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The Translation of Research Central Tendencies in Clinical Practice: Power and Limitations of Statistics

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A B S T R A C T

The clinician's ability to provide evidence-based orthodontics is directly related to their adeptness at dissecting published research, which in turn is heavily dependent on the proper understanding of the tenets of research design and biostatistics. Using relevant clinical examples, we discuss key principles affecting the translation of the results of single research studies into clinical practice, including effect modifiers and confounders, study design, central tendency and outliers. The application of the same scrutiny to higher level meta-epidemiological evidence is also illustrated in addition to a detailed discussion of the applicability and limitations of prediction studies. We conclude by highlighting how the particulars of publishing undermine the ultimate goal of transparency in dissemination of research findings and how they may restrict the ability to critically scrutinize and build upon seminal landmark studies that, just like other research, are limited by the original research design and statistical protocols employed.

Introduction

The application of evidence-based orthodontics relies on the interaction between the orthodontist's educational background and clinical expertise, and the updated research conclusions as they apply to the patient's specific condition within the scope of that patient's chief complaints and treatment preferences.[1,2] The clinician's adeptness at understanding the nuances of research design and statistical analysis is critical. Statistics may not be simplified as merely the analysis of existing raw data; they are rather an integral prerequisite to the proper planning, implementation and interpretation of research.[3]

Even in well-conducted research, authors' biases for significant results may lead to inaccurate reporting ("spin") that inflates, especially in abstracts and conclusions, the significance of beneficial results and distracts from non-significant findings.[4] In a review of empirical dental research, substantial waste and inadequacies were identified in research design, analysis and reporting.[5] The learned reader appreciates the role and limitations of statistics in meta-epidemiological (ME) studies that summarize data from multiple investigations to arrive at generalizable and reliable conclusions.

We aim to highlight the impact and relevance of statistical analyses in orthodontic publications on clinical practice, particularly as they translate to the individual patient. We focus on research planning, data analysis and information dissemination with specific examples and treatment reports that highlight the barriers to translation of conclusions derived from orthodontic clinical research and ME studies.

Clinical reports

One- versus two-phase treatment of Class II malocclusion

A 9.8-year-old healthy boy presented with a Class II division 1 malocclusion including a severe 12mm overjet and impinging overbite (Fig. 1). The dental emergence age was advanced by 2 years, and bone age was estimated at 10 years. The parents' concern was the child's prominent maxillary incisors, particularly after the traumatic fracture of a small angular part of the maxillary left central incisor. The patient complained of the teeth appearance and was eager to start treatment. The question for the clinician was whether to initiate treatment or to postpone until the patient was older.

Available evidence: Several randomized clinical trials (RCT) and systematic reviews (SR) have addressed the efficiency of two-phase versus one-phase intervention to correct Class II malocclusions. A Cochrane Collaboration review on the treatment of "prominent upper front teeth in children"[6] included studies evaluating various fixed or removable appliances, treatment duration, trauma to teeth, jaw joint problems,

