International Orthodontics 2022; 20: 100603

Websites:
www.em-consulte.com
www.sciencedirect.com

Original Article

A retrospective long-term comparison of early RME-facemask versus late Hybrid-Hyrax, alt-RAMEC and miniscrew-supported intraoral elastics in growing Class III patients

Alexandra K. Papadopoulou [1], Despina Koletsi [2], Caterina Masucci [3], Veronica Giuntini [4], Lorenzo Franchi [5], Mehmet Ali Darendeliler [6]

Available online: 28 December 2021

1. Division of Orthodontics, University Clinics of Medicine and Dentistry, University of Geneva, rue Michel-Servet 1, 1206 Geneva, Switzerland
2. Clinic of Orthodontics and Paediatric Dentistry, Centre of Dental Medicine, University of Zurich, Zurich, Switzerland
3. Sous-section Orthopédie Dento-Faciale, Faculté de Chirurgie dentaire, Université Côte d'Azur, Nice, France
4. Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy
5. Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy. Thomas M. Graber Visiting Scholar, Department of Orthodontics and Paediatric Dentistry, University of Michigan, Ann Arbor, Michigan, USA
6. Discipline of Orthodontics and Paediatric Dentistry, School of Dentistry, Faculty of Medicine and Health, The University of Sydney, Sydney Dental Hospital, Sydney Local Health District, Surry Hills, NSW, Australia

Correspondence:
Alexandra K Papadopoulou, Division of Orthodontics, University Clinics of Medicine and Dentistry, University of Geneva, rue Michel-Servet 1, 1206 Geneva, Switzerland.
alexandra.papadopoulou@unige.ch

Keywords
Class III malocclusion
Maxillary protraction
RME
Facemask
Alt-RAMEC
Hybrid-Hyrax
TADs
Palatal mini-implants

Summary

Objective > To compare the long-term dentoskeletal effects of early treatment with banded or bonded RME (Rapid Maxillary Expansion)-Face Mask (RME-FM) versus late treatment with bonded Hybrid-Hyrax, alt-RAMEC (Alternate Rapid Maxillary Expansion and Contraction) and intraoral Class III elastics anchored to miniscrew-reinforced-Lower-lingual-Arch (alt-RAMEC-HH-LLA) in growing, maxillary retrognathic patients.
Materials and Methods > Two groups were matched at long-term follow-up retrospectively. Patients received either early RME-FM ($n = 16$, 5 males, 11 females, age T1: 6.5 $\pm$ 0.9 years, age T2: 15.8 $\pm$ 2.5 years) or late alt-RAMEC-HH-LLA ($n = 15$, 7 males, 8 females, age T1: 12.52 $\pm$ 0.94 years, age T2: 16.8 $\pm$ 0.9 years). Total follow-up was 9.2 $\pm$ 2.3 years and 4.2 $\pm$ 0.2 years respectively, including fixed appliances to compete treatment.
Results > Both treatments resulted in Class III correction except one unsuccessful case of alt-RAMEC-HH-LLA. Active maxillary protraction was 1.6 $\pm$ 0.5years with RME-FM and 0.5 years with

https://doi.org/10.1016/j.ortho.2021.100603

alt-RAMEC-HH-LLA being significantly shorter ($P < 0.001$). Values at T2 estimation with multivariate linear regression for correlated multiple outcomes, conditional on baseline estimates, age and sex showed alt-RAMEC-HH-LLA inducing significantly more retroclined lower incisors (mean: −6.11°; 95%CI: −10.66, −1.57; $P = 0.01$), less overbite (mean: −1.28 mm; 95%CI: −1.79, −0.761; $P < 0.001$), less maxillo (Co-A)- (mean: −4.54 mm; 95%CI: −7.91, −1.16; $P = 0.01$) mandibular (Co-Gn) (mean: −10.5 mm; 95%CI: −17.45, −3.55; $P = 0.003$) projections/size, more open gonial angle (mean: 4.93°; 95%CI: 2.27, 7.59; $P < 0.001$), and less S-N length (mean: -5.04 mm; 95%CI: −6.57, −3.51; $P < 0.001$).

Conclusions > Patients treated with either early RME-FM or late Alt-RAMEC-HH-LLA had comparable overall post-pubertal skeletal and overjet corrections. However, the late Alt-RAMEC-HH-LLA showed less correction of dentoalveolar compensations and in particular of the mandibular incisors. The overbite, maxillary and mandibular projection and size were lower and the gonial angle was more open.

Introduction

Patients with Class III malocclusion display unique dentofacial growth discrepancies that appear early in life and are characterised by retrusive maxilla with reduced effective length, increased mandibular effective length, increased vertical measurements and dentoalveolar compensations such as increased maxillary incisors' proclination and mandibular incisors' retroclination. These features are established as early as the age of 4 with the correlations of short anterior cranial base to the mandibular morphology and size indicating a biological connection to the Class III phenotype compared to Class I controls [1,2]. Mandibular pubertal growth peak ensues during cervical vertebra maturation (CVM) stages 3 and 4, lasts 6 months longer than in normal growers until young adulthood (CVM stages 4–6) with the average increases in length being twice the magnitude in Class III girls and 3 times greater in boys compared to their normal counterparts [3,4]. This persistence of mandibular growth further to the adolescent growth spurt combined with the inability of the maxilla to catch-up contribute to worsening of the maxillomandibular relationship and create difficulties in predicting, controlling, and successfully treating Class III subjects in a conservative manner [5,6].

Distinct subtypes of Class III malocclusion have been identified with combinations of sagittal and vertical developmental discrepancies. Within the Class III studied populations, a significant proportion exhibit either pure maxillary retrognathia (25%) or a combination of maxillary retrognathism and mandibular prognathism (22.2%) meaning that almost half of the affected individuals have midface underdevelopment [1,7,8]. Since maxillary retrognathia is within the aetiologic factors of Class III malocclusion, maxillary protraction protocols are widely utilized for Class III correction in growing patients.

Rapid maxillary expansion (RME) either with banded or bonded expanders combined with Face Mask (FM) result is maxillary protraction while some dental side-effects and anchorage loss due to mesialization of the dentition are unavoidable because these appliances are anchored on teeth [9,10]. Skeletal response to 6-month RME-FM treatment in growing 6–11-year-olds results in significant improvements in the angular (SNA, SNB, ANB) and linear measurements with enhancement of maxillary length and reduction of the negative Wits. The corresponding soft tissue changes equal 50–79% of forward maxillary and 71–81% of mandibular downward and backward hard tissue changes, contributing to more balanced and pleasing profiles [11] and irrespective of vertical skeletal features [12]. RME-FM treatment is more effective when patients are in the early mixed dentition rather than in later dental development stages, especially with regards to the magnitude of maxillary advancement and the favourable post-pubertal modifications in both maxillary and mandibular

Glossary

RME	Rapid Maxillary Expansion
RME-FM	Rapid Maxillary Expansion-Face Mask
HH	*Hybrid-Hyrax*
Alt-RAMEC	Alternate Rapid Maxillary Expansion and Contraction
Alt-RAMEC-HH-LLA	Alternate Rapid Maxillary Expansion and Contraction and intraoral Class III elastics anchored to miniscrew-reinforced-Lower-lingual-Arch

structures [13,14]. Grouping RME-FM treated patients in 4–7, 7–10, 10–14-year-olds and showed that all groups demonstrated maxillary anterior and vertical movement, mandibular repositioning and improvement in their soft tissue convexity; however, greater apical base changes and total molar correction was noted in the younger age groups [15]. Nevertheless, part of the correction is due to dental movements namely molar extrusion, upper incisor proclination and lower incisor retroclination [16,17], findings that also apply to conservative approaches other than RME-FM for the treatment of Class III [18–20].

