Predictors of non-adherence to pre-surgical naso-alveolar molding therapy in infants with cleft lip & palate

By

Nick Orem Esmonde

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CERTIFICATE OF APPROVAL

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This is to certify that the Master's thesis of

Nick Esmonde, M.D.

has been approved

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William Lambert, PhD – committee chair

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Anna Kuang, M.D.

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Yiyi Chen, PhD

Introduction

Cleft lip and palate (CLP) deformity is the most common human embryopathy of the craniofacial structures, with an estimated incidence of 1:750 live births. It involves the lip, nasal structure, gum line and hard and soft palates. It is thought to be the result of a complex interplay of genetic and antenatal exposure factors, which are not yet fully understood (CLAPA, 2009). Patients are treated by a multidisciplinary care team that begins the process of family education, assesses for associated congenital anomalies, and plans for surgical and non-surgical treatment. Surgical correction consists of a series of surgeries characterized first by primary cleft lip and nose repair at age 3-5 months old, followed by palate repair at 12 months old, with successive operations for the gum-line, nose, and jaw, as needed (Kramer, 2007).

Achieving an optimum aesthetic and functional result is the goal of surgical repair. Reconstruction is made challenging by the enormity of the cleft lip and palate defects, deformed nasal cartilage, and a protruding pre-maxilla. If the defect could be made more narrow, and each segment brought into closer approximation, this would improve the surgical outcome. The first pre-surgical device designed to address these challenges was developed in the 1950's. Subsequent improvements in the device included attention to shaping the nose in addition to the maxillary segments. The most state of the art naso-alveolar molding (NAM) device was further developed by Grayson, *et al*. (1999). The NAM device is an intra-oral prosthetic which is custom-fit by an orthodontist during the infant's first to second month of life, and serially modified, to achieve the goal of improved anatomical position of the nasal cartilage and maxillary arch prior to surgical repair (Levy-Bercowski, 2009). The nasal shape is molded with a stent which is connected to the maxillary plate by a wire. Elastic taping of the lip is also part of the pre-surgical molding process (Shetye, 2012). The entire process requires weekly or bi-weekly clinic visits for 3-5 months. Treatment with the NAM prosthesis has been shown to improve aesthetic and surgical outcomes of the lip and palate and improve nasal symmetry and form (Lee, 2008). Ideally, patients undergoing successful NAM pre-surgical treatment are less likely to have additional corrective surgeries over their life course, which translates to less surgery and surgery related risk and cost (Grayson, 1999; Yang, 2004; Shetye 2012).

NAM treatment is characterized by difficulties in compliance with the full course of treatment (Grayson, 1999; Levy-Bercowski, 2009). The frequent visits and demands of having the parents faithfully do the lip taping and have the child wear the device place a burden on the family and patient. The reason for failure to complete treatment is multi-factorial: financial issues, economic pressures, frequent clinic appointments and prosthesis adjustments, broken or lost device, irritation of soft and hard tissues leading to gagging and choking, patient removing the device, device migration, and parental and caregiver factors.

Among these, there is a paucity of data in the literature to suggest what may contribute most strongly to non-compliance. Age at first treatment and number of broken

appointments have been considered previously, but the number of subjects and frequency of complications was small and the results were not convincing (Levy-Bercowski, 2009). Anecdotally, it has been suggested that size of cleft prior to NAM treatment may be positively associated with success of NAM treatment (Kozelj, 2007), as parents are able to witness more demonstrable improvement in the reduction in size of the cleft and are thus more willing to continue treatment despite various challenges along the way. Other suggestions include family composition, with the presence of a sibling impeding the parent's ability to take close care of the NAM device (Shetye, 2012). There is a clear need to characterize the potential determinants that underlie successful pre-operative NAM treatment in order to achieve the best aesthetic and functional outcomes, as well as least cost and surgical risk for the patient and medical system.

For this study, we aimed to measure NAM treatment adherence. 'Adherence' is '*the extent to which the patient's behaviour matches agreed recommendations from the prescriber*' (Nunes, 2009) and has replaced the term compliance in the literature. The nature of adherence research in the pediatric population differs from adults, as the effect of the parent or caregiver on adherence becomes more central. NAM treatment requires close parental involvement to achieve success. In one systematic review of the pediatric adherence literature, Santer, *et al.* (2014) described six themes to consider when investigating adherence: (1) Caregiver belief about the severity of the condition and effectiveness of treatment, (2) difficulty of treatment, (3) child resistance, (4) conflict with family, (5) preserving 'normal life' [for the child, despite the illness], (6) input from health professionals. For the infant population, themes (3) and (4) become less important. Additionally, adherence has been found to decrease with larger families, lower socio-economic status, and single caregiver in the home (Rapoff, 2010). Based upon our clinical experience, we hypothesized that public insurance, increased distance from the patient's home to the clinic, and a cleft of the hard palate (+ soft palate) would be associated with non-adherence. This study seeks to discover those factors which are related to the caregiver, the patient, and the social and structural context in which medical care takes place that most strongly predict NAM treatment non-adherence.