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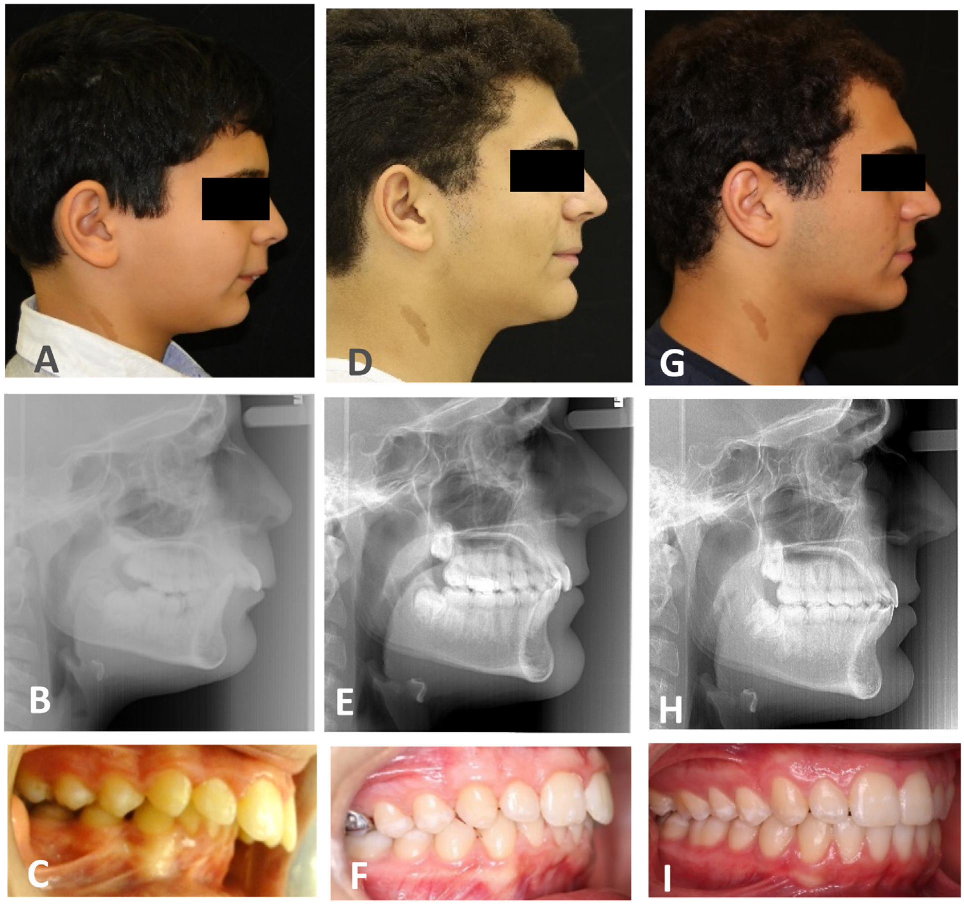

Fig. 1. A-C: A 9.8 year old boy presenting a skeletal Class II malocclusion with 12 mm of overjet. The skeletal age is concomitant with his chronological age, still away from his pubertal peak of growth; D-F: A functional appliance (Activator type) followed by a cervical head gear were delivered for three years: Note the improvement in occlusion and facial appearance; G-I: The second phase of treatment consisted of one year of fixed appliance ending in ideal Class I occlusion and well-balanced facial proportions.

self-esteem, and patient satisfaction. Significant decreases in overjet and ANB angle were found after phase I with no significant differences between treatment with headgear or functional appliances. In comparisons of children treated early with adolescents who had not received early treatment, no significant differences were found in overjet, final ANB angle, or peer assessment rating (PAR) scores. Ghafari et al.[7,8] reported that treatment of Class II malocclusions may be optimal in the late mixed dentition, but earlier intervention in mid-childhood may be required for several conditions (e.g., risk of trauma to maxillary incisors, psycho-social problems related to severe overjet), or when dental and skeletal developments deviate significantly in the individual patient.

The higher evidence suggested delaying treatment of the 9.8 years-old patient. However, early intervention was indicated considering the risk of (repeated) trauma and patient motivation (psychosocial element), particularly in a boy whose growth spurt was more than 3 years away (13.5 years) should full advantage be taken from differential growth between the jaws. The risk for trauma and fracture of the front teeth before adolescence in children with an overjet greater than 9.5mm was reported to be 3.7 times higher than in children with normal anterior occlusion.[9] Accordingly, to prevent trauma to incisors, treatment should be started shortly after the eruption of the central incisors.[10]

Clinical decision versus evidence: Rationalized by the increased risk of trauma and the patient's psychologically justified motivation, treatment was started with a functional appliance followed by a cervical headgear. Three years later, his appearance improved through differential inter-jaw growth. The later phase of fixed appliances yielded an ideal neutrocclusion with balanced facial proportions (Fig. 1). The evidence-based recommendation of treatment in late childhood was balanced by the consideration of risks also documented in research, regardless of whether the same outcome would have been achieved with a later intervention that would have saved the patient years of treatment.