Adjunctive interventions to RME-FM have been trialled to investigate their effectiveness in enhancing Class III dentofacial orthopaedic treatment and its applicability to older patients. "Alternate Rapid Maxillary Expansion and Constriction'' (alt-RAMEC) for 9 weeks was initially conceived for disarticulating the circumaxillary sutures, before maxillary advancement with intraoral springs, in cleft patients with maxillary hypoplasia [21]. A shorter 4-week alt-RAMEC protocol was successfully used on tooth-borne acrylic RME-FM for early treatment of class III patients outside of cleft cases [22]. Alt-RAMEC-FM had more favourable short-term outcomes compared to RME/FM therapy, generating greater maxillary advancement and intermaxillary improvement as an early Class III treatment modality [23]; however, a parallel quasi-randomised trial of patients at CVM 1-2 stages using 3D CBCT volume superimpositions showed that both protocols produced similar maxillary advancement of 2 mm in point-ANS [24]. The combination of early 8-week Alt-RAMEC, hybrid-Hyrax (HH) and FM has been effective in Class III cases [25]. A shorter 4-week alt-RAMEC anchored to HH and FM in older adolescents advanced point-A by 3.4 mm with minimal extrusion and mesialization of the maxillary molars within 4 months [26]. In a similar late adolescent sample, alt-RAMEC-HH was combined with full time heavy intermaxillary elastics to a miniscrew-anchored lower lingual arch (LLA) for minimising FM partial daily use and cooperation issues with FM. This treatment approach resulted in significant short-term improvement of skeletal variables; however, overjet correction was coupled with proclination of maxillary incisors and retroclination of mandibular incisors [27].

Public health care systems suffer from extensive waiting times for eligible patients to receive treatment. As a result, patients can be on the waiting lists for many years; thus, crucial time is missed during which conventional dentofacial orthopaedic treatment with RME-FM could have been applied for successful resolution of their skeletal malocclusion. Therefore, the aim of the present study was to compare the long-term dentoskeletal effects and changes produced in maxillary retrusive growing individuals when treated either early with conventional RME-FM or late with alt-RAMEC-HH in conjunction with full-time heavy intermaxillary Class III elastics anchored on a miniscrew-reinforced lower lingual arch (alt-RAMEC-HH-LLA). The null hypothesis was that the addition of adjunctive procedures would overcome the shortfalls of late treatment [13–15] and no differences would exist in the long-term skeletal, dental and soft tissue parameters between the two treatment protocols, either early RME-FM or late alt-RAMEC-HH-LLA.

Materials and methods

Sample

The alt-RAMEC-HH-LLA group was recruited prospectively and treated in the Department of Orthodontics, Sydney Dental Hospital. Inclusion criteria were skeletal Class III malocclusion due to retrognathic maxilla. This baseline diagnosis was performed by standard orthodontic procedures such as the combination of clinical and cephalometric examination. Facial profile had to be concave with underdeveloped midface characteristics such as flat malar bases. The baseline cephalometric values of SNA, SNB, ANB and Wits were also considered and further confirmed the clinical examination. Inclusion criteria were also the presence of anterior crossbite, permanent dentition with dental Class III of molars and canines, no previous orthodontic or orthopaedic treatment, absence of congenital abnormalities (facial clefts and/or syndromes), and a Cervical Vertebrae Maturation (CVM) Stage of 2–4 [28]. All patients, parents or guardians were informed of the study protocol and complications associated with the treatment including Temporary Anchorage Devices (TADs) failure, possible long-term ineffectiveness and relapse. Informed consent was obtained. A comparison group having been treated with conventional RME-FM was obtained retrospectively from the Department of Orthodontics, University of Florence, Italy. This group was matched to the test group for the initial maxillary retrognathia (SNA°) at T1 requiring maxillary protraction as part of the treatment, age and post pubertal maturation at T2 as all patients in both groups were required to have reached post-pubertal stages (CVM 5-6) at the long-term follow-up. Lateral cephalograms were available for both time points. Ethics approval was obtained from the Human Research Ethics Committee of New South Wales Health (Approval number X10-010).

Treatment protocol

Alt-RAMEC-HH-LLA group

A bonded HH anchored in 2×9 mm palatal mini-implants BENEfit® (PSM, Tuttlingen, Germany) with ball hooks embedded in the acrylic was cemented on first and second permanent premolars and first permanent molars. The palatal mini-implants were inserted bilateral to the midpalate suture with a distance of at least 5 mm between them to allow unimpeded

FIGURE 1

Intraoral photos of the appliances *in situ* for the alt-RAMEC, hybrid-Hyrax (HH), lower-lingual-arch (LLA) group

attachment of each implant's transfer-copying for the polyvinylsiloxane (PVS) impressions. Their sagittal position was between the first and second premolars. The LLA was cemented with bands on the first permanent mandibular molars and included "S" shape hooks bonded with composite resin to the permanent canines and wire extensions to the lingual surface of the incisors to prevent their retroclination. Two self-drilling Aarhus® miniscrews were inserted between the mandibular canines and lateral incisors, in attached gingiva in the area of the mucogingival junction and hosted two sectional 0.019×0.025 stainless steel wires bonded passively with composite resin to the lower incisors aiming to reinforce anchorage and maintain them in their initial position (*figure 1*). All TADs were inserted under local infiltration anaesthesia (2% lidocaine with 1:80.000 epinephrine). The alt-RAMEC protocol included expansion and constriction of 1 mm/day in a weekly interchangeable manner for a total of 8 weeks and an additional 1 week of expansion. Upon completion of alt-RAMEC, full-time heavy Class III elastic forces of 400gr were applied from the HH ball hooks to the LLA "S" hooks for 8-9 weeks [27]. Immediately after maxillary protraction scheme, all appliances were removed and preadjusted fixed appliances were used for completion of orthodontic treatment.