Patients and Methods

This study was approved by the Oregon Health & Science University (OHSU) Institutional Review Board.

We conducted a retrospective review of all patients referred for NAM treatment at the OHSU multi-disciplinary Craniofacial Disorders (CFD) clinic. In this cohort design, all NAM consultations were performed by a single author (JG), who is a NAM-trained craniofacial orthodontist. During the NAM consultation, parents view a short slide show demonstrating the appearance of the device and some representative photos of NAM treatment outcomes. Patients were identified by the surgeon performing the cleft lip repair, and patient data were collected in a prospectively maintained repository.

Inclusion criteria included patients with a cleft lip, with or without palate involvement, who were referred to the craniofacial orthodontist for possible NAM treatment prior to primary cleft lip repair. Three referring surgeons were responsible for NAM referrals and cleft repair, including the author (AAK). Patients were classified as (1) completing NAM treatment, (2) prematurely discontinuing NAM treatment, (3) declining NAM treatment recommendations, (4) not recommended for NAM treatment by craniofacial orthodontist. Category (4) was excluded from the cohort.

Definitions: Treatment adherence was described as either adherent to NAM treatment (parent report of continuous use of device, regular attendance of appointments leading up to surgery) or non-adherent to NAM treatment (prematurely discontinuing device, or declining to enroll in NAM after it was recommended for them). Predictor variables were selected based upon anecdotal reports in the craniofacial literature, or known or suspected associations with adherence to pediatric medical regimes in the medical, behavioral, and psychological literature. Cleft morphology was described as affecting the lip, with or without palatal involvement, and whether it was unilateral or bilateral. We also noted whether the cleft affected the hard palate or not, as hard palate involvement prolongs the alveolar molding phase and requires more frequent appointments. For bilateral clefts, if the hard palate cleft was complete on at least one side, it was categorized as a complete cleft. Insurance status was classified into private payer or public payer, which included Tricare, a military health insurance program for families of military personnel. Ethnicity and race were collected from self-reported family questionnaires. Race was subsequently grouped into white and non-white, owing to the disproportionate racial composition of the cohort. Distance was measured as the shortest driving route from the patient's home billing address to OHSU using Google Maps (Google Inc., Mountain View, California). The age of the patient was defined as age at first clinic consultation with the CFD team. Composition of the family, including caretakers, number of siblings, and whether parents lived together was collected from clinic notes and family in-take questionnaires. Family history of a cleft was considered positive if any relative (proximal or remote) was known to have a cleft lip or palate.

Statistical analysis: We generated descriptive statistics using the mean and standard deviation for continuous variables, and the frequency and percentage for binary variables. For the analysis of variables by insurance type, the student t-test was used to compare continuous variables and $\chi 2$ test was used to compare categorical variables. Logistic regression was performed to examine independent relationships between the predictor variables and the outcome of NAM non-adherence. To build the multivariable model, we included those variables from the univariate analysis with a mild association with the outcome ($p<0.25$). These variables were included in a single model, and subjected to forward and backward stepwise variable selection. Those variables which remained significant were included in the final model. Effect modification was then assessed for the remaining variables in the model. The likelihood ratio test was performed to assess whether a more parsimonious model, containing fewer variables, was a better predictor of our outcome of interest. Odds ratios (OR's) and 95%

confidence intervals (CI's) were calculated for each association. Any OR for an association not containing unity (1.0) was considered to be significant at 0.05 level. The Hosmer-Lemeshow goodness-of-fit statistic and area under the curve (AUC) for the receiver operating characteristic (ROC) were calculated to assess the overall fit of the model. All statistical analyses were performed using Stata 13.1 (StataCorp LP, College Station, Texas).

Results

A total of 135 patients met the criteria for inclusion in this analysis. 101 (75%) were classified as adherent to the NAM therapy. In the non-adherent group (n=34), 9 patients (26.5%) declined NAM despite recommendations. The study period includes those patients consulted for NAM at OHSU between the years 2008-2013. NAM services were introduced to the OHSU CFD program in 2008. No patients were excluded from NAM referral for reasons of insurance status or medical co-morbidities. Patient characteristics are summarized in Table 1. The mean age of the patients at their first CFD appointment was 14.1 days (SD 13.7 days). 77.0% of the patients were male, 81.9% were identified by their parents as white, and 82.2% as non-Hispanic.

