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Information on co-morbidities collected by history is useful for assigning Otitis Media risk to children[☆]

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Abstract

Objectives—Determine if a 2-Step multivariate analysis of historical symptom/sign data for comorbid diseases can abstract high-level constructs useful in assigning a child's "risk" for different Otitis Media expressions.

Methods—Seventeen items related to the symptom/sign expression of hypothesized Otitis Media comorbidities were collected by history on 141 3-year-old children. Using established criteria, the children were assigned to 1 of 3 groups: Control (no significant past Otitis Media, $n = 45$), Chronic Otitis Media with Effusion ($n = 45$) and Recurrent Acute Otitis Media ($n = 51$). Principal Component Analysis was used to identify factors representing the non-redundant shared information among related items and Discriminant Analysis operating on those factors was used to estimate the best predictor equation for pairwise group assignments.

Results—Six multivariate factors representing the assignable comorbidities of frequent colds, nasal allergy, gastroesophageal disease (specific and general), nasal congestion and asthma were identified and explained 81% of the variance in the 17 items. Discriminant Analysis showed that, for the Control-Chronic Otitis Media with Effusion comparison, a combination of 3 factors and, for the Control-Recurrent Acute Otitis Media comparison, a combination of 2 factors had assignment accuracies of 74% and 68%, respectively. For the contrast between the two disease expressions, a 2-factor combination had an assignment accuracy of 61%.

Conclusion—These results show that this analytic methodology can abstract high-level constructs, comorbidities, from low-level data, symptom/sign scores, support a linkage between certain comorbidities and Otitis Media risk and suggest that specific comorbidity combinations contain information relevant to assigning the risk for different Otitis Media expressions.

Keywords

Otitis Media; Risk factors; Children; Multivariate analysis

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1. Introduction

Otitis Media (OM), inflammation of the middle ear (ME) mucosa, is very common in the pediatric population [1]. The onset of an OM episode is most often coincident with a viral upper respiratory tract infection (vURI) [2,3] and OM presentation can be symptomatic acute OM (AOM), or asymptomatic OM with effusion (OME). Usually, OM episodes are self-limited [4] but, in a subset of children, resolution is delayed for months to years, chronic OME (COME). Alternatively, some children are at high risk for frequently recurring AOM episodes (RAOM) [1]. Both COME and RAOM are difficult to manage, troublesome conditions and there is long-standing interest in developing intervention strategies that reduce their risks [5,6].

A large body of published work identified specific traits, behaviors, environments and conditions that increase an individual's risk for the different OM expressions [7]. For example, COME and, perhaps, RAOM risk is heritable [8,9], is increased by behaviors and environments that promote infection with upper-respiratory bacterial pathogens and viruses [10–12] and is higher in individuals with certain comorbid conditions such as craniofacial dysmorphologies, frequent viral upper respiratory infections (vURIs), nasal allergy and gastro-esophageal reflux (GER) [4,13–17]. These types of studies are needed to develop the database for construction of individual risk profiles that allow a child to be identified as at high risk for OM and “in need” of close clinical observation for early OM diagnosis and management. Also, an individual's risk factors can be targeted for reduction by modifying the individual's behaviors, environments and conditions [5,10,13,15,18].

For those applications, it is important that the risk factor database be specific, complete and not contaminated by spurious associative factors. However, a review of the literature shows that some identified “risk factors” have poor reproducibility across studies while others are redundant expressions of a more inclusive, higher level construct. For example, there is a conceptual linkage among such diverse childhood OM “risk factors” as socioeconomic status, breastfeeding, day care attendance, pacifier use, home crowding and frequent upper respiratory infections, among others. There, socioeconomic status partially determines the probability that a child will be breastfed, exposed to crowded conditions, enrolled in daycare and use pacifiers. These considerations show that the previously identified “risk factors” can be hierarchically classified with the lowest level occupied by groups of related elements containing redundant information and successively higher levels occupied by broader constructs representing the shared information for each group of related items in the immediately lower level. In this typology, the lower level elements are reasonably referred to as “risk modifiers” and the higher level constructs as “risk factors”.