RME-FM group

A maxillary expander, a protraction FM, and heavy elastics were used in the RME-FM group [29]. Bonded or banded maxillary expander (Leone A2620, Leone Orthodontic Products, Sesto Fiorentino, Florence, Italy) with soldered vestibular hooks in the canine region was cemented to the deciduous canines and first and second primary molars. In cases that the first permanent molars were present, the expander extended along the first maxillary molars and first and second primary molars. The expander was activated daily once or twice until overcorrection, with the palatal cusps of the maxillary posterior teeth matching the corresponding buccal cusps of the mandibular posterior teeth. After expansion completion, FMs were fitted and elastic forces of 400–500gr per side were adjusted from the expander's hooks to the FM in a downward and forward direction of 30° to the occlusal plane. Patients were advised to wear

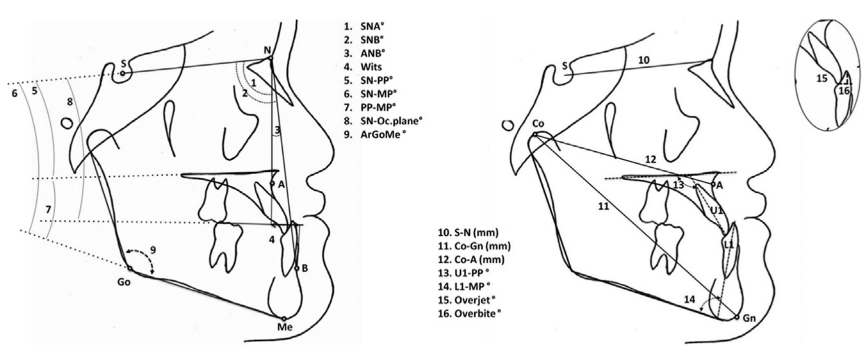

FIGURE 2

Conventional angular and linear cephalometric measurements

the FM for a minimum of 14 h per day until positive overjet and overcorrection to almost a Class II occlusal relationship. After active therapy with FM, all patients wore a removable mandibular retractor as retention appliance for at least one year. Treatment was finalised with preadjusted fixed appliances in permanent dentition. Removable or fixed retention appliances were delivered to the patients after the end of treatment.

Cephalometric analysis

Ten angular and 6 linear conventional cephalometric measurements were used for the evaluation of skeletal and dental parameters (*figure 2*). All cephalograms were traced and measured by the same operator (AKP), who was not blinded on the treatment group and the time points; however, there was considerable wash-out period between tracing and measuring the two groups. Additionally, numbers of the one group were not accessed when performing the measurements of the other group in an effort to avoid bias, thus rendering the process utterly blinded.

Method error

Twenty lateral cephalograms were re-measured after 4 weeks for method error analysis by the same assessor. Method of moments' estimator (MME) was used for calculating the random error and the Intraclass Correlation Coefficient (ICC) to assess intra-observer reproducibility [30].

Statistical analysis

Data were assessed for normality of the residuals of the distributions, visually through qq-plots and statistically through Shapiro- Wilk tests. Descriptive statistics were calculated, as appropriate (mean and standard deviation: SD or median and interquartile range: IQR) for all cephalometric variables at T1 and T2 for both groups, as well as for the changes over time within each group. Statistical comparisons at baseline (T1) were avoided, due to the considerable age difference between the two groups and this was also followed for the estimated change (T2-T1) comparisons. In the long-term (T2), independent-sample t-tests or the non-parametric equivalent Mann Whitney U test across the two groups were performed, following data distribution of variables, as appropriate, and allowing for an evaluation of crude differences between the groups. The Bonferroni correction was applied for this and the level of statistical significance under the prism of the 16 comparisons attempted was determined to $P = 0.003$. Multivariate linear regression for correlated multiple outcomes was performed to assess the effect of treatment on the final (T2) cephalometric variable estimates, conditional on the respective baseline variables (T1) and the respective estimates and 95% confidence intervals (CIs) were reported. This effect was adjusted for sex and age at T2. The standard errors were derived using the bootstrap method (1000 replications), in an attempt to account for the relatively small sample size and any deviations from the normal distribution assumption for some cephalometric variables. The Stata v. 15.1 software (Stata Corporation, College Station, Tx, USA) was used for all data processing and analysis and the level of significance for the regression model was set at $P < 0.05$.

Results

Demographic and treatment duration/follow-up data

The alt-RAMEC-HH-LLA group comprised of 15 Class III patients (7 male, 8 female) and the RME-FM group of 16 patients (11 females, 5 males). At baseline meaning at initiation of maxillary protraction mean age for the alt-RAMEC-HH-LLA group was 12.5 ± 0.9 years old and 6.5 ± 0.9 years for the RME-FM group (mean diff: 6 years, 95% CI: 5.2, 6.6, $P < 0.001$). At T2 the ages were 16.8 ± 0.9 years and 15.8 ± 2.5 years respectively (mean diff: 1 year, 95% CI: 0.5, 2.5, $P = 0.185$).

Treatment was completed by all patients. In the Alt-RAMEC-HH-LLA group, one mandibular miniscrew was mobile before the initiation of Class III elastics. This was replaced and remained stable with no further losses noted. Additionally, the buccal attachment of a lingual arch was fractured. Same day laboratory repair was delivered for the unimpeded continuation of Class III elastic wear. Maxillary protraction was completed in 0.5 years in the Alt-RAMEC-HH-LLA group and 1.5 ± 04 years in the RME-FM group (mean diff: 1 year, 95% CI: 0.8, 1.3, $P < 0.001$). Follow-up period after the initiation of the overall treatment was 4.5 ± 0.2 years for the Alt-RAMEC-HH-LLA group and 9.2 ± 2.3 years for the RME-FM group (mean diff: 4.7 years, 95% CI: 3.4, 6.1, $P < 0.001$).

Method error

No significant error was found for any of the variables. The MME ranged between 0.1–0.5 mm for the linear measurements of the conventional cephalometric analysis and between 0.3–0.7 mm for the variables measured in the x-y co-ordinate system. Angular measurements displayed MME between 0.2°–1.2°. The ICC range was 0.956–0.991 for all parameters.

Baseline measurements (T1)

At baseline, maxillary retrognathia (SNA), divergence of the Sassouni planes (SN-PP, SN-MP, PP-MP), mandibular morphology as described by the gonial angle (ArGoMe) and lower incisor angulation relative to the mandibular plane were similar for both groups (*table I*). SNB was greater in the alt-RAMEC-HH-LLA group with a value of $81.9° \pm 3.8°$ and $78.0° \pm 3.0°$ in the RME-FM group. Regarding sagittal intermaxillary relationships, ANB was more negative in the alt-RAMEC-HH-LLA group ($-3.4° \pm 2.6°$) compared to the RME-FM group ($-0.7° \pm 2.0°$). Similar findings were for the Wits appraisal, which was -9.1 ± 2.3 mm in the alt-RAMEC-HH-LLA group and -5.2 ± 2.5 mm in the RME-FM group. All linear measurements describing the cranial base, maxillary and mandibular lengths were greater in the alt-RAMEC-HH-LLA group and so was the inclination of the upper incisors to the palatal plane (alt-RAMEC-HH-LLA: $112.2° \pm 5.6°$;

Table I

Descriptive statistics and statistical comparisons (independent-samples t tests, or Mann-Whitney U tests, as appropriate) of the cephalometric values at T1: baseline, T2: long-term and T2-T1: Changes