Palatal expansion in post-pubertal subjects

A 15-year-old healthy female (bone age 16 years) complained of malaligned upper teeth, bilateral posterior cross-bite and a constricted maxillary arch with 7-mm space deficiency (Fig. 2), characteristics favoring the incorporation of maxillary expansion in treatment.

Available evidence: Most clinical research of RME is limited to treatment in prepuberty and up to ages 13-14.[11–14] Comparing the skeletal and dental effects of RME in early and late treatment groups classified on cephalometic cervical vertebral maturation (CVM; 1-3, prepubertal; 4-6, post-pubertal), Bacetti et al[15] concluded that the gain in maxillary transverse dimension was more skeletal in the pre-peak group and more dentoalveolar in the post-peak group. Two SRs share the same conclusion.[10,11] Evaluating differences between RME and mini-screw assisted RME (MARME) in late adolescence, the conclusions in a RCT[16] and similarly in SR and meta-analysis[17] (MA) expectedly indicated that bone-borne expanders produce greater orthopedic effects and less dental side effects than conventional expanders.

Clinical decision versus evidence: The orthodontist recommended the use of MARME but the patient refused mini-implants and any minimally invasive surgery. The patient and family were informed of the limitations and risks of the alternative conventional RME treatment, which nevertheless resulted in a 2.5 mm midline diastema 3 weeks after expansion, a reliable indicator of an underlying midpalatal suture split.[18,19]

Fig. 2. A-C, G: A 15-year-old healthy female presenting bilateral posterior cross-bite and a constricted maxillary arch with 7-mm space deficiency; D-F, H: A conventional Rapid Palatal Expander (modified Hyrax type) was delivered, and activation for 3 weeks was performed. Note the diastema of 2.5 mm that was developed, indicating a mid-palatal suture split.

Interceptive treatment of palatally displaced canine (PDC)

In a routine orthodontic check-up, clinical assessment of a 10-year-old girl revealed a rotated maxillary left permanent lateral incisor, absent buccal permanent canine bulge and a suspected palatal bulge. On a panoramic radiograph, the canine was off the path of eruption, in sector 4 − mesial to mesial heights of contour of lateral incisor crown and root[20,21] and overlapping with the fully developed lateral incisor.[22,23]

Available evidence: The clinical and radiographic signs reflected the risk of canine impaction.[24] By applied logistic regression analyses in a sample of 82 impacted canines, Warford et al[21] identified the probability of impaction of a canine located in sector 4 at 99%. The interventions recommended to prevent PDC impaction include the extraction of primary canines and space creation using RME and/or a headgear and fixed appliances.[25-32] Among the reported results 65.1% of PDC erupted after RME (a percentage arguably close to chance [50%]) compared to 13.6% in untreated subjects,[30] 80% emerged after RME and primary canine extraction compared to 28% in control subjects,[31] 82.3% successful eruption after headgear (HG) treatment, and 85.7% with HG/RME, compared to 36% in the control group.[32] The 3 articles did not consider the severity of PDC location, suggesting that the remaining 15-40% of unerupted PDCs despite treatment were the most severely displaced, many likely located in sector 4.[21] The most recent Cochrane review indicated uncertain evidence for the extraction of one or both primary canines to prevent PDC impaction,[25] underlining the limitations of the original research by Ericsson and Kurol[33] that did not include an untreated control group to explore the probability of permanent canine eruption without extracting the primary canines. The same review notes that orthodontic methods of space gaining (RME, HG, fixed orthodontics) appear to increase the likelihood of spontaneous eruption of PDC but that the risk of bias and reporting errors in the original studies were too great to arrive at any reliable conclusions.[25]

Clinical decision versus evidence: RME was planned to provide space for the four incisors and mesialize the lateral incisor away from the PDC. RME was followed by segmental limited maxillary fixed orthodontics (2 × 4) to save the diastema-induced space and gather the anterior spaces. Twenty-three months later, the canine had erupted spontaneously. Periodic panoramic radiographs revealed gradual spontaneous distal movement of the canine and root resorption of the predecessor primary canine.