This typology cannot be generated using the analytic methodology commonly used to identify OM “risk factors”. Specifically, most past studies used a two-step analysis consisting of an initial set of univariate Control-disease comparisons for a set of hypothesized “risk factors” followed by a multivariate selection procedure operating on set members identified as being “significant” [14,19–23]. Because the set of hypothesized risk factors likely contains subsets of mutually correlated elements, the first step will identify as significant all elements in those subsets whose shared information construct predicts OM

risk. The second step simply selects from each predictive subset the member with the highest accuracy assignment. However, the identified subset member is not a risk factor but rather an exemplar for a class of variables whose shared information is the risk factor. Consistent identification of that same member across studies requires that it is included in the set of hypothesized factors and has the highest group assignment accuracy among all other subset members.

The present study introduces an alternative statistical methodology that is expectedly capable of abstracting the higher level constructs (risk factors) from a set of lower level risk modifiers. The procedure requires two procedural steps and a third step to test efficiency. First, a multivariate data reduction procedure is used to extract the shared information contained in a set of hypothetical risk modifiers for representation as a smaller number of independent “factors”. Then, the set of extracted factors is analyzed using a comparative multivariate procedure to identify those that discriminate between groups defined by disease state. Finally, the efficiency of the analytic methodology for identifying risk factors is quantified as measures of assignment accuracy for the identified risk factor combinations. Here, this analytic procedure was used to determine if constructs representing the non-redundant information contained in a symptom/sign set for comorbid diseases collected by history is useful in assigning a child’s “risk” for different OM expressions.

2. Material and methods

The study is a multivariate analysis of the cross-sectional, historical data for 3-year-old children relating to the symptoms/signs of those comorbidities suspected to increase OM risk for purposes of identifying information-rich constructs that impact the risk for the different OM expressions. The data were abstracted from a standard history questionnaire completed by parents at the time of enrolling their 3-year-old child into either of two parallel longitudinal studies. The enrollment criteria for these studies were similar with the exception that, while the first study enrolled 3-year-old children in each of the three OM expression groups to describe maturational changes in Eustachian tube anatomy and function [24], the second enrolled 3- to 7-year-old children in the COME group to determine if Eustachian tube function tests are predictive of disease recurrence after tympanostomy tubes became dysfunctional [25]. Those studies were approved by the University of Pittsburgh Institutional Review Board with enrollment between 2007 and 2011.

The information collected by questionnaire included: general demographics for the child and family; socio-economic measures for the household; OM and other disease histories for the extended family; typical OM “risk factors” for the child, sibs and parents, and the child’s history of the typical symptom/sign presentations for comorbid conditions associated with OM. Based on an ENT examination done at entry and a review of the parent-provided OM history supplemented by information available in the child’s medical charts, each child was assigned to one of three groups: Control, COME and RAOM [26]. Briefly, children were classified as: (1) Controls if they had not had tympanostomy tubes or satisfied the criteria for a positive history of COME or RAOM; (2) RAOM if they had three or more episodes of symptomatic OM in one year or five or more episodes by study entry with at least two AOM episodes or tympanostomy tubes inserted for RAOM within the year prior to enrollment

irrespective of whether or not they also had OME episodes; and (3) COME if they had three or more consecutive months of middle ear effusion if bilateral, six consecutive months of effusion if unilateral or three or more episodes of OM lasting for at least two months with at least one episode of OME or tympanostomy tube insertion in the year prior to entry and had not met the criteria for RAOM. Children were excluded if presenting with craniofacial anomalies, syndromes predisposing to OM, significant orthodontic treatment, cholesteatoma or ear surgery other than tympanostomy tube insertion.

2.1. Data analyses

The data analyzed were limited to the 17 symptom/sign items listed in Table 1 and representing the expression of presumed OM-related comorbid diseases for the enrolled children who were 3-years-old at entry. Parents responded to these items by recording a positive, scored as 1, or negative, scored as 0, history for the item in their child. These data were analyzed in three steps.