	Baseline (T1)				Long- term (T2)					Changes (T2- T1)			
Variables	AltRamec Group (*n* = 15)		RME/FM Group (*n* = 16)		AltRamec Group (*n* = 13)		RME/FM Group (*n* = 16)		*P*-value	AltRamec Group (*n* = 13)		RME/FM Group (*n* = 16)	
	Mean [Median*]	SD [IQR*]	Mean [Median*]	SD [IQR*]	Mean [Median*]	SD [IQR*]	Mean [Median*]	SD [IQR*]		Mean [Median*]	SD [IQR*]	Mean [Median*]	SD [IQR*]
Age (years)	12.5	0.9	6.5	0.9	16.8	0.9	15.8	2.5	0.19	4.2	0.2	9.2	2.3
Cephalometric DATA													
SNA°	78.5	3.0	77.3	3.5	80.5	3.5	79.3	4.4	0.45	2.1	1.1	2.0	3.1
SNB°	81.9	3.8	78.0	3.0	82.0	4.3	79.8	5.0	0.22	0.4	1.5	1.8	3.7
ANB°	−3.4	2.6	−0.7	2.0	−1.5	3.0	−0.4	2.9	0.34	[1.7]	[0.9]	[1.0]	[1.5]
WITS (mm)	−9.1	2.3	−5.2	2.5	−6.8	2.3	−4.3	2.9	0.02	2.2	2.0	1.0	2.3
SN-PP°	8.8	3.9	8.9	3.3	9.5	4.0	8.4	4.8	0.52	0.1	2.6	−0.5	3.1
SN-MP°	36.6	6.0	35.3	4.5	36.1	7.6	32.9	6.0	0.22	[−0.9]	[−3.1]	[−0.5]	[3.5]
PP-MP°	27.8	4.2	26.4	4.8	26.6	6.1	24.6	6.6	0.42	−1.5	3.5	−1.8	4.8
SN-OP°	16.4	4.4	20.6	4.3	14.7	6.1	17.2	5.6	0.27	−2.0	2.6	−3.4	4.7
ArGoMe°	[125.9]	[7.0]	[129]	[7.0]	[125.4]	[10.3]	[126.0]	[7.5]	0.57[1]	[−1.1]	[−0.6]	[−3.5]	[−3.5]
S-N (mm)	63.9	4.1	60.5	3.2	64.9	4.6	66.9	3.5	0.18	[0.9]	[0.8]	[6.8]	[3.5]
Co-Gn (mm)	[109.9]	[6.9]	[91.4]	[10.8]	[116.1]	[11.0]	[113.8]	[10.8]	0.10[1]	8.9	4.7	20.0	6.5
Co-A (mm)	76.0	4.4	70.2	3.8	81.4	4.8	81.2	5.1	0.91	5.4	2.5	11.1	4.2
U1-PP°	112.2	5.6	102.1	11.4	121.7	4.9	113.7	8.7	0.006	9.0	6.5	11.6	2.1
L1-MP°	83.7	5.6	84.1	6.2	82.2	6.2	87.8	8.0	0.05	−1.8	7.3	3.7	7.7
Overjet (mm)	[−3.1]	[2.1]	[−1.9]	[3.2]	[2.5]	[0.9]	[2.3]	[1.2]	0.79[1]	5.1	1.8	4.3	2.1
Overbite (mm)	2.6	1.9	0.4	1.3	1.2	0.6	2.3	0.6	< 0.001	−1.4	1.9	1.9	1.3

PP: Palatal plane; MP: mandibular plane; OP: Occlusal plane; U1: Upper incisor; L1: Lower incisor; SD: Standard Deviations; Diff.: Differences; CI: Confidence intervals; IQR: Interquartile range.

*[brackets indicate non-normal distribution of the residuals of the data and respective descriptives are presented].

[1]Indicates Mann-Whitney U test according to data distribution/otherwise independent sample *t*-test [according to post-hoc Bonferroni correction, the statistical significance level was determined at $P < 0.003$].

Table II
Multivariate linear regression with standard errors (1000 replications) derived with the bootstrap method, for the effect of type of treatment on the recorded cephalometric variables in the long-term (T2) conditional on baseline estimates (T1) and after adjusting for sex and age at T2

Variable		b coef.	95% CI	*P*-value*
		Vertical		
SNA at T2 (mm)	RME-FM	Reference		
	alt-RAMEC-HH-LLA	−0.53	−2.40, 1.33	0.58
	Female	Reference		
	Male	2.07	−0.12, 4.27	0.06
	Age per year	0.24	−0.32, 0.81	0.39
SNB at T2 (mm)	RME-FM	Reference		
	alt-RAMEC-HH-LLA	−1.86	−4.37, 0.64	0.15
	Female	Reference		
	Male	2.41	−0.59, 5.41	0.12
	Age per year	0.02	−0.86, 0.91	0.96
ANB at T2 (°)	RME-FM	Reference		
	alt-RAMEC-HH-LLA	1.11	−0.42, 2.63	0.15
	Female	Reference		
	Male	−0.51	−1.85, 0.83	0.46
	Age per year	0.24	−0.26, 0.74	0.35
Wits at T2 (mm)	RME-FM	Reference		
	alt-RAMEC-HH-LLA	−0.01	−1.96, 1.95	0.99
	Female	Reference		
	Male	−1.18	−2.59, 0.23	0.10
	Age per year	0.65	0.23, 1.07	0.002
SN-PP at T2 (°)	RME-FM	Reference		
	alt-RAMEC-HH-LLA	0.54	−2.23, 3.30	0.70
	Female	Reference		
	Male	−0.77	−3.64, 2.10	0.60
	Age per year	0.13	−0.80, 1.06	0.78
SN-MP at T2 (°)	RME-FM	Reference		
	alt-RAMEC-HH-LLA	2.38	−1.05, 5.80	0.17
	Female	Reference		
	Male	−5.55	−9.83, −1.26	0.01
	Age per year	−0.18	−1.10, 0.74	0.70

Table II **(Continued).**

Variable		b coef.	95% CI	*P*-value*
PP-MP at T2(°)	RME-FM	Reference		
	alt-RAMEC-HH-LLA	1.70	−1.48, 4.88	0.29
	Female	Reference		
	Male	−4.42	−8.00, −0.84	0.02
	Age per year	−0.44	−1.16, 0.28	0.23
SN-OP at T2(°)	RME-FM	Reference		
	alt-RAMEC-HH-LLA	2.56	−0.18, 5.31	0.07
	Female	Reference		
	Male	−3.65	−6.43, −0.87	0.01
	Age per year	−0.81	−1.74, 0.11	0.09
ArGoMe at T2 (°)	RME-FM	Reference		
	alt-RAMEC-HH-LLA	4.93	2.27, 7.59	< 0.001
	Female	Reference		
	Male	−4.40	−6.90, −1.90	0.001
	Age per year	0.15	-0.60, 0.89	0.70
S-N at T2 (mm)	RME-FM	Reference		
	alt-RAMEC-HH-LLA	−5.04	−6.57, −3.51	< 0.001
	Female	Reference		
	Male	1.11	−0.64, 2.88	0.21
	Age per year	0.02	−0.53, 0.56	0.96
Co-Gn at T2 (mm)	RME-FM	Reference		
	alt-RAMEC-HH-LLA	−10.5	−17.45, −3.55	0.003
	Female	Reference		
	Male	4.52	0.05, 9.00	0.05
	Age per year	−0.69	−2.37, 1.00	0.42
Co-A at T2 (mm)	RME-FM	Reference		
	alt-RAMEC-HH-LLA	−4.54	−7.91, −1.16	0.01
	Female	Reference		
	Male	3.23	0.81, 5.64	0.01
	Age per year	0.07	−1.14, 1.28	0.91
U1-PP at T2 (°)	RME-FM	Reference		
	alt-RAMEC-HH-LLA	2.51	−5.09, 10.11	0.52
	Female	Reference		
	Male	−0.10	−6.50, 6.30	0.98
	Age per year	−0.01	−2.03, 2.00	0.99

TABLE II **(Continued).**

Variable		b coef.	95% CI	*P*-value*
L1-MP at T2 (°)	RME-FM	Reference		
	alt-RAMEC-HH-LLA	−6.11	−10.66, −1.57	0.01
	Female	Reference		
	Male	−1.97	−7.53, 3.59	0.49
	Age per year	1.49	0.10, 2.88	0.04
OJ at T2 (mm)	RME-FM	Reference		
	alt-RAMEC-HH-LLA	−0.06	−1.20, 1.08	0.91
	Female	Reference		
	Male	0.67	−0.80, 2.14	0.37
	Age per year	−0.14	−0.57, 0.29	0.52
OB at T2 (mm)	RME-FM	Reference		
	alt-RAMEC-HH-LLA	−1.28	−1.79, −0.76	< 0.001
	Female	Reference		
	Male	0.17	−0.37, 0.71	0.53
	Age per year	−0.01	−0.12, 0.12	0.97

*Statistical significance set at $P < 0.05$.

