obtained from the patients or their relatives/representatives prior to the radiographic examinations. The study was approved by the ethics committee of Bakirkoy Prof. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology and Neurosurgery (2019/350).

Power analysis using the G*power software (version 3.1.9.7 University Dusseldorf, Phychologia, HHU, Germany) was carried out as described previously [20]. The sample size calculations were conducted separately for males and female participants. The power analysis for males showed that a total of 128 males (64 in each group) were required to obtain a clinically relevant difference between the two groups, at a 2-sided significance level of 0.05 and 80% power, based on moderate effect size (Cohen's d [d] = 0.50). The power analysis for females showed that a total of 90 females (45 in each group) was required to obtain a clinically relevant difference between the two groups, at a 2-sided significance level of 0.05 and 80% power, based on moderate effect size (Cohen's d [d] = 0.60) [21].

A simple randomized sampling method was used to assign subjects to the patient and control groups. The schizophrenia group consisted of patients who were diagnosed with schizophrenia at the Bakırköy Prof. Mazhar Osman Mental Health and Neurological Diseases Training and Research Hospital between January 2017 and January 2019 and who applied to the Bahcelievler Oral and Dental Health Center with various dental complaints. The patients met the criteria for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-4) for the diagnosis of schizophrenia [22]. The control participants consisted of patients who applied with various dental complaints to the Bahcelievler Oral and Dental Health Center between January 2018 and January 2019. Finally, a total of 302 recorded diagnostic DPRs obtained from 143 schizophrenia (98 males, 45 females) and 159 (73 males, 86 females) non-psychiatric controls who met the study criteria were retrospectively evaluated in the present study.

The inclusion criteria for both groups consisted of adults aged 18 to 45 years with dentition (at least 20 teeth excluding third molars) and the availability of a panoramic radiography image suitable for measurements. The presence of motion artifacts in panoramic radiography, a history of cranial trauma, fractures involving the jaws, orthodontic treatment and/or orthognathic surgery, and diseases that may affect bone metabolism, such as osteogenesis imperfecta, hyperparathyroidism, osteomalacia, osteopetrosis, diabetes mellitus, renal insufficiency, Paget's disease and Cushing's disease were considered as exclusion criteria. The inclusion and exclusion criteria were verified by reviewing the health records of the patients. To avoid eventual confounders due to the unavailability of ethnic and racial references of mandibular parameters, both patients and controls recruited to the study were of Turkish origin.

Data collection The DPRs were randomly selected from radiographs taken on the same device (Sirona, XG 3, Munich, Germany) to ensure standardization of the data. The tube voltage was varied between 65 and 75 kVp (15 mA, 9 s exposure time) according to the patient size. The following measurements were made in DPRs.

- Ramus height: The distance between the lines drawn perpendicular to the ramus tangent line that was measured at the level of the most lateral image of the ramus [23].
- Condylar height: The line was drawn perpendicular to the ramus tangent line at the level of the most lateral image of the condyle. Another line was drawn perpendicular to the ramus tangent line at the level of the most superior image of the condyle. Condylar height was measured at a perpendicular distance between the lines [23].
- Gonial angle: The angle between the imaginary tangential line along the ramus posterior border and the mandible's inferior border [24].
- Antegonial angle: The angle of the two lines parallel to the antegonial region, which intersects at the deepest point of the antegonial notch [23].
- Antegonial notch depth: The distance along a perpendicular line from the deepest point of the antegonial notch concavity to a line parallel to the inferior cortical border of the mandible [25].
- Ramal notch depth: The distance along a perpendicular line from the deepest point of the ramus notch concavity [24].
- Bigonial width: The horizontal distance between the left and right gonion [25]. Angular and linear mandibular measurements of DPRs are shown in Fig. 1.

The DPRs were measured by an experienced oral and maxillofacial radiologist (NY), who was blind to the group that the subjects were allocated to. The digital panoramic images of the 30 patients were repeated 4 weeks later by the same investigator to ensure intra-observer