The successful treatment (Fig. 3) despite the severe canine position was related to the individualized mechanics that accounted for PDC severity. If part of an RCT, such mechanics would introduce a “high risk of bias” and “sources of error” frequently qualified in SRs.[34] Inherent to proper research and statistics, generalization, consistency and reproducibility may not be translated in individualized clinical treatment. RME could not be used consistently in prospective studies because the amount of expansion necessarily varies with the severity of crossbites and initial degree of space deficiency, aside other variables (e.g., malocclusion, clinician’s skills and treatment preferences, patient’s compliance and response to treatment). While randomization controls for various biases, the numerous variables in the study of PDC treatment led authors of a recent SR to conclude that a well-designed RCT is unlikely.[35] The same may be true for other if not most orthodontic interventions.

The chasm between evidence and practice − limitations to the translation from research to clinical practice

Based on a sample project, we discuss the limitations of translating research findings to practice. The work by Bacetti et al[15] is commonly used to recommend conventional RME in pre-pubertal children and the alternative MARME in post-pubertal patients. A close look at the data reveals similar immediate skeletal responses in the early and late treatment groups. Statistically significant (SS) differences were absent ($p > 0.05$) in 15 of 16 measurements, including the maxillary skeletal width (3.4mm vs. 2.8mm) and incisor apex width (5.6mm vs 5.5mm). The only SS different variable was the increase in the lateronasal width in the early treated group (3.3mm vs. 2.2mm, $p < 0.05$), which is of limited clinical significance. The authors’ main conclusion that treatment before the pubertal peak induced “more pronounced” transverse skeletal craniofacial changes was based on a comparison of long post-retention phase of 7-9 years in each treatment group separately compared to non-treatment induced growth changes in a control group. The comparison

Fig. 3. A-C: A 10 years old girl presenting a rotated maxillary left permanent lateral incisor, absent buccal permanent canine bulge and suspected palatal bulge; D: The panoramic radiograph reveals an abnormal eruption path of the canine in sector 2; E-G: Rapid maxillary expansion was implemented followed by segmental limited maxillary fixed orthodontics (2 × 4) to gather anterior spaces; H: A panoramic radiograph after expansion and alignment of maxillary anterior teeth shows the self-correction path of eruption of the maxillary left permanent canine; I-K: At a follow up visit 23 months later, the canine erupted spontaneously.

entails numerous sources of error, leading us to discuss elements of research design and methodology that affect the quality and interpretation of clinical research.

Comparison groups: effect modifiers and confounders

Studies are developed around focused clinical questions to understand the effects of specific interventions on identifiable outcomes, frequently in orthodontic research by gauging specific variables before and after the applied therapy. Because the study variables are measured at different time points, the outcome variable may be affected by factors other than the intervention. Groups of subjects are often compared, and a control/untreated group is included to determine how effective the treatment was compared to no treatment. Alternatively, the question asked is how effective is intervention "A" compared to intervention "B", whereby two "similar" groups of subjects receive different or modified versions of the intervention. The research questions may target the effectiveness of intervention "A" when applied to patients with characteristic "X" compared to patients with characteristic "Y", as in the comparison of RME treatment effects in pre- and post-pubertal subjects.[15]

In the Baccetti et al's paper, various sources of error were likely in the 7-9 years post-expansion, such as maintaining the RME for variable periods (42-75 days) and variations in treatment plans and mechanics and retention protocols. These factors may have *"interacted"* with the effect of RME as *"effect-modifying"* variables that may not influence transverse width alone but in conjunction with RME. In addition, *"confounding factors"*, often intrinsic to the subjects being assessed, relate to the outcome being studied independent of the assessed intervention. These factors may affect patient growth and maturation; they include age, sex and individual growth pattern. Confounders "distort" the relationship between intervention and outcome, thus the efforts to "control" for these effects in sound research. Such control may be through advanced statistical techniques, requiring sufficient power with large sample sizes. When the latter are not realistic or feasible, confounding variables are accounted for by applying appropriate inclusion criteria and comparing to a control group of untreated individuals similar to the treatment group with respect to the identified confounders.