Table 1: Patient characteristics N = 135

Parameter	**Definition**	**Mean (SD) or Frequency (%)**	**NAM treatment adherence (N=101)**	**NAM treatment non-adherence (N=34)**
			Mean (SD) or Frequency (%)	*Mean (SD) or Frequency (%)*
Sex	Male	104 (77.04)	83 (82.2)	21 (61.8)
	Female	31 (22.96)	18 (17.8)	13 (38.2)
Cleft type	Unilateral	92 (68.1)	75 (74.3)	17 (50)
	Bilateral	43 (31.9)	26 (25.7)	17 (50)
Insurance	Private payer	57 (42.2)	47 (46.5)	10 (29.4)
	Public payer	78 (57.8)	54 (53.5)	24 (70.6)
Race	White	109 (80.7)	80 (79.2)	29 (85.3)
	Non-White	24 (17.8)	19 (18.8)	5 (14.7)
	Missing	2 (1.5)	2 (1.0)	
Ethnicity	Hispanic	23 (17.0)	18 (17.8)	5 (14.7)
	Non-Hispanic	111 (82.3)	82 (81.2)	29 (85.3)
	Missing	1 (0.7)	1 (1.0)	
Distance	Miles between patient home and hospital	66.8 (69.6)	58.8 (66.5)	90.5 (74.2)
Age	Age (days) at first clinic appointment	14.1 (13.7)	15.0 (15.3)	11.7 (6.8)
Caretakers in home	Two or more	126 (93.3)	95 (94.1)	31 (91.2)
	Single caretaker	9 (6.7)	6 (4.9)	3 (7.8)
Biological parents live together in home	No	15 (11.1)	11 (8.1)	4 (11.8)
	Yes	120 (88.9)	90 (91.9)	30 (88.2)
Sibling in home	No	52 (38.5)	36 (35.6)	16 (47.1)
	Yes	83 (61.5)	65 (64.4)	18 (52.9)
Family history of cleft	No	91 (67.4)	68 (67.3)	23 (67.6)
	Yes	44 (32.6)	33 (32.7)	11 (32.4)
Prenatal diagnosis	No	34 (25.2)	24 (23.8)	10 (29.4)
	Yes	100 (74.1)	76 (75.2)	24 (70.6)
	Missing	1 (0.7)	1 (1.0)	
Structures involved	Palate + lip	120 (88.9)	91 (90.1)	29 (85.3)
	Lip only	15 (11.1)	10 (9.9)	5 (14.7)
Hard palate cleft	No	27 (20)	18 (17.8)	9 (26.5)
	Yes	108 (80)	83 (82.2)	25 (73.5)

Cleft type was divided into two basic groups - unilateral or bilateral (with or without palatal involvement). 68.2% of clefts were unilateral in morphology and 88.9% involved both lip and palate. A complete cleft of the hard palate was present in 80% of patients. Family composition was found to primarily include two or more caretakers (93.3%), with both parents living together in the home (88.9%), and with one or more siblings (61.5%) also dwelling in the home at the time of the patient's birth. A family history (proximal or remote) of cleft lip or palate was present in 32.6% of the patients. All patients resided in Oregon or Washington State at the time of first NAM consultation. Mean travel distance from home to the CFD clinic was 66.8 miles, and the maximum distance traveled - 284 miles - reflects the tertiary referral function of the CFD clinic at our academic medical center.

The distribution of domestic characteristics and factors relating to access to care was analyzed according to insurance type (Table 2). 78 patients (58%) had public health insurance. There were no significant differences between patient sex and race, but non-Hispanic ethnicity was significantly more common in the public insurance group (p=0.032). Patients with public insurance had a significantly greater distance from home to clinic (p=0.025), age at first CFD appointment (p=0.039), likelihood of having a single caretakers in the home (p=0.008), and their biological parents living separately (p=0.016) as compared to the private insurance cohort. Patients with public insurance also had a greater number of siblings (p=0.063), which approached significance.

Table 2: Domestic characteristics and structural barriers to care by insurance type

Parameter	**Definition**	**Public Insurance (N=78)**	**Private Insurance (N=57)**	**P-value (t-test or χ2) ¥**
		Mean (SD) or Frequency (%)	*Mean (SD) or Frequency (%)*	
Sex	Male	58 (74.4)	46 (80.7)	0.387
	Female	20 (25.6)	11 (19.3)	
Race	White	62 (79.5)	47 (82.5)	0.614
	Non-White	15 (19.2)	9 (17.5)	
	Missing	1 (1.3)		
Ethnicity	Hispanic	18 (23.1)	5 (8.8)	0.032*
	Non-Hispanic	60 (76.9)	51 (89.6)	
	Missing		1 (1.6)	
Distance	Miles between patient home and hospital	78.2 (8.6)	51.1 (7.6)	0.025*
Age	Age (days) at first clinic appointment	16.2 (1.8)	11.3 (1.4)	0.039*
Caretakers in home	Two or more	69 (88.5)	57 (100)	0.008*
	Single caretaker	9 (11.5)	0 (0)	
Biological parents live together in home	No	13 (16.7)	2 (3.5)	0.016*
	Yes	65 (83.3)	55 (96.5)	
Sibling in home	Total number of siblings in house	1.4 (0.2)	1.0 (0.15)	0.063
Pre-natal diagnosis	No	20 (25.6)	14 (24.6)	0.933
	Yes	58 (74.4)	42 (73.6)	
	Missing		1 (1.8)	

* P-value <0.05

¥ Student t-test used for continuous variables; χ2 test used for binary variables

Univariate analyses revealed several significant associations between predictors and the outcome (Table 3). These included female sex (OR = 2.85, 95% CI 1.21-6.74), bilateral cleft (OR = 2.88, 95% CI 1.29-6.46), and increasing distance (OR = 1.01, 95% CI 1.00 -

1.01) which were all predictive of NAM non-adherence. Families with public payer insurance approached significance (OR = 2.09, 95% CI 0.91- 4.81; p = 0.084).