RME-FM: 102.1° ± 11.4). Overbite and negative overjet were also greater in the alt-RAMEC-HH-LLA group (*table I*).

Long-term measurements (T2)

All conventional linear and angular measurements were similar in both groups at T2 except for statistically significant differences existing between them for the overbite, according to the crude analysis (*tables I and II*). Specifically, the alt-RAMEC-HH-LLA group achieved an overbite of 1.2 ± 0.6 mm, as compared to the RME-FM group that exhibited higher values, of 2.3 ± 0.6 mm at T2 ($P < 0.001$). Wits appraisal, upper and lower incisor angulations relative to their apical bases (PP: palatal plane and mandibular plane: MP respectively), appeared as variables with the greatest differences between the two groups at T2; however, and after the appropriate corrections for multiple testing, these were not confirmed statistically. Indeed, Wits was more negative in the alt-RAMEC-HH-LLA group (−6.8 ± 2.3 mm) compared to the RME-FM group (−4.3 ± 2.9 mm). Upper incisors were more proclined in the alt-RAMEC-HH-LLA group (121.7° ± 4.9°) compared to the RME-FM group (113.7° ± 8.7°). Lower incisors were more retroclined in the alt-RAMEC-HH-LLA group (82.2° ± 6.2°) compared to the RME-FM group (87.8° ± 8.0°) (*table I*). All cases in the RME-FM group had positive overjet; however, one case in the alt-RAMEC-HH-LLA group had negative overjet.

According to the multivariate analysis, the effect of treatment on the long-term T2 values, conditional on baseline estimates, and after adjusting for age and gender, was confirmed for the gonial angle (ArGoMe) and the linear measurements S-N, Co-A and Co-Gn in millimetres. RME-FM was associated with greater closure of the gonial angle (mean difference: 4.93°; 95%CI: 2.27, 7.59; $P < 0.001$). For the three linear variables (S-N, Co-A, Co-Gn), alt-RAMEC-HH-LLA was associated with significantly smaller changes compared to RME-FM. Regarding dental measurements, alt-RAMEC-HH-LLA was associated with significantly greater reduction in the inclination of the lower incisors to the mandibular plane (mean difference: −6.11°; 95%CI: −10.66, −1.57; $P = 0.01$) and less change in the overbite (mean difference: −1.28 mm; 95%CI: −1.79, −0.76; $P < 0.001$) compared to RME-FM (table II).
Moreover, an effect of gender was confirmed for the vertical dimensions of the cephalometric data, with males presenting greater changes towards hypo-divergence compared to female subjects (SN-MP, PP-MP, SN-OP). The above was coupled with greater closure of the gonial angle-ArGoMe (mean difference: −4.40°; 95%CI: −6.90, −1.90; $P < 0.001$), as well as greater increase in the Co-A measurement (mean difference: 3.23 mm; 95%CI: 0.81, 5.64; $P = 0.01$). Last, after adjusting for all covariates including treatment, each additional year of age at T2 was associated with evidence demonstrating increases on both the Wits appraisal (mean difference: 0.65 mm; 95%CI: 0.23, 1.07;

P = 0.002) and the lower incisor inclination to its apical base (mean difference: 1.49°; 95%CI: 0.10, 2.88; P = 0.04) (*table II*).

Discussion

Stability of dentofacial orthopaedic treatment for Class III correction remains controversial. Most of the studies report that skeletal changes induced by treatment and reflected in the cephalometric variables rebound in an unfavourable manner when patients are followed up longitudinally [31,32]. Subsequently, Class III skeletal growth pattern remains unchanged over time with 27–36% of the cases treated with RME-FM before the pubertal growth spurt needing orthognathic surgery as a definitive treatment of their malocclusion [31–33].

In the present retrospective study, the aim was to identify if Class III cases treated early with the well-established protocol of RME-FM would differ at post-pubertal stage from patients who received late treatment with a modified maxillary protraction protocol.

It was found that patients treated with either early RME-FM or late Alt-RAMEC-HH-LLA had comparable overall post-pubertal skeletal and overjet corrections. However, the late Alt-RAMEC-HH-LLA showed less correction of dentoalveolar compensations and in particular of the mandibular incisors. The overbite, maxillary and mandibular projection and size were lower and the gonial angle was more open. The null hypothesis that the addition of adjunctive procedures would overcome the shortfalls of late treatment was accepted as no differences were found for most of the tested parameters in the long-term across the two groups. The results were both related to the combined effect of treatment procedures, growth and the fixed orthodontic treatment. At the long-term follow-up, all patients in the RME-FM group still had positive overjet while one case in the alt-RAMEC-HH-LLA group had negative overjet; however, this case did not respond positively to treatment during active maxillary protraction so it cannot be considered a long-term relapse. Factors such as the baseline increased gonial angle, steep mandibular plane angle, divergence of the maxillomandibular planes and possibly advanced zygomaticomaxillary suture maturation could have contributed to this unfavourable response [34–37]. Full time use of heavy intermaxillary elastics was utilised as more patient friendly means because only 68.2% of patients have shown previously good compliance with FM [31].

Demographic characteristics of groups at baseline showed that they shared similar features regarding angular measurements of maxillary retrognathia and vertical skeletal developmental pattern; however, the severity of the skeletal maxillomandibular discrepancy, mandibular position and size as well as all linear measurements describing the size of the facial components differed and were greater for the alt-RAMEC-HH-LLA group. This is expected because patients of this group were older before treatment initiation. In addition, the sustained and prolonged unfavourable Class III growth pattern had resulted in greater dentoalveolar compensation with the maxillary incisors being more proclined at baseline compared to the RME-FM group; however, lower incisors were equivalently retroclined in both groups. These results corroborate with findings from previous studies that followed up Class III cases longitudinally and reported that the mandible outgrows the maxilla in magnitude and duration of growth [3]. Additionally, between 8y8m ± 2y5 m to 15y2m ± 1y11 m years of age the upper incisors show continuing and significant proclination while the lower incisors show progressive and insignificant retroclination [5].

Assessment of all cephalometric parameters at the long-term, post-pubertal stage follow-up, which also included treatment with fixed appliance, revealed that both treatment options reached similar endpoints with non- significant differences across groups regarding SNA, SNB, ANB, Wits, and vertical skeletal parameters. Linear size of skeletal components was significantly smaller for the alt-RAMEC-HH-LLA group. In addition, overbite and lower incisor inclination were significantly smaller in the alt-RAMEC-HH-LLA group at T2, revealing increments of dental compensation for the correction of the Class III component for the late treatment group.