Research design: prospective/retrospective and randomization

Retrospective studies are inspired by trends observed in the clinical setting.[36] Data collection is limited to available and retrievable documentation from reviewed records. Lacking in this scheme are "a priori" research questions, the assessment of potential confounders and effect modifiers, a wide application of inclusion criteria, the original recruitment of subjects, and the possibility to modify or ensure consistency of the intervention and to control the quality of data acquisition, thus affecting the measurement of outcome variables.

Ideal studies are "*prospective*", accounting for subject characteristics, applied interventions, outcome variables, the myriad of potential known and unknown confounders and effect modifiers,[37] and factors often either unknown or impossible/impractical to measure. The only way to account for unknown variables and confounders is through *"randomization"* of subjects into treatment or control groups after applying inclusion and exclusion criteria.[38] Incorporating a control group is faced with the ethical dilemma when denying a patient treatment that may be time- and growth- sensitive. In a study of facemask with and without palatal expansion, Vaughn et al[39] partially overcame this obstacle (but not without a risk of bias on the success of RME) by assigning a temporary (for 12 months) control group of subjects who were still growing at 12 months from study initiation and received treatment after random reassignment to a treatment group.

Central tendency, statistical significance, power and sample size

Research limitations relate to the reliance on statistics derived from specific samples to draw *"inference"* or conclusions regarding populations. A *"statistically significant"* difference indicates confidence that an obtained finding reflects a "real" and not a chance effect of the intervention.[40] The improper assumption is that all subjects in a pooled group behave similarly when in reality the *"central tendency"* or average behavior of that group is what statistical methods describe. In a normally distributed sample, the individual values are distributed evenly around (above and below) the mean, with variance and standard deviation describing the extent to which the values within the sample deviate from the mean.[41]

Detecting a difference between two populations using means and standard deviations depends on the study *"power"* or the ability to avoid a false negative result; an insufficiently powered study will miss a SS effect of the intervention when it is present. Power relates to sample size, larger samples being better suited to disclose smaller differences.[40] In prospective research, sample size calculation is determined *a priori* using information on the outcomes being assessed. Retrospective studies are limited by the sample available, which may not always be equally distributed between comparison groups or large enough for sufficient power. In the Baccetti et al study,[15] if within the late treatment group a significant proportion of CVS4 and/or CVS5 subjects responded to expansion similarly to the early treatment cohort, and RME treatment was less effective only in CVS6 subjects, the behavior of the entire group would still be affected by the behavior of the CVS6 subjects since all subject values are summarized into one mean. The cut-off point used by researchers to compare treatment groups often traces back to sample size and power. The early and late treatment groups contained 29 and 13 subjects respectively, the late treatment group already at a disadvantage in terms of sample size. Other cut-offs (for e.g. including CVS4 with the early treatment group) would have likely produced a late-treatment group with too few subjects, inadequate power, and inability to detect a SS result.

The issue of clinical versus statistical significance also warrants attention. The statistical judgment (presence of a SS difference) must be made relative to the average value, but clinicians must also look through the lens of clinical significance. Studies with excessively large sample sizes can still attain statistical significance with minute, clinically inconsequential, effect sizes.[40] Similarly, even when the average behavior of a group of subjects as a whole does not reach SS, the response that presents in specific "outliers" (e.g., at or beyond 1 SD) within that group may still be considered clinically significant and may warrant further consideration of the specific moderating and risk factors that may have contributed to a greater-(or smaller)-than-average response.

Evidence from meta-epidemiological studies

The benchmark *"randomized controlled study (RCT)"* is difficult to perform for many orthodontic research questions because of objective limitations such as the control group-related ethical considerations and availability of eligible subjects who accept to enroll in the study. Research questions that address phenomena of low incidence often are only assessed through lower-level evidence such as controlled non-randomized and retrospective studies, or even case reports. ME research can be used to compare large numbers of studies for consistencies and contradictions to arrive at general conclusions. In addition to SRs of adequately performed research, MAs utilize statistics to extract summary numbers from data pooled from multiple studies, potentially overcoming the statistical and confounding errors encountered in single RCTs by increasing sample size, thus randomizing confounders. However, applying statistics on numbers originating from different studies necessitates a minimal level of "homogeneity" or similarity in methodology.[42] The inability to perform MAs in a SR reflects heterogeneity among studies of a scientific topic.