Table 3: Univariate and multivariable analyses of predictors for NAM treatment non-adherence. N = 135

Parameter	Definition	p-value	Univariate OR (95% CI)	Multivariable OR (95% CI) - *Male*	Multivariable OR (95% CI) - *Female*
Sex (CL ± CP) §	Male Female	0.017	*Reference* 2.85 (1.21 - 6.74)*	-	-
Insurance	Private payer Public payer	0.084	*Reference* 2.09 (0.91 - 4.81)	3.67 (1.13 - 11.91)*	2.78 (0.44 - 17.59)
Race	White Non-White	0.558	0.73 (0.25 - 2.12)	-	-
Ethnicity	Hispanic Non-Hispanic	0.660	*Reference* 1.27 (0.43 - 3.74)	-	-
Distance	Distance from patient home to CFD (continuous variable)	0.025	1.01 (1.00 - 1.01)*	-	-
Uni- vs bi-lateral CL ± CP §	Unilateral Bilateral	0.010	*Reference* 2.89 (1.29 - 6.46)*	8.35 (2.72 - 25.64)*	
CL ± CP §	Palate + lip Lip only	0.443	*Reference* 1.569 (0.50 - 4.97)	-	-
Complete hard palate cleft	No Yes	0.278	1.66 (0.66 - 4.15) *Reference*	-	-
Age	Age at first clinic appointment (continuous variable)	0.238	0.979 (0.945 - 1.014)	-	-
Sibling in home	No Yes	0.239	*Reference* 0.62 (0.28 - 1.37)	- 	 0.17 (0.03-1.01)
Caretakers in home	Two or more Single caretaker	0.562	*Reference* 1.53 (0.36 - 6.49)	-	-
Biological parents live together in home	No Yes	0.889	*Reference* 0.92 (0.27 - 3.10)	-	-
Family history of cleft	No Yes	0.973	*Reference* 0.99 (0.43 - 2.26)	-	-
Prenatal diagnosis	No Yes	0.532	*Reference* 0.76 (0.32 - 1.81)	-	-

§ CL ± CP = cleft lip, either with or without cleft palate involvement
* P-value <0.05

When constructing our multivariable model, we discovered a highly significant interaction between sex and unilateral vs bilateral clefts. Because of this, we stratified our analysis by sex. For the female group, presence of a sibling was protective against treatment non-adherence, which was nearly significant (OR=0.17, 95% CI 0.03-1.01). This relationship was confounded by public insurance status, and was therefore included in the multivariable model. For males, the strongest model contained the variables cleft type and insurance. The multivariable logistic regression analysis demonstrated that presence of a bilateral cleft (OR=8.35, 95% CI 2.72 - 25.64) and public payer insurance (OR=3.67, 95% CI 1.13 - 11.91) best predicted NAM treatment non-adherence. This model considered the possible confounding effects of several predictors which were either clinically suspected to be confounders, or demonstrated at least a mild association ($p \leq 0.25$) with treatment non-adherence in univariate models.

These included presence of a *sibling*, *distance*, and *age at first CFD appointment*. None were found to have significant confounding effects. Finally, when we compared the parsimonious models for males and females to a less restrictive model containing the variables *siblings*, *distance*, and *age at first CFD appointment*, we found the parsimonious model to be a better fit in both instances, using the likelihood ratio test (female p=0.716; male p=0.533).

Between males and females, there were no significant differences in the distribution of cleft lip ± cleft palate (p=0.718), hard palate involvement (p=0.152), and uni- vs bi-lateral cleft (p=0.701), There was no significant difference in whether an infant was born at term or pre-term, between males and females, (p=0.166).

For the multivariable models, the Hosmer-Lemeshow goodness-of-fit statistic indicated that the model was a good fit, (female p=0.131; male p = 0.134). Goodness-of-fit was also assessed with calculation of the area under the curve (AUC) for the receiver operating characteristic (ROC) curve which was found to be p=0.718 for female and p = 0.783 for male, also indicating a good fit for the multivariable models.

Discussion

NAM therapy is associated with failure to complete the full course of treatment and is well recognized to be a burden of care for the parents as well as for the patient. To our knowledge, this study is the first of its kind to examine factors associated with non-adherence to NAM treatment. As non-adherence is thought to be multifactorial (Rapoff, 2010), we wanted our analysis to include factors that are related to the caregiver, the patient, and the social and structural context in which care takes place. Our main findings were that female sex, bilateral clefts, and increased distance to the CFD clinic were independent predictors of treatment failure. In our gender-stratified multivariable analysis, public insurance and bilateral cleft predicted non-adherence for males, and surprisingly, absence of siblings was nearly significant in association with non-adherence. In a separate analysis of the cohort by insurance type, several family characteristics were found to be significantly more common in patients with public insurance: non-Hispanic race, increased distance to clinic, increased age at first appointment, single caretaker in home, and biological parents dwelling separately. Additionally, the mean number of siblings was greater in the public insurance group, and this difference approached statistical significance.