Maxillary response

Regarding maxillary protraction efficacy, short-term comparisons between alt-RAMEC-FM (tooth-borne expanders) versus RME-FM in matched groups have shown results that favoured the alt-RAMEC protocols. More specifically, Masucci et al. [23] retrospectively assessed 4 weeks alt-RAMEC-FM versus RME-FM in 6.4 ± 0.8 and 6.9 ± 1.1 year-olds respectively. SNA improved 2.7° ± 1.6° in the former and 1.5° ± 1.4° in the later with the difference of 1.2° being statistically significant. Similar results were reported in a randomized clinical trial [38], using 7-week alt-RAMEC in 7–13-year-old patients. SNA improved by 1.93° ± 0.79° in the RME-FM group and 2.67° ± 1.31° in the alt-RAMEC group with their difference being significant [38]. The use of palatal skeletal anchorage in the form of HH-FM has been proposed to enhance maxillary advancement potentials [39]. The HH-FM option in 9.5 ± 1.3 year old Class III patients induced, within 5.8 ± 1.6 months, a 2.0° ± 1.5° increase in SNA, and 2.2 ± 2.9 mm increase in maxillary length (Co-A). This effect was 2.4° and 1 mm significantly greater compared to untreated controls [40].

Early RME-FM has significantly greater beneficial effects in maxillary protraction relative to late RME-FM [14]. SNA improved 3.71° in 4–7 year-olds, 1.98° in 7–10 year-olds and 1.89° in 10–14 year-olds being significantly greater in the first group compared to the other groups indicating that even through RME-FM treatment can induce maxillary changes in older patients these are of a lesser magnitude [15]. In the present study, the mean overall improvement in both groups for the SNA was approximately 2°, which is in agreement with previous findings of an RCT that reported 2.3° ± 2.1° SNA improvement when RME-FM patients were re-evaluated 3 years post-treatment [41]. The greater improvement in maxillary protraction by using adjunct procedures such as alt-RAMEC or HH as reported in previous literature [23,38–40], in conjunction with the full-time use of Class III elastics in the alt-RAMEC-HH-LLA group might have assisted in catching-up with the maxillary changes induced in the early RME-FM treated group and explain the maxillary position and size similarities between the two groups at the end of the observation period of the present study. Indeed, after accounting for other implicated covariates, the alt-RAMEC-HH-LLA group had significantly less treatment induced projection changes, as noted by the Co-A cephalometric data. Nevertheless, this difference in the changes of linear variables could be attributed not only to the different treatment protocols but also to the difference in the total follow-up time, which was 4.5 $\pm$ 0.2 years for the alt-RAMEC-HH-LLA group and 9.2 $\pm$ 2.3 years for the RME-FM group.

Mandibular response and divergence

Despite the differences in appliance design and anchorage between the two treatment protocols of the present study, the two groups were not utterly different in mandibular projection and size longitudinally. This was reflected in the absolute numbers of SNB and mandibular length (Co-Gn) at T2. Controversial results exist regarding comparisons of the short-term changes and their differences between protocols that utilised either alt-RAMEC-FM versus RME-FM regarding their effects in the mandible. Masucci et al. [23] have reported non- significant difference for the changes induced to SNB for both treatment options with alt-RAMEC-FM reducing the SNB by $-1.5^\circ \pm 1.6^\circ$ and the RME-FM by $-0.8^\circ \pm 1.4^\circ$. Liu et al. [38] reported similar reduction in the SNB for the alt-RAMEC-FM group being $-1.49^\circ \pm 0.89^\circ$ versus $-2.35^\circ \pm 1.21^\circ$ in the RME-FM; however, the difference across their groups were found significant and favoured RME-FM.

All the above studies, which implement adjunctive procedures for maxillary protraction, report non- significant changes within and between groups in the short-term regarding palatal and mandibular plane divergence. Long-term effects of RME-FM treatment to maxillary and mandibular plane divergence have been reported to be minimal, stable over time and similar to untreated controls [31], irrespective to the addition of bite-blocks in the design of the appliances [42]. Our results agree with the existing evidence while the use of bonded expanders did not have any effect in altering the vertical divergence in the long term. Indeed, a gender effect was noted in the present study, with male subjects achieving a more horizontal growth pattern, irrespective of the appliance used and the timing of the intervention.

Both protocols did not change mandibular position (SNB) nor had any effect in creating differences across groups to its size and projection (Co-Gn) at the long-term in the crude T2 analysis. However, for the latter it should be noted that conditional on all covariates including baseline cephalometric measurements, the alt-RAMEC-HH-LLA group exhibited a less pronounced size and projection changes and the explanation to this is the dependence of linear growth amount to the duration of follow-up. In any case, various genetic factors have been associated from mandibular prognathism interfering to osteoblastic and synovial tissue homeostasis [43], or mutations of genes leading to short mandibular ramus and longer corpus body [44]. Skeletal muscle composition has been associated to sagittal and vertical growth of the face as well as differences amongst malocclusions [45,46]. These findings could explain the insignificant changes in mandibular size and divergence overall effects exerted by various Class III treatment modalities indicating that other biologic factors related to the functional matrix component may govern these parameters rather than any clinical treatment intervention per se.

Maxillomandibular relationships & dental effects

Maxillomandibular relationships as described by the ANB angle were similar at T2 in both groups; however, the alt-RAMEC-HH-LLA group exhibited a median of 0.7° more improvement between T1 and T2. Even though at the initiation of treatment this group had significantly more severe sagittal discrepancy, this was evened with treatment. This was not the case for the Wits appraisal though, as it remained more negative in the alt-RAMEC-HH-LLA group. Overjet did not show significant differences in absolute values at T2.

Stability of ANB and overjet correction with RME-FM were confirmed in a meta-analysis [47]. In the short term, the effect of alt-RAMEC-FM protocol to the ANB is similar to more invasive procedures, such as skeletal plates, and better to RME-FM when data from individual studies were pooled in a network meta-analysis [48]. This is in agreement with the findings of the present study regarding ANB; however, the increment of 0.7° difference has to be considered under the prism of its clinical significance.

Late treatment did not resolve baseline dentoalveolar compensations. Regardless of the similar trend of longitudinal changes leading to increases of the inclination of the upper incisors relative to their apical base (mean increase of 9° in the alt-RAMEC-HH-LLA group and 11.6° in the RME-FM group), these remained more proclined in the late treated group. Contrary to the analogous response of the maxillary incisors, mandibular incisor inclination changes differed across groups (mean change -1.8° in the alt-RAMEC-HH-LLA group and 3.7° in the RME-FM group). Even though these were similarly retroclined at baseline, early treatment with RME-FM normalised their position relative to the mandibular plane while alt-RAMEC-HH-LLA combined with fixed appliances resulted in more retroclination. Both the absolute values at T2 and the longitudinal changes conditional on other parameters, were significantly different amongst the two treatment options and were in favour of the early approach. Treatment with either Alt-RAMEC-FM or RME-FM results in more proclined upper incisors and less retroclined lower incisors relative to controls in the short term [48]. In addition, treatment with RME-FM produces highly interconnected and thus more compact network structure between dentoalveolar and skeletal cephalometric variables when assessing large datasets of treated versus untreated individuals, a finding that highlights a dynamic interaction of those components to produce or resolve the malocclusion [49]. Baseline increased severity, later start of dentofacial orthopaedics, and full-time Class III elastics to the dentition in conjunction with continuation of the Class III growth pattern may have been the factors that worsened mandibular incisor retroclination in the present alt-RAMEC-HH-LLA group. As lower incisor initial stabilization with stiff stainless-steel wires on miniscrews did not control for their final inclination, the effectiveness of this adjunctive part in the overall appliance design could possibly be omitted in future studies.