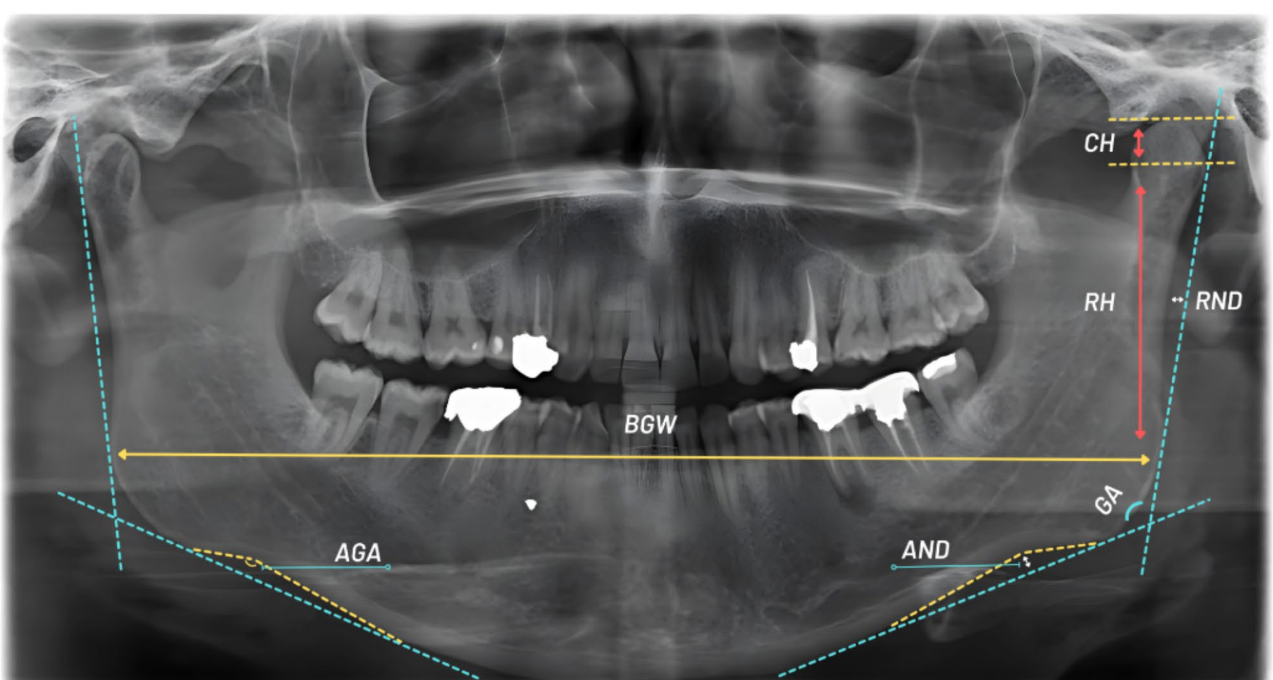

Fig. 1 Dental panoramic radiograph and a diagrammatic representation of measurements of the ramus height (RH), condylar height (CH), gonial angle (GA), antegonial angle (AGA), antegonial notch depth (AND), ramal notch depth (RND), and bigonial width (BGW) on digital panoramic radiographs (DPRs)

reliability. In addition, thirty randomly selected images were measured separately by the second radiologist (HB) two weeks later using the same protocols with the requirement of being blind to the first measurements. The mandibular measurements were evaluated in the "jpeg" format of the DPRs. Angle measurements were carried out using Irfan View 4.40 software (a 64-bit version) (Wiener Neustadt/Austria), and linear measurements were carried out using the Radiant Dicom Viewer (Poznan/Poland). The observers used an ASUS (ASUSTEK Computer Inc., Taiwan) brand ROG Zyphyrus model 16" LED monitor with 1920×1200 resolution in a darkened environment at a distance of 30 cm for all mandibular measurements. 1:1 images were automatically generated on the screen. All mandibular morphology measurements were carried out bilaterally on the left and right sides of the DPRs, and average values were obtained and recorded.

Statistical analysis

Data were analyzed using SPSS Windows Version 26 (SPSS, Chicago, IL, USA). The Shapiro−Wilk test was carried out to assess the normality of the variables. Pearson's χ2 test was used for categorical variables. Bivariate comparisons were carried out with independent-t test for data that was normally distributed and Mann–Whitney U test was used for data that was non-normally distributed. The intraclass correlation coefficient (ICC) was used to measure the intra-observer and inter-observer agreement on mandibular measurements.

Binary logistic regression analyses were carried out to identify specific mandibular morphological measurements that most accurately distinguished patients with schizophrenia from controls. The confounding effect of sex was eliminated by evaluating female and male groups separately. The age factor was included in the model in the regression analysis for both female and male groups. Patient versus control status was used as the dependent variable, age and the seven mandibular measurements were considered as independent variables. The goodness of fit for logistic regression models was assessed using Hosmer-Lemeshow statistics. The model showed no significant difference between the model and the observed data as the *P*-value was greater than 0.05 for both male ($P=0.090$) and female ($P=0.418$) groups. Logistic regression analysis was applied with a 95% confidence interval. A *P* value less than 0.05 was considered statistically significant.