First, because the 17 items contained redundant information, a variable reduction procedure called Principal Component Analysis (PCA) with varimax rotation was done. There, a minimum 80% total explained variance cut-off was used to limit the number of factors to be considered and, for each factor, a minimum item loading communality of 20% (shared variance between variable and factor) was required to assign an item to the factor. This procedure extracts from those items a lesser number of independent, higher level variables, called "factors". Each factor represents the shared information for a subset of correlated items and, together, the set of factors capture the majority of non-redundant information contained in all 17 items.

Then, for each of the three possible 2-way comparisons (Control vs. COME, Control vs. RAOM, COME vs. RAOM), a procedure called Discriminant Analysis (DA) was done on the factor scores for each individual in the comparison groups to identify an equation that best assigns individuals to their respective group based on a weighted combination of meaningful factors. The DA consisted of 20 successive iterations with each iteration defined by an alpha of 0.10 to enter the equation and of 0.05 to be retained in the next step.

Finally, for each 2-way comparison, a 4-cell contingency table was constructed by cross-listing the known number of children in each comparison group vs. the number of children in each group predicted by the DA equation. Using standard definitions, three measures of DA efficiency for correct group assignment were calculated from each table, the sensitivity, specificity and accuracy of the DA for group assignment.

3. Results

The data for 141 children (45 Control, 45 COME and 51 RAOM) were analyzed. The demographics for these children are reported in Table 1. While there is a slight over-representation of black children in the Control group compared to the RAOM and COME groups, the distributions of the other variables are well balanced.

The 17 symptom/sign items included in the history questionnaire and the percent of children in each group with positive histories for each item are listed in Table 2. Most of these frequencies were higher in the two OM groups when compared to the Control group. Also listed for each item are the univariate probability levels for the three possible comparisons calculated using the Mann–Whitney *U* test.

PCA identified six multivariate factors that together captured 81% of the total variance in the 17 items. These factors and the items loading on each are listed in Table 3. The set of individual items loading on each factor was examined to identify a grouping theme common to those items, the factor “name”. The three comorbidities believed to be associated with OM and targeted in designing the questionnaire, allergy, vURI and GER, are represented in the set of factors as are presentations interpreted as isolated nasal congestion and asthma. Of interest, the symptom cluster attributed to GER loaded on two factors, Factors 1 and 4. These were labeled “general” and “specific” GER with the former characterized by a broad grouping of typical GER symptoms/signs and the latter including a GER specific symptoms/sign for infants (spit-up) and children (reflux).

The DA results for the three pairwise comparisons are reported in Table 4. For the Control vs. COME comparison, the discriminant function included Nasal Allergy, vURI and specific GER as significant predictors of group assignment. Contingency analysis showed that function to have a 74% assignment accuracy with a sensitivity of 0.84 and specificity of 0.64. The items loading on each of these factors were more often history-positive for the COME group. The discriminant function for the Control vs. RAOM comparison included two factors, general GER and vURI, and had an assignment accuracy of 68% with a sensitivity of 0.82 and specificity of 0.55. All items loading on those factors were more often history-positive for the RAOM group. At a retention alpha of 0.05, no factor was identified as a significant predictor for the COME vs. RAOM comparison. Widening the retention cutoff to an alpha of 0.10 yielded a discriminant function that included specific GER and Nasal Obstruction with an assignment accuracy of 61%, a sensitivity of 0.76 and a specificity of 0.44.

4. Discussion

Past studies reported that certain genetic, behavioral, morphological and conditional characteristics moderate an individual’s OM risk [6,8–18]. While the specific variables in each of these domains are often referred to as “risk factors”, many are members of subsets, each defined by a higher level representation of the information shared among subset variables, the true risk factor. Identifying these higher level constructs introduces a generalizability to set membership and allows predicting new set members from expected correlations with existing set members. Moreover, while the specific set members can vary across studies, the same higher level construct will emerge from the extraction analysis if any member is included in the data base. Identification of these constructs can be used to inform the design of child-specific interventions that lower OM risk and prevent or moderate OM expression.