The limitations of the present study include its retrospective design, the baseline age difference with subsequent severity of the malocclusion in the two groups and the small samples with attrition in the alt-RAMEC-HH-LLA group because it was not possible to contact 2 patients for the longitudinal recall. Another factor that was not measured was compliance with FM and intraoral elastics, however this reflected real-practice conditions. Moreover, the present results correspond to the combined effect of the maxillary protraction protocols, the additional use of fixed appliances and longitudinal growth.

Future research could focus on multi-centre randomized trials that could possibly assist in pooling large datasets for elucidating the efficacy and efficiency of various treatment modalities used in Class III malocclusion treatment and stability. Randomization though into early and late treatment groups could raise ethical issues of deliberately leaving patients untreated until they reach later maturation stages. The implementation of accurate diagnostic methods could also account for genetic variants that define patients' biological background and thus allow better and patient-tailored treatments [50]. Additionally, evaluation of the dental, osseous and gingival tissues is recommended in the short and long-term for confirming the safety of the methods and their possible side effects such as tooth root resorption, bone resorption and dehiscence formation and gingival recessions, all of which possibly exerted from orthopaedic force overload to the supporting tissues.

Conclusion

Sagittal and vertical skeletal parameters did not differ overall in the long-term between patients treated during adolescent growth spurt with alt-RAMEC-HH-LLA and those who received early treatment with RME-FM. Treatment induced maxillary and mandibular projection estimates appeared lower for the alt-RAMEC-HH-LLA group, as represented by Co-A and Co-Gn measurements, and regarding less closure of the gonial (ArGoMe) angle. Overjet corrections were similar in both groups, contrary to the overbite; however, late treatment did not manage to relieve baseline dentoalveolar compensations and unfavourable incisor angulations relative to their apical bases, especially this of the mandibular incisors.

Contribution: Alexandra K. Papadopoulou: conceptualization and study design, methodology and investigation, data acquisition, analysis and interpretation, project administration, writing original draft and revisions of the manuscript, final approval of the submitted version.
Despina Koletsi, methodology, data analysis and interpretation, drafting and revisions of the manuscript, final approval of the submitted version.
Caterina Masucci: conceptualization and study design, methodology and investigation, data acquisition, analysis and interpretation, drafting and revisions of the manuscript, final approval of the submitted version.
Veronica Giuntini: conceptualization and study design, methodology and investigation, data acquisition, analysis and interpretation, drafting and revisions of the manuscript, final approval of the submitted version.
Lorenzo Franchi: conceptualization and study design, methodology and investigation, data acquisition, analysis and interpretation, statistical analyses, drafting and revisions of the manuscript, final approval of the submitted version.
Mehmet Ali Darendeliler: conceptualization and study design, methodology and investigation, data acquisition, analysis and interpretation, drafting and revisions of the manuscript, final approval of the submitted version.

Disclosure of interest: the authors declare that they have no competing interest.

References

[1] Guyer EC, Ellis EE, McNamara JA, Behrents RG. Components of Class III malocclusion in juveniles and adolescents. Angle Orthod 1986;56:7–30.
[2] Tollaro I, Baccetti T, Bassarelli V, Franchi L. Class III malocclusion in the deciduous dentition, a morphological and correlation study. Eur J Orthod 1994;16:401–8.
[3] Baccetti T, Reyes BC, McNamara Jr JA. Craniofacial changes in Class III malocclusion as related to skeletal and dental maturation. Am J Othod Dentofacial Orthop 2007;132:171–8.
[4] Kuc-Michalska M, Baccetti T. Duration of the pubertal peak in skeletal Class I and Class III subjects. Angle Orthod 2010;80:54–7.
[5] Baccetti T, Franchi L, McNamara Jr JA. Growth in the untreated Class III subject. Semin Orthod 2007;13:130–42.
[6] Wolfe SM, Araujo E, Behrents RG, Buschang PH. Craniofacial growth of Class III subjects six to sixteen years of age. Angle Orthod 2011;81:211–6.
[7] Bui CB, Profitt W, Frazier-Bowers S. Phenotypic Characterization of Class III Patients A Necessary Background for Genetic Analysis. Angle Orthod 2006;76:564–9.
[8] Ellis 3rd E, McNamara Jr JA. Components of adult Class III malocclusion. J Oral Maxillofac Surg 1984;42:295–305.
[9] Ngan P, Cheung E, Wei SH. Comparison of protraction facemask response using banded

