## Prevalence of temporomandibular joint dysfunction in Ehlers–Danlos syndromes

In vol. 7, pp. 40–46, of *Orthodontics and Craniofacial Research* (1), Dr Hagberg and co-workers reported on their findings on temporomandibular joint (TMJ) problems in a population affected with Ehlers–Danlos syndrome (EDS). They stated that, on the basis of a self-administered questionnaire study, subjects with EDS are naturally predisposed to TMJ problems. On the basis of our experience with both clinical diagnostics and management of patients affected with EDS and with the methodology of TMJ-related epidemiological research, however, we feel that there are a number of puzzling methodological flaws that considerably weaken the scientific power and clinical relevance of the study.

The first puzzling thing about the present study is that the authors went to the trouble to select a large study population with EDS without concerning about selection bias. The assignment of individuals to the study population, consisting of members of the Swedish EDS Association volunteering to respond to a mailed questionnaire, appears to be exclusively based on data provided by the subjects. The authors failed to report how and where the patients were diagnosed, neither did they seek for clinical/laboratory confirmation of the individual EDS type diagnosis, resulting in a first major methodological error: over 46% of the study population did not know their EDS subtype diagnosis. Discrimination of the EDS type, however, may be of critical importance since linking of signs and symptoms of TMJ disorders to generalized joint hypermobility (GJH), as featuring in *a number* of (*not all*) EDS types (2), appears to be a central theme in this study. Furthermore, in 32% hypermobility EDS (former type III) was reported by questionnaire, a condition in which diagnostic criteria still remain indistinct in the absence of clear molecular testing (2). It is most common that patients with severe/degenerative hypermobility of the peripheral joints take refuge with hypermobility EDS profile and join an EDS self-help group, moreover, since submission of diagnostic results is not required for membership of self-help groups. Hence, one can assume that the selection of the study population may have been considerably biased by a lack of unambiguous selection criteria, and may well have included an unspecified number of non-EDS persons.

Second, it is difficult to assess the diagnostic specificity/validity of a number of 'self-examination' methods (and consequent study results) which are critical to the argumentation and to the study outcome. The methods section would also benefit from reporting of values of intra-examiner measurement consistency for the different clinical variables, giving appropriate diagnostic weight to the measurements. Since previous studies reported abundantly on rather moderate reliability of, e.g. linear measurement of active range of mandibular movement (AROM), even in settings with trained and calibrated examiners (3–5), the relevance of self-measurement still remains a subject of controversy. Unfortunately, the authors also failed to use the full, appropriate terminology for diagnostics of temporomandibular disorders (TMD) and for TMJ-related research as recommended by several international organizations (6,7). For instance, since apparently 'permanent lockings of the TMJ' are a central theme in characterizing the condition of the TMJs in EDS, it remains elusive how the authors did instruct the patient *by letter* to make distinction between a TMJ dislocation (also known as a mandibular subluxation) and a closed lock (disc dislocation without reduction), given the resembling clinical symptoms of both conditions. A TMJ dislocation can be defined as a condition in which the condyle is positioned anterior to the articular eminence, and is unable to return to a closed position. It is manifested clinically as an inability to move the lower jaw and to close the mouth without a specific manipulative maneuver. There is usually a clinical history of excessive range of motion that is not painful, but pain can occur at the time of joint dislocation with residual pain following the episode. TMJ dislocation may be the result of a physical jamming of the disc-condyle complex beyond the articular eminence that is maintained by muscle activity or a true hyperextension of the disc-condyle complex beyond its normal trans-

lation position (8). In the methods section, one would also expect to learn how, and with which diagnostic weight, the authors qualified and/or quantified 'problems in the TMJs' among their study subjects, hence leading to important generalizing conclusions as to the prevalence of TMD in EDS.