Evidence from prediction studies

A major limitation of cross-sectional studies and corresponding statistics is the difficulty to ascertain causality from association. In a SS association, a variable and an outcome have been found together frequently enough that the relationship between them is deemed significant beyond chance, but this finding does not confirm that the associated variable has both preceded and caused the outcome.[38] To explore causative associations, researchers conduct "prediction" research, following-up on subjects who initially present without the outcome of interest for a specific duration (cohort studies), then applying more advanced statistical techniques to ascertain which subjects developed the outcome, and which did not. Subsequently, the outcome is related to pre-existing variables. Thus, considering a set of initially presenting variables, the development of a disease or condition in subjects who are free of the condition can be "predicted." The clinical aim is to detect high risk subjects before the development of a condition and the application of preventive measures.

The practical translation of results is related to regression modeling, through which the principle of "parsimony" applies: detecting the smallest number of variables that can predict the largest variation in a particular outcome.[43] "Parsimonious" models are easier to interpret clinically and are more applicable and amenable to generalization because information involving a large number of variables may not always be available or financially feasible.[43] Prediction models are, however, *not* inherently generalizable; they are equations that describe the extent to which the variability exhibited by the outcome of interest, in the *particular dataset assessed*, can be predicted using a specific set of explanatory variables.[43] Subject to the principles of research design and the limitations of biostatistics, prediction research is similarly sensitive to population specifics (sample size, chance, outliers).[44] However, unlike the more direct statistical tests used to determine the binary association between two variables, statistical regression and modeling techniques are numerous and operator-sensitive. The reduction techniques employed to move from an exploration of tens of potential associated variables to a final prediction model involving only the most clinically and SS predictors are sensitive to subjective decisions regarding the clinical importance of these variables, the nature of the variables (and potential between-variable correlations) and the specific statistical methods employed at various stages of model building.[43]

In orthodontics, prediction studies have addressed the risk of canine impaction,[45,46] the successful skeletal response to rapid maxillary expansion,[47,48] and craniofacial growth directions in either treated[49,50] or untreated growing patients.[51,52] For illustration, the prediction of maxillary canine impaction was considered through a cohort assessment of panoramic radiographs from 82 subjects at multiple time-points.[21] The authors concluded that the impaction could be predicted solely on the basis of sector location, without including the canine angulation to a constructed horizontal. In a more recent retrospective cohort of 60 subjects, canine angulation to the first premolar was identified as a significant predictor of canine impaction among other factors which included the canine angulation to the midline, itself significantly associated with canine impaction.[45]

The lack of added benefit to the variable canine angulation to horizontal[21] or canine angulation to midline[45], should not be equated with a non-significant association between these variables and the risk of canine impaction. In the datasets specific to each of the two studies,[21,45] different variables provided more predictive value, and the addition of other variables was either impossible (due to high correlations) or did not improve the model's predictive value significantly enough to justify making the model more complex by adding more variables. Highly correlated variables cannot be included in the model because they provide little independent information. Therefore, prediction models should not be used to make conclusions regarding the variables not included in the final model.

Probabilities are clinically usable when the outcome being assessed is dichotomous (yes/no probability), with clear success and failure, such as the probabilities of canine impaction or successful midpalatal suture opening have non-negotiable clinically meaningful value. A high probability of canine impaction warrants clinical intervention. The clinical translatability of predictive research on more complex topics relating to craniofacial growth and orthodontic growth modification is more challenging, such as the identification of skeletal parameters that could distinguish poor and good growers without orthodontic treatment among 8-years-old patients with moderate skeletal Class II malocclusion.[52] Growth is a dynamic process subject to more long-term variations among different components than the static present condition of an impacted canine or narrow maxilla.