and bonded expansion appliances as anchorage. Semin Orthod 2017;13:175–82.
[10] Lione R, Buongiorno M, Laganà G, Cozza P, Franchi L. Early treatment of Class III malocclusion with RME and facial mask: evaluation of dentoalveolar effects on digital dental casts. Eur J Paediatr Dent 2015;16:217–20.
[11] Ngan P, Hägg U, Yiu C, Merwin D, Wei SH. Soft Tissue and Dentoskeletal Profile Changes Associated With Maxillary Expansion and Protraction Headgear Treatment. Am J Orthod Dentofacial Orthop 1996;109:38–49.
[12] Pavoni C, Masucci C, Cerroni S, Franchi L, Cozza P. Short-term effects produced by rapid maxillary expansion and facemask therapy in Class III patients with different skeletal relationships. Angle Orthod 2015;85:927–33.
[13] Baccetti T, McGill JS, Franchi L, McNamara Jr JA, Tollaro I. Skeletal Effects of Early Treatment of Class III Malocclusion With Maxillary Expansion and Face-Mask Therapy. Am J Orthod Dentofacial Orthop 1998;113:333–43.
[14] Franchi L, Baccetti T, McNamara Jr JA. Postpubertal Assessment of Treatment Timing for Maxillary Expansion and Protraction Therapy Followed by Fixed Appliances. Am J Orthod Dentofacial Orthop 2004;126:555–68.
[15] Kapust AJ, Sunclair PM, Turley PK. Cephalometric effects of facemask/expansion therapy in Class III children: A comparison of three age groups. Am J Orthod dentofacial Orthop 1998;113:204–12.
[16] Ngan P, Hägg U, Yiu C, Merwin D, Wei SH. Treatment response to maxillary expansion and protraction. Eur J Orthod 1996;18:151–68.
[17] Mandall N, DiBiase A, Littlewood S, et al. Is early Class III protraction facemask treatment effective?. A multicentre, randomized, controlled trial: 15-month follow-up. J Orthod 2010;37:149–61.
[18] Perillo L, Vitale M, Masucci C, D'Apuzzo F, Cozza P, Franchi L. Comparisons of two protocols for the early treatment of Class III skeletal disharmony. Eur J Orthod 2016;38:51–6.
[19] Cozza P, Marino A, Mucedero M. An orthopaedic approach to the treatment of class III malocclusions in the early mixed dentition. Eur J Orthod 2004;26:191–9.
[20] Kilic N, Celikoglu M, Oktay H. Effects of the functional regulator III on profile changes in subjects with maxillary deficiency. Eur J Orthod 2010;32:729–34.
[21] Liou EJ, Tsai WC. A new protocol for maxillary protraction in cleft patients: repetitive weekly protocol of alternate rapid maxillary expansions and constrictions. Cleft Palate Craniofac J 2005;42:121–7.
[22] Franchi L, Baccetti T, Masucci C, Defraia E. Early alt-RAMEC and facial mask protocol in Class III malocclusion. J Clin Orthod 2011;45:601–9.
[23] Masucci C, Franchi L, Giuntini V, Defraia E. Short-term effects of a modified Alt-RAMEC protocol for early treatment of Class III malocclusion: a controlled study. Orthod Craniofac Res 2014;17:259–69.
[24] Fischer B, Masucci C, Ruellas A, et al. Three-dimensional Evaluation of the Maxillary Effects of Two Orthopaedic Protocols for the Treatment of Class III Malocclusion: A Prospective Study. Orthod Craniofac Res 2018;21:248–57.
[25] Wilmes B, Ngan P, Liou E, Franchi L, Drescher D. Early Class III facemask treatment with the hybrid Hyrax and alt-RAMEC protocol. J Clin Orthod 2014;48:84–93.
[26] Maino G, Turci Y, Arreghini A, Paoletto E, Siciliani G, Lombardo L. Skeletal and dentoalveolar effects of hybrid rapid palatal expansion and facemask treatment in growing skeletal Class III patients. Am J Orthod Dentofacial Orthop 2018;153:262–8.
[27] Al-Mozany SA, Dalci O, Almuzian M, Gonzalez C, Tarraf NE, Ali Darendeliler M. A novel method for treatment of Class III malocclusion in growing patients. Prog Orthod 2017;18 (1):40.
[28] Baccetti T, Franchi L, McNamara Jr JA. The Cervical Vertebral Maturation (CVM) method for the assessment of optimal treatment timing in dentofacial orthopedics. Semin Orthod 2005;11:119–29.
[29] McNamara Jr JA, Brudon WL. Orthodontics and dentofacial orthopedics. Ann Arbor, Mich: Needham Press; 2001p. 375–85.
[30] Springate SD. The effect of sample size and bias on the reliability of estimates of error: a comparative study of Dahlberg's formula. Eur J Orthod 2012;34:158–63.
[31] Masucci C, Franchi L, Defraia E, Mucedero M, Cozza P, Baccetti T. Stability of rapid maxillary expansion and facemask therapy. Am J Orthod Dentofacial Orthop 2011;140:493–500.
[32] Mandall N, Cousley R, DiBiase A, et al. Early class III protraction facemask treatment reduces the need for orthognathic surgery: a multi-centre, two-arm parallel randomized, controlled trial. J Orthod 2016;43:164–75.
[33] Souki BQ, Nieri M, Pavoni C, et al. Development and validation of a prediction model for long-term unsuccess of early treatment of Class III malocclusion. Eur J Orthod 2020;42:200–5.
[34] Baccetti T, Franchi L, McNamara Jr JA. Cephalometric variables predicting the long term success or failure of combined rapid maxillary expansion and facemask therapy. Am J Orthod Dentofacial Orthop 2004;126:16–22.
[35] Franchi L, Bacceti T, Tollaro I. Predictive variables for the outcome of early functional treatment of Class III malocclusion. Am J Orthod Dentofacial Orthop 1997;112:80–6.
[36] Fudalej P, Dragan M, Wedrychwska-Szulc B. Prediction of the outcome of orthodontic treatment of Class III malocclusion - a systematic review. Eur J Orthod 2011;33:190–7.
[37] Angelieri F, Ruellas AC, Yatanabe MS, et al. Zygomaticomaxillary suture maturation: Part II-The influence of sutural maturation on the response to maxillary protraction. Orthod Craniofacial Res 2017;20:152–63.
[38] Liu W, Zhou Y, Wang X, Liu D, Zhou S. Effect of maxillary protraction with alternating rapid palatal expansion and constriction vs expansion alone in maxillary retrusive patients. Am J Orthod Dentofacial Orthop 2015;148:641–51.
[39] Nienkemper M, Wilmes B, Pauls A, Drescher D. Maxillary protraction using a hybrid hyrax-facemask combination. Prog Orthod 2013;14:5.
[40] Nienkemper M, Wilmes B, Franchi L, Drescher D. Effectiveness of maxillary protraction using a hybrid hyrax-facemask combination: a controlled clinical study. Angle Orthod 2015;85:764–70.
[41] Mandall N, Cousley R, DiBiase A, et al. Is early Class III protraction facemask treatment effective?. A multicentre, randomized, controlled trial: 3-year follow-up. J Orthod 2012;39:176–85.
[42] Cozza P, Baccetti T, Mucedero M, Pavoni C, Franchi F. Treatment and posttreatment effects of a facial mask combined with a bite-block appliance in Class III malocclusion. Am J Orthod Dentofacial Orthop 2010;138:30010.
[43] Ikuno K, Kajii TS, Oka A, Inoko H, Ishikawa H, Iida J. Microsatellite genome-wide association study for mandibular prognathism. Am J Orthod Dentofacial Orthop 2014;145:757–62.
[44] Zhang Y, Blackwell EL, McKnight MT, Knutsen GR, Vu WT, Ruest LB. Specific inactivation of Twist1 in the mandibular arch neural crest cells affects the development of the ramus and reveals interactions with hand2. Dev Dyn 2012;241:924–40.
[45] Moawad AH, Sinanan AC, Lewis MP, Hunt NP. Grouping Patients for Masseter Muscle Genotype-Phenotype Studies. Angle Orthod 2012;82:261–6.
[46] Sciote JJ, Horton MJ, Rowlerson AM, Ferri J, Close JM, Raoul G. Human Masseter Muscle Fiber Type Properties, Skeletal Malocclusions, and Muscle Growth Factor Expression. J Oral Maxillofac Surg 2012;70:440–8.
[47] Lin Y, Guo R, Hou L, Fu Z, Li W. Stability of maxillary protraction therapy in children with Class III malocclusion: a systematic review and meta-analysis. Clin Oral Investig 2018;22:2639–52.
[48] Wu Z, Zhang X, Li Z, et al. A Bayesian Network Meta-Analysis of Orthopaedic Treatment in Class III Malocclusion: Maxillary Protraction With Skeletal Anchorage or a Rapid Maxillary Expander. Orthod Craniofac Res 2020;23:1–15.
[49] Scala A, Auconi P, Scazzocchio M, Caldarelli G, McNamara Jr JA, Franchi L. Complex networks for data-driven medicine: the case of Class III dentoskeletal disharmony. New J Phys 2014;16:115017.
[50] Dehesa-Santos A, Iber-Diaz P, Iglesias-Linares A. Genetic factors contributing to skeletal Class III malocclusion: a systematic review and meta-analysis. Clin Oral Inverstig 2021;25:1587–612.