Results

A total of 143 schizophrenia patients (98 males, 45 females) with a mean age of 34.73±7.36 years, and 159 control participants (73 male, 86 female) with a mean age of 34.27±6.74 years were included in the study. There was no significant difference in the age distribution between the schizophrenia and control groups ($P=0.574$), but a significant difference was identified in the sex distribution ($P<0.001$). Therefore, the data collected for male and female patients were analyzed separately. The ICC ranges for intra-observer and inter-observer assessments were 0.876–0.923 and 0.724–0.879 respectively, indicating consistency of measurements. The differences between the repeated measurements did not reach statistical significance ($P>0.05$ for all comparisons).

A comparison of age and seven different mandibular measurements between schizophrenia patients versus controls as a function of sex is shown in Table 1. The Ramus height ($P<0.001$), condylar height ($P<0.001$), antegonial notch depth ($P<0.001$), ramus notch depth ($P<0.001$), bigonial width ($P<0.001$) values were significantly higher while the antegonial angle values were significantly lower ($P<0.001$) in male schizophrenia patients compared to their respective male controls (Table 1). In females with schizophrenia, the ramus height ($P<0.001$), condylar height ($P<0.001$), ramus notch depth ($P<0.001$) and bigonial width ($P<0.001$) values were significantly

Table 1 Comparison of age and mandibular parameters between schizophrenia and non-psychiatric control participants as a function of sex

	Males, *N*=171		**Females, *N*=131**		**Statistical significance**			
	Schizophrenia	**Controls**	**Schizophrenia**	**Controls**				
	(*N*=98)(1)	**(*N*=73)(2)**	**(*N*=45)(3)**	**(*N*=86)(4)**	**(1)(2)**	**(3)(4)**	**(1)(3)**	**(2)(4)**
Variables	mean±SD	mean±SD	mean±SD	mean±SD	P	P	P	P
Age	34.11±7.49	34.19±6.32	36.08±6.97	35.55±6.47	†0.944	†0.665	††0.150	††0.155
Ramus height	60.27±5.18	50.56±5.60	54.3±5.51	44.77±6.34	†<0.001*	† <0.001*	† <0.001*	† <0.001*
Condylar height	9.88±1.83	8.50±1.41	9.43±1.45	7.84±1.55	† <0.001*	††<0.001*	†0.147	††0.006*
Gonial angle	120.02±8.04	122.17±6.30	120.79±5.30	123.56±5.79	††0.096	††0.008*	†0.498	†0.169
Antegonial angle	157.3±10.30	163.32±10.07	166.7±11.15	168.37±8.39	† <0.001*	††0.731	††<0.001*	††0.002*
Antegonial notch depth	2.7±0.98	1.97±0.75	1.67±0.86	1.52±0.78	††<0.001*	††0.235	††<0.001*	†† <0.001*
Ramal notch depth	3.77±0.91	3.01±0.71	3.38±0.97	2.88±0.86	†† <0.001*	††0.011*	††0.009*	†0.325
Bigonial width	229.46±15.85	189.99±24.46	216.98±16.29	180.42±24.14	†† <0.001*	†† <0.001*	††<0.001*	††0.023*

SD: standard deviation, N: number of participants; †Student t-test, ††Mann-Whitney U test, *Statistically significant difference at the 0.05 level

Table 2 Results of logistic regression analysis in males

Dependent variable: Control / Schizophrenia (Group) Independent variables↓	ß	SE	OR (95% CI)	*P*
Age	0.049	0.046	1.051 (0.961–1.149)	0.281
Ramus height	0.195	0.057	1.216 (1.087–1.359)	0.001*
Condylar height	0.070	0.206	1.072 (0.716–1.607)	0.735
Gonial angle	-0.058	0.044	1.060 (0.972–1.156)	0.188
Antegonial angle	-0.097	0.031	0.908 (0.855–0.964)	0.002*
Antegonial notch depth	0.272	0.607	0.762 (0.232–2.501)	0.653
Ramal notch depth	0.442	0.452	1.556 (0.641–3.775)	0.328
Bigonial width	0.074	0.017	1.076 (1.042–1.112)	< 0.001*

*Statistically significant difference at the 0.05 level. Odds ratios (OR) with 95% confidence intervals (CI)