One domain of “risk factors” identified by the usual statistical methodology is the presence of certain comorbid diseases such as frequent colds, allergic rhinitis and gastroesophageal reflux (GER), among others [2,27–30]. However, different studies do not consistently identify the same set of comorbidities. Specifically, while frequent colds is an accepted and reproducible OM “risk factor”, nasal allergy and GER (and some other less well-studied diseases) are less consistently identified and are considered to be possible but, unproven, OM risk “factors”. Explanations for the inconsistencies include differences among studies in design, definitions, populations and analytic methodology.

For comparisons across studies, each study must have included same aged individuals, analytic plan and set of accurately diagnosed comorbidities. However, in studies focused on infants and young children, the last criterion is not easily satisfied. For example, a confirmed diagnosis of many common conditions in that population is expectedly sporadic and dependent on such factors as socio-economic status, health care access, degree of caregiver involvement and the child’s expressed severity of signs and symptoms.

In this study, we explored the usefulness of a history for the presence of typical symptoms/signs of proposed OM comorbidities with respect to predicting the known OM presentations for a population of 3-year-old children. There, we expected that different symptom/sign subsets predict the presence/absence of the different comorbidities even in the absence of physician confirmation and, therefore, that a measure of subset representation for individual children would predict their OM group presentation if, and only if, the representative comorbidity is a “true” OM risk factor. The results showed that PCA identified six independent factors that, together, explained more than 80% of the total variance in the symptom/sign items. Those factors corresponded to five independent morbidities: frequent vURIs, nasal allergy, GER (specific, general), nasal blockage and asthma. DA operating on these factors identified five that were significantly different among the three groups: frequent vURIs, nasal allergy, nasal obstruction and GER (specific, general), a list that reproduces the set of comorbid diseases typically identified as OM risk factors. Contingency analysis showed the discriminant equations had reasonable disease-group assignment accuracies [4,13–17].

New information from this analysis of particular interest to understanding disease pathogenesis is that the set of discriminating factors is not the same for the Control-COME comparison and the Control-RAOM comparison and, that for the RAOM vs. COME comparison, two factors, specific GER and nasal obstruction, approached significance at the typical 0.05 level. Interpretively, frequent vURIs characterize the group of children at risk for both OM presentations and a concurrent diagnosis of GER, nasal allergy or nasal obstruction further specifies the disease expression to COME risk. While it is tempting to incorporate these observations into modeling the divergent pathways leading to COME and to RAOM, this is premature in the absence of confirmatory work.

It is important to appreciate that, like all statistical analyses operating on non-interventional data sets, causal associations cannot be established between the extracted factors and the OM expressions. This requires a different type of study design wherein a comorbid factor is modulated experimentally and the effect on disease presentation evaluated. There are other

limitations to the extrapolative use of these results. First, the characteristics of the analyzed dataset constrain the applicability of these results to similar populations of children, i.e. 3-year-olds who satisfy the inclusion–exclusion criterion for this study. Second, the item set was not optimized prospectively for this type of analysis. This does not affect the extracted comorbidities but does exclude identifying any discriminating comorbidity not represented in the set of symptom/sign items. Finally, values for the accuracy measures are presented only to demonstrate a relative scaling of assignment efficiency and are not intended to represent the achievable limits for those measures using this analytic methodology.

In this first application of the described analytic methodology, the data were limited to the single subdomain, comorbid disease. This was done intentionally to preserve the relative simplicity of interpreting the developed associations. However, it is expected that future work on expanded sets of elements to include other domains will increase the number of independent risk factors identified and improve the accuracies of the predictive models. However, the exact approach to such analyses needs to be carefully considered. It is anticipated that this would include the use of independent PCAs operating on each domain to extract the core factors representative of the non-redundant information for each, and then a second level PCA operating on the identified factors across domains to extract the non-redundant information contained in the among-domain factors. This would require large numbers of subjects given the recommended numeric relations of 10 persons and 3–6 variables per identified factor. Also, because the factors identified by PCA and other information extraction procedures such as latent class analysis do not have an explicit meaning, interpretation of the higher level factors may be difficult.