Gender differences

The strong sex difference observed in non-adherence was unexpected. The effect of sex observed in our study is likely multifactorial and includes innate biologic differences, as well as psychosocial factors between parent and child. Parents of children with cleft anomalies report a feeling of stigmatization related to their child's appearance, with subsequent social discomfort and impairment (Nelson, 2012). It is known that sex of the child also plays a large role in parental expectations and perceptions. Tobiasen (1987) found that the appearance of female children with cleft lip anomalies were

judged more negatively compared to males. Parents or caregivers may be more overprotective of the daughters and not wish to see them "suffer" through NAM therapy (Tobiasen, 1987; Guinsburg, 2000). Other issues to consider include acceptance issues of daughters vis-à-vis cultural and social values (Wright, 1983; Broder, 1985; 1992; Goffman, 1963; Kagan, 1964).

Unilateral vs bilateral cleft

The strong association between bilateral clefts and NAM non-adherence was suspected at a clinical level but not previously confirmed in the literature. Compliance issues have been found to be equally distributed between unilateral and bilateral cleft palates (Mobin, 2011). Sischo, *et al.* (2012) also found that families were no more likely to choose NAM over non-NAM treatments if their child had a bilateral cleft. In the general population, the frequency of unilateral to bilateral clefts is 9:1 (Thorne, 2007). In our cohort, the distribution of unilateral to bilateral clefts was 2:1, with no significant difference in the distribution of unilateral vs bilateral clefts between males and females. Perhaps our differing distribution reflects a referral pattern of patients to our tertiary center with more complex issues (insurance, infant co-morbidities, complications of pregnancy or post-partum parenting issues).

In our experience, a bilateral cleft is felt to be more challenging in terms of designing the NAM appliance's plate and often requires a larger extra-oral portion of the plate. It is possible that the extra-oral portion may result in more challenging biomechanics in aligning the plate against the palate, thus resulting in more sores or sub-clinical irritation to the infant's mouth. Alternatively, it may be the parental perception of appearance, rather than the difficulty of the cleft morphology, that underlies the observed association with non-adherence. Parsons, *et al*. (2011) found that when adults viewed an anonymous group of infants that increasing cleft severity was associated with decreased ratings of attractiveness. This perspective on the infant's face, which is an essential medium for how the parent-infant relationship develops, may lead to an impaired relationship and more difficulties with the course of the cleft care.

We had predicted that compared to patients with cleft lip only, those with palate involvement would be more likely to be non-adherent, owing to increased anatomic extensiveness of the anomaly. Moreover, we expected that cleft of the hard palate would cause families more hardship, owing to a longer treatment time, more frequent adjustments, and difficulty in creating a plate that is stable in the mouth. Why this association would be significant for males and not observed for females is unknown and warrants further exploration.

Distance

We hypothesized that distance and public insurance were significant predictors of non-adherence. In the univariate analysis, distance had a weak, but significant association with non-adherence. Travel distance and frequency of appointments are routinely discussed as concerns by the family during NAM consultation appointments. In a

systematic review of literature on the psychological adjustment of the parents in response to a cleft, Nelson, *et al*. (2012) described the strain and decrease in family quality of life associated with the frequent appointments and overall treatment course. Indeed, multidisciplinary cleft care requires a significant time commitment. Nationally, the average travel distance to a craniofacial center offering NAM is 66.5 miles (Sischo, 2012) which was consistent with our cohort's experience (66.8 miles). However, distance was not significant in our multivariable analysis. The work of Cassell, *et al*. (2012) supports this assertion, as they found that 33% of mother of children with cleft lip $\pm$ palate felt it was a problem for them to get their child to their craniofacial clinic appointments, but 88% felt that their children got the necessary care despite that barrier.

Our analysis also showed that distance traveled was significantly higher for the public insurance group, as was having a single caretaker, and a greater number of siblings. Perhaps this constellation of socio-economic and familial factors act as confounders and obscures the association of distance with non-adherence. Our findings are in contrast to the work of Cassell, *et al.* (2013), which found no association between increased distance and having public health insurance. Distance may also represent the effect of living in a rural setting. Mayer, *et al.* (2005) demonstrated that for children with special healthcare needs, rural residence was associated with decreased perception of need for care. Zuckerman, *et al.* (2011) showed that low correlation of parent-provider perception of the seriousness of a condition, and necessity for treatment, are associated with failure to complete a referral to a specialist. NAM treatment requires extensive parental participation, and as the sole decision makers for this child, their belief in the benefit of the treatment is paramount.