Table 3 Results of logistic regression analysis in females

Dependent variable: Control / Schizophrenia (Group) Independent variables↓	ß	SE	OR (95% CI)	*P*
Age	0.015	0.046	1.015 (0.929–1.110)	0.740
Ramus height	0.217	0.064	1.243 (1.095–1.410)	0.001*
Condylar height	0.381	0.193	1.463 (1.003–2.135)	0.048*
Gonial angle	-0.025	0.056	0.975 (0.873–1.088)	0.651
Antegonial angle	-0.058	0.044	0.953 (0.864–1.029)	0.188
Antegonial notch depth	0.449	0.591	0.639 (0.200-2.034)	0.448
Ramal notch depth	0.141	0.366	0.868 (0.424–1.778)	0.699
Bigonial width	0.078	0.022	1.082 (1.035–1.130)	< 0.001*

*Statistically significant difference at the 0.05 level. Odds ratios (OR) with 95% confidence intervals (CI)

higher, while the gonial angle values ($P=0.008$) were significantly lower compared to female controls (Table 1).

A logistic regression analysis for males and females is presented in Tables 2 and 3, respectively. Age was not a significant variable in both sexes. The greater ramus height (OR = 1.216, 95% CI: 1.087–1.359, $P=0.001$), bigonial width (OR = 1.076; 95% CI: 1.042–1.112, $P<0.001$) and lower antegonial angle (OR = 0.908; 95% CI: 0.855–0.964, $P=0.012$) were found to be significant variables for males with schizophrenia (Table 2). A greater ramus height (OR = 1.243; 95% CI:1.095–1.410, $P=0.001$), condylar height (OR 1.463; 95% CI: 1.003–2.135, $P=0.048$) and bigonial width (OR = 1.082; % 95 CI:1.035–1.130, $P<0.001$) were found to be significant variables for female patients with schizophrenia (Table 3).

Discussion

The primary strength of the current study is that it is the first to compare mandibular measurements from panoramic radiography images between schizophrenia patients and non-psychiatric controls. We focused on a total of seven morphological and anatomical parameters of the mandible, including two angular and five linear parameters from the DPRs of schizophrenia patients compared to controls. The main finding of the current study was that the linear measurements made in the mandibular region were significantly higher, while the angular measurements were significantly lower in patients with schizophrenia. That patients with schizophrenia display a specific mandibular dysmorphology is difficult to postulate; nonetheless, our observations could be confirmed in both males and female patients separately, validating our findings. These differences in mandibular morphology are noteworthy in view of the emerging literature on the topography of craniofacial anomalies in schizophrenia.

Five primordia, namely the frontonasal process, which is most closely related to the development of the forebrain, the paired maxillary processes, and the paired mandibular processes fuse in early fetal life, ultimately forming the facial form [26]. The neurodevelopmental hypothesis of schizophrenia states that brain development is closely related to facial development; therefore, any deregulation in brain development may be reflected by craniofacial morphology [10]. The measures of mandibular arc, possibly reflecting the increased facial depth and height of the lower face, are considered to be the most prominent difference in schizophrenia [4, 11]. We observed that the ramus and conydlar heights were significantly higher in schizophrenia patients than the controls in both sexes. A higher ramus and lower facial height leads to a square facial form and vice versa [27]. The direct proportionality between an increase in the posterior height of the face to the increase in the ramus height is also of clinical interest [28]. Studies evaluating mandibular morphology in individuals with different vertical skeletal patterns have shown that hypodivergent individuals tend to have a longer ramus height [27, 29–31] and condylar height compared to the other vertical patterns [30]. Linear vertical mandibular values such as ramus height, and condylar height are correlated with facial shapes and possible malformations in the vertical and sagittal planes [27, 29–32]. Thus, increased ramus height and condylar height values in the current population of schizophrenia patients may provide clues about the different skeletal patterns, facial types and possible malformations compared to controls. We observed that the ramus notch depth was deeper in schizophrenia patients compared to controls in both sexes. The increased depth of the ramus notch may be one of the signs of long-faced syndrome without openbite [33]. An elongation of the face was previously reported in schizophrenia patients versus controls in a 3D morphometric study [10]. Compton et al. [34] reported sex-specific differences in quantitative facial measurement between schizophrenia cases and controls. Thus, our results corroborate prior studies that have reported morphometric facial differences between control and schizophrenia patients [4, 8, 10–13, 18, 19, 34]. A broader bigonial width as a linear horizontal measurement of the mandible was a significant variable for the discrimination of schizophrenia patients from controls in both sexes in the present study, supporting previous studies reporting a wider mandible, upper face, palate, and wider skull base in schizophrenia patients [4, 11–13, 18, 19].