Growth predictions engender various questions: Should a favorable grower with Class II not receive treatment? What "predictive" variables other than initial skeletal/dental parameters may have affected treatment? Are outliers identifiable from the start? Should poor growers be denied orthodontic treatment and committed to orthognathic surgery if their condition is too severe? Or should a poor grower undergo more interventions and longer treatment? In this context, growth research may be valuable to understand craniofacial growth but may have limited value in clinical application in the individual patient.

The "labyrinth" of publications

"Spin" reflects the biased desires of authors to show favorable results, leading to the conscious or unconscious inflation in reporting beneficial results and distraction from non-significant results. Spin is frequently employed in the abstract and conclusions.[4] Ghafari[53] assigns the term "impermeability" in reference to seminal "waterproof" landmark articles of pioneer researchers that are commonly accepted as descriptive canons yet lack controlled testing, such as the six keys of occlusion.[53] These phenomena should not be immune from scrutiny, particularly with the multiplication of online commercial publishing companies, which in turn complicate the work of peer reviewers in verifying the content of submissions to recognized journals.

In a SR of systematic reviews, Bucci et al[54] discuss two SRs[12,14] that suggest "significantly more favorable skeletal changes when [RME] was performed before the pubertal growth peak." In one of the 2 SRs,[12] the authors concluded based on one of 3 eligible studies that long-term stability of transverse changes was better in less mature individuals (prepuburtal peak) and "questionable" in "skeletally mature groups." The conclusion in the second SR[14] was that RME always produces skeletal opening of the midpalatal suture in growing subjects. Bucci et al[54] fail to mention that the ages of the "growing" subjects were between 7 and 17 years. The authors of the third SR were unable to draw accurate conclusions because of the low quality of included studies but stated that "generally speaking" the opening of the suture becomes more difficult as the patient grows old, although they also reported that in two studies the sample was older than 18 years, but the suture still separated.[13]

In SRs of treatment timing with RME,[11,13,14,54] most of the included studies had been performed on patients younger than 14 years. Studies in subjects older than 16 years also reported successful treatment.[55,56] The SR with the specific aim of assessing pre- and post-pubertal transverse changes with RME[11] included 6 studies only one of which, a retrospective study with inherent errors[15] was the basis for a questionable conclusion made in the abstract, although the authors properly discussed the limitations of this study, stating that the research quality was "not sufficient to draw conclusive evidence." This discrepancy between abstract conclusion and manuscript content should invite the researcher looking for credible evidence to dissect the methods and results section of any manuscript and not blindly rely on the provided conclusions.

Conclusions

1. Study designs typically include comparisons of similar conditions in groups of individuals presenting with the natural and inevitable biological and environmental variability. Summary statistics are critical to develop evidence-based recommendations and clinical guidelines.
2. Individual variation is a principal challenge to the clinician whose judgment must be guided by tested principles (at least with defined central tendencies) despite inconclusive or even contradicting specific evidence.
3. Research data provide central tendencies that may or may not be generalized, depending on the power of the investigation. The farther "outliers" fall from the average, the more the treatment outcome will depend on the assessment and control of moderating and risk factors. This reality fosters the rationale and need to develop research that helps identify and categorize the sources of extreme variations, and registries across educational and organizational entities that would include greater numbers of outliers.
4. Case reports/case series and retrospective research are a valuable source of evidence. Some reports represent outliers and potential sources of variation and modification of common treatment approaches.
5. Limitations are inherent to quantitative research. Controlled research is limited by the rigidity of the protocol, a necessity for research and statistics but a possible obstacle to clinical applications. This seeming contradiction calls for recognizing the gaps between research and clinical practice. Some are bridgeable but could require major funding; others may be invasive to tissues and not ethically viable.
6. Single studies are limited by their methods and statistics. ME studies are limited by the shortcomings of the original single studies and the methods used to extract, summarize and compile the SR.
7. Predictive research reveals associations among variables that are inherently specific to the sample from which predictions were derived, the reason why they have limited generalizable application.
8. Research publications, regardless of how high on the evidence ladder, should be scrutinized by orthodontists seeking informed conclusions to eventually integrate their evidence-based clinical judgement in treatment planning for the individual patient.

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Patient consent was obtained.

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Author contributions

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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