Insurance

Public insurance was weakly associated ($p<0.10$) with non-adherence in the univariate analysis, and for males, strongly associated in the multivariable analysis (OR=3.67). This difference between sexes was perplexing, and we believe it is most likely the result of the smaller sample size for females. Furthermore, we cannot conclude how public insurance leads to treatment non-adherence. In one systematic review of the literature on the effects of insurance type on specialty care, Skinner, *et al.* (2007) found that children with public insurance have less access to, and fare worse with, specialty care, compared to those with private insurance. They speculate that this may be either related to patterns of provider insurance acceptance or other hardships unique to public insurance population. In our study, the patients with public insurance were more often coming from homes with fewer caretakers, biological parents living separately, more siblings, and beginning their CFD care later in the child's life. Perhaps it is these domestic factors that inform the association between public insurance and non-adherence. In a related study, Sischo, *et al.* (2012) compared patients who began NAM treatment with those who declined it and found that families with no other children more often chose NAM than those with one or more children. Public insurance was more common in those who did not choose NAM, however longer distance traveled was

not. Additionally, Zuckerman, *et al.* (2014) found that while families may cite transportation, childcare, excusal from work as barriers to specialty care for their children, they do not significantly predict the ability to attend a specialty clinic referral. Instead, scheduling and medical system navigation barriers predicted a failed referral to a specialist. Cassell, *et al.* (2012) examined maternal perceptions of barriers to cleft care and found that 20% of their cohort cited financial issues as a barrier to care for their children, while the prevalence of uninsured families was only 6.1%. This highlights the financial challenges that patients face, despite having some form of insurance coverage.

Siblings

Among our female cases, there was a strong protective effect (OR=0.17) of having a sibling. This relationship was confounded by insurance status. This is the opposite of what we predicted and indeed, what has been described regarding the effect of siblings on decision to pursue NAM (Sischo, 2012) or on pediatric medical adherence, generally (Rapoff, 2010). What is unique about cleft lip and palate in children is the irrefutable presence of disease and 'difference' that is perceptible to the sibling. This fact may bring some unique forces to bear on the relationship between family composition and adherence. Indeed, Lavigne, *et al.* (1979) found that siblings of children with visible deformities had poorer psychosocial adjustment compared to those infant-sibling dyads with more severe, but less visible disease. This dynamic has been examined more in depth in the pediatric burn population. In their review of psychological response to pediatric burns, Bakker, *et al.* (2013) found that sibling behavior was not significantly perturbed after initial adjustment, but rather they tended to exhibit increased signs of warmth, closeness, and protectiveness toward their disfigured sibling. Perhaps a similar phenomenon is at work in our cohort. Alternatively, there is some evidence that a larger family may positively affect compliance with medications in a chronically ill population (Lansky, 1983), or that siblings of patients with visible deformity become more difficult for the parent, in terms of behavior and psycho-pathology, only when the family's socio-economic status is lower (Lavigne, 1979). Our findings provide some support to this idea, as public insurance status was a significant confounder of the protective effects of having a sibling against NAM non-adherence. Perhaps these larger families include parents who are more experienced caregivers and have achieved a greater degree of education or occupational stability which affects their ability to be resilient against the emotional, financial, and logistical challenges to participating in NAM treatment.

Limitations

The primary limitation of this study is the use of a retrospective chart review to capture the interplay of medical, social, and psychological factors that underlie NAM adherence. We were able to identify multiple risk factors, but given the nature of our study, we were unable to identify a strong predictive model for non-adherence. The psychosocial disposition and cognitive abilities of the caregiver has been shown to be a significant predictor of pediatric adherence (Mellins, 2004), but our study design did not allow

consideration of these factors. Additionally, data on caregiver age, education, and socio-economic status was missing or unavailable for too many patients such that we had to exclude those valuable factors from analysis. Therefore, our significant predictors may be a partial representation of what leads families toward non-adherence, and should be cautiously interpreted as a first view towards understanding the true causal relationships.

We may have introduced selection bias with the decision to group the families which declined treatment with those who prematurely discontinued treatment. This was done because, anecdotally, the reasons people declined were often similar to those given when they failed treatment. Consequently, this may inflate the effects of distance, insurance and family composition factors, and diminish the effects of cleft morphology, which would presumably not be relevant until NAM treatment had begun.

Our findings may also represent the unique challenges of treatment in this area. Compared to other more densely populated areas of the country, there are fewer tertiary medical centers and cleft care groups. Therefore, the extent to which our findings are generalizable may be limited. Finally, the size of our study cohort was relatively small, and the distribution of factors between adherent groups was quite unequal. This resulted in less precise OR's and the higher likelihood that some of the associations we observed were due to chance. Additionally, the calculated c-statistic for the AUC suggested our model was not strongly predictive of the outcome. This indicated that there still are some unexamined confounders or covariates that would improve the predictive ability of our multivariable model.