Another critical issue that was not addressed in the study concerns the assessment of hypermobility of the TMJs, which was reported in puzzling terms (experience of hypermobile joints during mouth opening) by 65% of the enrolled subjects. At present, and despite of numerous suggestions in literature (9–12), universally accepted radiographical and/or clinical criteria to define a hypermobile TMJ are still lacking. In addition, it is highly contestable to postulate that 'maximal mandibular opening measures are excellent to use for studying the mobility of the TMJs'. Since the range of mandibular movements is reported to be closely related to facial morphology (13,14), linear measurement of mandibular border positions generally is not considered as a highly reliable method for assessing condylar (hyper)mobility (15–17). Only a few weak correlations were found between linear measurement of maximal mandibular opening capacity and peripheral joint mobility either at active or assisted range of motion (18–20). It is also known that a lot of factors, such as age, gender, pain in the masticatory system, and degenerative joint conditions, have great influence on mouth opening (16). Previous authors stated that evaluation of TMJ mobility should be performed by (qualitative) assessment of the condition of the joint capsulae or ligaments, which are limiting condylar movement (4). The capsular condition may be assessed clinically by means of registration of, e.g. reproducible 'jumping' and/or jiggling during mandibular movement (12), and, more reliably, by evaluation of the quality of joint endfeel, and joint play under distraction. Jumping/jiggling of the mandible during jaw movements most often reflects incoordination of condylar movement (more precisely, of the disc-condyle complex) of both TMJs, as a result of decreased restraining properties (i.e. increased laxity) of the joint capsulae. Joint endfeel, appearing to be a means for assessing condylar function during the range of motion testing, may be assessed during assisted maximal opening by noting the quality of the movement at the end of the assisted opening. Its quality can be scored either as normal, hard, soft or stiff, with or without pain. Joint play, performed to test the capsular ligaments by applying caudal force on the joint, permits a discrimination between joint and muscle as sources for restriction. The quality of the movement on caudal joint distraction can be classified either as normal, hypomobile or hypermobile, with or without pain (21). As a rule, a hypermobile TMJ will display all, or most, of these (hyperelastic) characteristics, as reported in previous studies (12,19). Any reader being familiar with the literature on TMJ research, would expect to find such fundamental themes discussed in the study. Since it may be clear that the capsular condition, determining TMJ mobility, can definitely not be assessed otherwise than clinically (by an experienced examiner), the self-assignment of TMJ hypermobility diagnosis in the present population is highly contestable. Hence, the relevance of the concerned findings are low.

Further, the authors stated that there was no difference in 'maximal mandibular bite opening' between EDS who did and those who did not report of TMJ hypermobility, hence surprisingly refuting their former assumption that 'maximal opening measures are excellent to use for studying the mobility of the TMJs. Continguously, one would expect to learn more about the clinical relevance and the factors contributing to this conflicting finding. The authors also failed to discuss the influence of the often circadian pattern in which myofascial and/or peripheral joint pain may present in EDS, on the range of mandibular movement. There are still a lot of other factors that may mimic orofacial pain in EDS but, unfortunately, these were not discussed. Another puzzling thing is what is meant by saying that 'EDS persons reporting of problems had significantly lower maximal mandibular opening capacity compared to EDS who did not when biting into thick pieces of food'. Continguously, the reader would expect to learn more about the nature of these problems and the interrelation between this finding and, e.g. the distribution of hypermobile TMJs among these clearly symptomatic subjects. In general, the study would have benefited from the use of appropriate research criteria and an operational and universally accepted terminology (6,7). This would have allowed for objective comparison with other studies on prevalence of TMD signs and symptoms.