We observed that angular measurements, gonial and antegonial, were lower in schizophrenia patients versus the controls in both sexes. However, the differences were significant only in females for the gonial angle, while the antegonial angle was significant only in males. This difference may be due to sex-specific differences in muscle strength, as well as differences in hormones and metabolism [35]. Individuals with thick mandibular muscles or strong bite forces are reported to have wider transversal mandibular dimensions, a narrower gonial angle and a rectangular facial shape. Individuals with narrow gonial angles tend to mimic the facial features of a long ramus with a square face and a shorter lower face compared to their midface [36]. A narrower antegonial angle was a significant variable in distinguishing male schizophrenia patients from their health counterparts. The antegonial notch depth and antegonial angle are inversely related such that the presence of a deeper antegonial notch and narrower antegonial angle in males is associated with a robust masticatory force [37]. Additionally, males tend to have more oversized mandibles and thus deeper antegonial notch [37]. The antegonial notch depth is the attachment site of the masseter and medial pterygoid muscles; hence, muscular movements can strongly affect this notch. Moreover, the antegonial notch was reported to be significantly deeper in individuals with bruxism compared to controls [20]. The presence of a deeper antegonial notch in male schizophrenia patients may also be related to the higher prevalence of bruxism in schizophrenia patients versus controls [38].

Sexual dimorphism in the size and shape of the mandibular morphology has been widely reported, differing between males and females [39, 40]. Of note, the observed mandibular morphological differences showed similar trends in control males compared to control females as the findings in schizophrenia males compared to schizophrenia females. Thus, given the sex differences in normal mandibular morphogenesis, dysmorphogenesis in schizophrenia patients produces different, yet overlapping, topographies of dysmorphology in males and females [13]. These results are consistent with our findings.

The current study has limitations that are inherent to studies with a retrospective design. Although the use of 3D methods such as cone beam computed tomography (CBCT) or magnetic resonance imaging (MRI), would produce more reliable measurements for this type of examination, such data was not available for the study population examined in the current study. We used panoramic radiography because it is routinely used, has the capability to enable independent measurements in the right and left sides; additionally, the cost and radiation doses are within acceptable limits [41]. Of note, the intra-observer and inter-observer reliability findings did not indicate the presence of significant errors between the two measurements. Due to the uniqueness of the current study, there is a lack of literature data for comparison, leading to speculative interpretations. Another limitation is that the mandible is not entirely reliable as a diagnostic tool for schizophrenia as mechanical forces are also exerted on the mandible; different clinical variables that may affect mandibular bone morphology, such as the occlusion type, different types of malocclusions, chewing habits, eating habits, and the presence of bruxism [29], were not evaluated.

Conclusions

In spite of the limitations of the current study, our data suggest that schizophrenia patients present significant differences in most mandibular measurements from their respective controls. Thus, our results support the hypothesis of abnormal neurodevelopment in schizophrenia patients in this context. Patients with schizophrenia exhibited significant and overlapping mandibular discriminant variables in both sexes, such as a higher ramus height and greater bigonial width. Additionally, some features appeared to be sex-specific, such as lower antegonial angle values in males and longer condylar height values in females. The interesting findings reported in the current study should motivate researchers to evaluate mandibular morphology further in a larger sample of schizophrenia patients using three-dimensional imaging methods.

Abbreviations

MPAs	Minor physical anomalies
kVp	Kilovoltage peak
mA	Miliamper
RH	Ramus height
CH	Condylar height
GA	Gonial angle
AGA	Antegonial angle
AND	Antegonial notch depth
RND	Ramal notch depth
BGW	Bigonial width
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
OR	Odds ratio
CI	Confidence interval
CBCT	Cone beam computed tomography
MRI	Magnetic resonance imaging

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Author contributions
H.B., Ö.O., N.Y. and M.E. contributed to the conception of the work, the data acquisition, analysis, validation and interpreted the patient data regarding the mandibular measurements. Ö.O. was a major contributor to the writing of the manuscript. H.B., Ö.O., N.Y., M.E. have drafted the revised work. All authors have read and approved the final manuscript.

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Data availability
The datasets used and/or analyzed during the current study is available from the corresponding author on reasonable request. Özlem Oflezer e-mail address: zlmgrbz@yahoo.com.

Declarations

Ethics approval and consent to participate
The study procedure was approved by the University of Health Sciences, Bakirkoy Prof. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology and Neurosurgery (Approval no: 2019/350). All methods were carried out according to relevant guidelines and regulations. Informed consent was obtained from the patients or their relatives/representatives prior to the radiographic examinations. The datasets are not publicly available to preserve individuals' privacy under the National General Data Protection Regulation.

Competing interests
The authors declare no competing interests.

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