Given the complexity of the device, the disease, and family and social factors which all may complicate the course of treatment, we believe adherence to NAM treatment remains impressively high. This speaks to the resilience of families and the exceedingly high level of multi-disciplinary coordination provided for each patient. The rate of non-adherence (25%) is still significant and merits efforts to reduce it. To do this, we argue that it is not enough to identify predictive factors for adherence, but rather provide the best argument for how and where to allocate the time and resources it takes to assist these non-adherent families. While this study provides some insight into how this may be accomplished, the conflicting findings with related studies, small study sample, unexpected findings, and limited pool of predictor variables point towards the presence of qualitative and psychosocial factors which require alternative means of assessment in subsequent research.

Recommendations for future research

This study offers a useful starting point for those investigators wishing to better understand adherence in this population. As this is a small, single-institution study, it would be very informative to see if these results were consistent in a larger population across multiple institutions. The role of gender, bilateral clefts, and insurance status all deserve closer examination to disentangle the social versus biological effects at work.

One way to approach this would be to conduct focus groups of 15-20 non-adherent families of the children who were enrolled in this study and perform a qualitative assessment of their perspective on barriers to NAM. At the end of this session, the CFD group could then present the findings of this present study and gather the family's perspective on the role of distance, uni- vs bi-lateral cleft, sex, siblings, and insurance and attempt to capture the family's reflections on the role those factors played in their child's experience with NAM. Assessment of quality of life (QOL) outcomes associated with NAM for these families would also be of interest. QOL metrics provide a patient-centric perspective that certainly could help with future NAM-related counseling and troubleshooting, and would be consistent with greater trends towards quality- and performance-based reimbursement schemes that are unfolding in surgery broadly. Additionally, the socio-economic and psychosocial disposition of the caregivers is almost certainly an important determinant of adherence. Therefore, we would recommend prospective questionnaires to assess family socio-economic status, parental level of education, parental stress and cognitive functioning, as well information on parental perception of the necessity of the device and severity of the disease, as these may represent a potential target for intervention. Finally, the process by which families learn about and are offered NAM was variable within our institution. Standardizing this process would improve the accuracy of our research, as we would be able to minimize the inter-provider variability in how NAM is introduced and discussed with the families. This would have the effect of reducing potential bias in provider NAM referral discussions.

Works Cited

Asheley, C. S., & Michelle, L. M. (November 28, 2007). Effects of insurance status on children's access to specialty care: a systematic review of the literature. Bmc Health Services Research, 7, 1.)

Bakker, A., Maertens, K. J., Van, S. M. J., & Van, L. N. E. (January 01, 2013). Psychological consequences of pediatric burns from a child and family perspective: a review of the empirical literature. *Clinical Psychology Review, 33,* 3, 361-71.

Broder, H. L., Smith, F. B., & Strauss, R. P. (January 01, 1992). Habilitation of patients with clefts: parent and child ratings of satisfaction with appearance and speech. *The Cleft Palate-Craniofacial Journal : Official Publication of the American Cleft Palate-Craniofacial Association, 29,* 3, 262-7

Broder, H., & Trier, W. C. (January 01, 1985). Effectiveness of genetic counseling for families with craniofacial anomalies. *The Cleft Palate Journal, 22,* 3, 157-62.

Cassell, C. H., Krohmer, A., Lee, K. A., Mendez, D. D., Strauss, R. P., & Meyer, R. E. (October 01, 2013). Factors associated with distance and time traveled to cleft and craniofacial care. Birth Defects Research Part a - Clinical and Molecular Teratology, 97,10, 685-695.

Cassell, C. H., Mendez, D. D., & Strauss, R. P. (January 01, 2012). Maternal perspectives: qualitative responses about perceived barriers to care among children with orofacial clefts in north Carolina. The Cleft Palate-Craniofacial Journal : Official Publication of the American Cleft Palate-Craniofacial Association, 49, 3, 262-9

Cleft Lip and Palate Association (2009) Regionalisation of cleft lip and palate services: has it worked? A report on users' perspectives of cleft care. Available at: http:// www.clapa.com

Garfinkle JS, King TW, Grayson BH, Brecht LE, Cutting CB. A 12-year anthropometric evaluation of the nose in bilateral cleft lip-cleft palate patients following naso-alveolar molding and cutting bilateral cleft lip and nose reconstruction. Plast Reconstr Surg. 2011 Apr;127(4):1659-67

Goffman E. Stigma – notes on the management of spoiled identity. Englewood Cliffs, NJ: Prentice-Hall, 1963.

Grayson BH, Santiago PE, Brecht LE, Cutting CB. Presurgical nasoalveolar molding in infants with cleft lip and palate. Cleft Palate Craniofac J. 1999 Nov;36(6):486-98

Guinsburg, R., de, A. P. C., Branco, . A. M. F., de, C. X. B. R., Cássia, B. R., Tonelotto, J., & Kopelman, B. I. (January 01, 2000). Differences in pain expression between male and female newborn infants. *Pain, 85,* 1-2.

Kagan, J. Acquistion and significance of sex typing and sex role identity. In: Hoffman M, Hoffman L, eds. Review of child development research. Vol 1. New York: Russell Sage, 1964.

Kozelj V. Experience with presurgical nasal molding in infants with cleft lip and nose deformity. Plast Reconstr Surg. 2007 Sep;120(3):738-45.