After reading, one would like to know if specific TMJ hypermobility signs and/or symptoms do exist more often/are more expressed in EDS as compared with

healthy subjects with TMD. If an association would exist between GJH and TMD, the reader would expect to find such a conclusion (12). On the basis of the present findings, it is inappropriate to conclude that persons with EDS are 'naturally' (or more correctly: intrinsically, i.e. related to the molecular cause of the disease) predisposed to TMJ problems. The reader remains ignorant about the molecular causes which comprise mutations in the genes encoding one of the major fibrillar collagens (types I, III or V) or enzymes essential to collagen biosynthesis, resulting in deficient processing and/or assembly of collagen fibrils (2). Only a thorough epidemiological/histopathological analysis of clinical TMJ manifestations in the distinct EDS types could allow for such generalizing conclusions. After conducting a similar study, and at his best, it might be assumed that persons affected with EDS may be significantly more prone to development and perpetuation of TMD because of the intrinsic structural laxity of the TMJ capsulae.

To our belief, the methodological flaws in question could have been avoided by performing a standardized, double-blind, clinical examination of a (smaller) population, using generally accepted criteria with known diagnostic validity, and taking into account all possible confounders. The generalizability of the relationships, found in this study, is therefore low.

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## REPLY TO LETTER

I have been offered to comment on the letter concerning our article (1).

The letter is valuable in promoting increased knowledge about both Ehlers–Danlos syndrome (EDS) and clinical diagnostics for temporomandibular joint (TMJ) evaluations. However, from a scientific methodological point of view the questionnaire design that Dr De Coster criticizes is commonly used in epidemiologic research. The strength lies in the ability to compare for example symptoms of temporomandibular disorders (TMD) in a specific group with a group of randomized controls. This is interesting since symptoms of TMD also exist in the general population. The design of the questions in the EDS study was similar to that in a previously published study on musculoskeletal symptoms and psychosocial factors among TMD patients (2). To evaluate symptoms on a nominal scale a fairly large sample is needed to have sufficient power to detect difference between patients and controls. The sample of in total 228 answers from both persons with EDS and controls corresponds to a power of 0.81 when the smallest detectable difference is set to 0.10 and the significance level alpha is 0.05 (Fig. 1). A reduction of participants, as was suggested by Dr De Coster, would imply a reduction in the power of the study. It is not possible to evaluate symptoms reported by persons with EDS the way a professional dentist would evaluate TMJ function and signs of TMD during a clinical examination. The results from this EDS questionnaire study provide hypotheses that can be addressed in clinical studies on oral problems in EDS.

I would finally like to make short comments on two specific matters in the letter. Dr De Coster believes that the EDS group consisted of an unspecified number of non-EDS persons and that a sub-type EDS diagnose would be essential for the study. In material and methods it has been stated that in the EDS group all persons who were included in the study had a medically confirmed diagnose of EDS. This means that they had received the EDS diagnose after consulting a medical doctor. Half of these persons also had a complimentary laboratory test of their individual EDS subtype diagnose. EDS often is hereditary and 64% of the persons with EDS reported that other family members also had the disease. None of the controls reported that they had a medically diagnosed EDS or knew of any

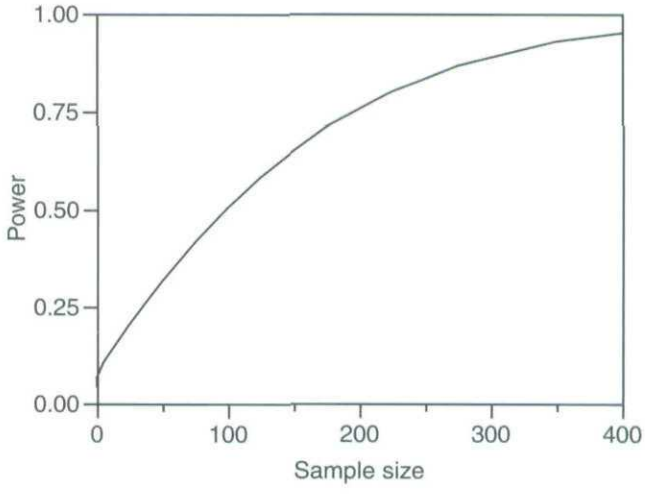


*Fig. 1.* Power as a function of the total sample size.