Kramer FJ, Baethge C, Sinikovic B, Schliephake H. An analysis of quality of life in 130 families having small children with cleft lip/palate using the impact on family scale. Int J Oral Maxillofac Surg. 2007 Dec;36(12):1146-52. Epub 2007 Sep 5

Lansky, S. B., Smith, S. D., Cairns, N. U., & Cairns, G. F. J. (January 01, 1983). Psychological correlates of compliance. The American Journal of Pediatric Hematology/oncology, 5, 1, 87-92

Lavigne, J. V., & Ryan, M. (January 01, 1979). Psychologic adjustment of siblings of children with chronic illness. Pediatrics, 63, 4, 616-27.

Lee CT, Garfinkle JS, Warren SM, Brecht LE, Cutting CB, Grayson BH. Nasoalveolar molding improves appearance of children with bilateral cleft lip-cleft palate. Plast Reconstr Surg. 2008 Oct;122(4):1131-7

Levy-Bercowski D, Abreu A, DeLeon E, Looney S, Stockstill J, Weiler M, Santiago PE. Complications and solutions in presurgical nasoalveolar molding therapy. Cleft Palate Craniofac J. 2009 Sep;46(5):521-8. McCorkell G, McCarron C, Blair S, Coates V. Parental experiences of cleft lip and palate services. Community Pract. 2012 Aug;85(8):24-7. Shetye PR. Presurgical infant orthopedics. J Craniofac Surg. 2012 Jan;23(1):210-1

Mayer, M., Slifkin, R., & Skinner, A. (January 01, 2005). The Effects of Rural Residence and Other Social Vulnerabilities on Subjective Measures of Unmet Need. Medical Care Research and Review, 62, 5, 617-628.

Mellins, C. A., Brackis-Cott, E., Dolezal, C., & Abrams, E. J. (January 01, 2004). The role of psychosocial and family factors in adherence to antiretroviral treatment in human immunodeficiency virus-infected children. The Pediatric Infectious Disease Journal, 23,11, 1035-41.

Nazarian, M. S. S., Karatsonyi, A., Vidar, E. N., Gamer, S., Groper, J., Hammoudeh, J. A., & Urata, M. M. (January 01, 2011). Is presurgical nasoalveolar molding therapy more effective in unilateral or bilateral cleft lip-cleft palate patients?. Plastic and Reconstructive Surgery, 127, 3, 1263-9.

Nelson, P., Glenny, A. M., Kirk, S., & Caress, A. L. (January 01, 2012). Parents' experiences of caring for a child with a cleft lip and/or palate: a review of the literature.*Child: Care, Health and Development, 38,* 1, 6-20.

Nunes V, Neilson J, O'Flynn N, Calvert N, Kuntze S, Smithson H, Blair J, Bowser A, Clyne W, Crome P, Haddad P, Hemingway S, Horne R, Johnson S, Kelly S, Packham B, Patel M, Steel J: Clinical Guidelines and Evidence Review for Medicines Adherence: involving patients in decisions about prescribed medicines and supporting adherence. London: National Collaborating Centre for Primary Care and Royal College of General Practitioners; 2009.

Parsons, C. E., Young, K. S., Parsons, E., Dean, A., Murray, L., Goodacre, T., Dalton, L., ... Kringelbach, M. L. (October 01, 2011). The Effect of Cleft Lip on Adults' Responses to Faces: Cross-Species Findings. *Plos One, 6,* 10.)

Santer, M., Ring, N., Yardley, L., Geraghty, A. W. A., & Wyke, S. (January 01, 2014). Treatment non-adherence in pediatric long-term medical conditions: systematic review and synthesis of qualitative studies of caregivers' views. Bmc Pediatrics, 14, 1, 63.

Sischo, L., Chan, J. W., Stein, M., Smith, C., van, A. J., & Broder, H. L. (January 01, 2012). Nasoalveolar Molding: Prevalence of Cleft Centers Offering NAM and Who Seeks It. The Cleft Palate-Craniofacial Journal : Official Publication of the American Cleft Palate-Craniofacial Association, 49, 3, 270-50.

Tobiasen, J. M. (January 01, 1987). Social judgments of facial deformity. *The Cleft Palate Journal, 24,* 4, 323-7.

Tobiasen, J. M., & Hiebert, J. M. (January 01, 1984). Parents' tolerance for the conduct problems of the child with cleft lip and palate. *The Cleft Palate Journal, 21,* 2, 82-5.

Thorne, C., Grabb, W. C., & Smith, J. W. (2007). Grabb and Smith's plastic surgery. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins.

Wright, B. Physical disability – a psychosocial approach. New York: Harper and Row, 1983.

Zuckerman, K. E., Nelson, K., Bryant, T. K., Hobrecker, K., Perrin, J. M., & Donelan, K. (July 01, 2011). Specialty Referral Communication and Completion in the Community Health Center Setting. Academic Pediatrics, 11, 4, 288-296.