Throughout this presentation, we have argued that the typically identified “risk factors” have a multi-level structural organization that can be unveiled using an analytic procedure that includes a front-end information extraction procedure. To exemplify the different types of variables identified by this and the more commonly used analytic procedure, the data for the present study were reanalyzed using the usual 2-step procedure of univariate between-group comparisons followed by a multivariate DA operating on those variables identified as being statistically significant. The results for the univariate analysis are reported in Table 2 as the significance level for each item and pairwise comparison calculated using the Mann–Whitney *U* test. A total of 8 items were significantly different between the Control vs. COME groups and between the Control vs. RAOM groups at an assigned, uncorrected Type I error of 0.05. Notably, the membership for the two “significance” sets was not identical. At that Type I error, no item achieved significance for the RAOM vs. COME comparison, but Snoring was significant at a Type I error of 0.10. The Discriminant functions for those comparisons in sequence included 3 items, Itchy Nose, Runny Nose and Reflux for the first, 3 items Watery Runny Nose, Belly Ache and Colds for the second, and at a 0.10 retention level, Snoring for the third. The assignment accuracies of those functions were comparable to those of the functions developed in this report, and specifically, 74% vs. 76%, 72% vs. 68% and 58% vs. 61%, respectively. Note that, for all comparisons, the item(s) identified as significant by the DA for the usual analysis are single members, exemplars, of the set of items identified in our analysis and labeled as a unique comorbidity. This demonstrates that the more commonly used analytic method is not sensitive to a hierarchical variable structure, and does not identify “true” risk factors as, for example a comorbid condition, but rather

identifies one representative for each class of related items that define a risk factor, as for example a specific symptom/sign.

Because the usual analysis identifies class exemplars as modifiers, the selected exemplar for each risk factor will depend upon the specific mix of variables included in the screen and the covariance matrix for that mix. Consequently, aggregate, combinational analytic procedures such as meta-analysis or summary reviews using those data are flawed as they operate on surrogate representatives of the true risk factors that can vary from study to study [17,31]. Also, the results for cross-population studies that use those methods are difficult to interpret because the covariance matrix, even for the same variable mix, is expected to be socioculturally variable [32].

5. Conclusion

The present study outlined a methodology to extract non-redundant information potentially relevant to group discrimination from a set of variables that include subsets of mutually correlated variables. When applied to data for the symptom/sign expressions of hypothesized OM comorbidities, the extracted information packets, or factors, corresponded to previously identified OM comorbidities. Different mixtures of factors predicted group assignment for the different pairwise comparisons, suggesting different pathogenic pathways to the expression of RAOM and COME. Extension of this analytic methodology to broader and more inclusive data sets is possible, but requires careful planning with respect to sample size and order of operations.

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References

1. Bluestone, CD.; Klein, JO. Otitis Media in Infants and Children. 5th. B.C. Decker, Inc.; Ontario: 2007.
2. Winther B, Alper CM, Mandel EM, Doyle WJ, Hendley JO. Temporal relationships between colds, upper respiratory viruses detected by polymerase chain reaction, and otitis media in young children followed through a typical cold season. *Pediatrics*. Jun; 2007 119(6):1069–1075. [PubMed: 17545372]
3. Winther B, Doyle WJ, Alper CM. A high prevalence of new onset otitis media during parent diagnosed common colds. *Int J Pediatr Otorhinolaryngol*. Oct; 2006 70(10):1725–1730. [PubMed: 16814403]
4. Mandel EM, Doyle WJ, Winther B, Alper CM. The incidence, prevalence and burden of OM in unselected children aged 1–8 years followed by weekly otoscopy through the “common cold” season. *Int J Pediatr Otorhinolaryngol*. Apr; 2008 72(4):491–499. [PubMed: 18272237]
5. Doyle WJ, Alper CM. Prevention of otitis media caused by viral upper respiratory tract infection: vaccines, antivirals, and other approaches. *Curr Allergy Asthma Rep*. Jul; 2003 3(4):326–334. [PubMed: 12791210]
6. Monasta L, Ronfani L, Marchetti F, Montico M, Vecchi Brumatti L, Bavcar A, et al. Burden of disease caused by otitis media: systematic review and global estimates. *PLoS ONE*. 2012; 7(4):e36226. [PubMed: 22558393]

7. Hoffman HJ, Daly KA, Bainbridge KE, Casselbrant ML, Homøe P, Kvestad E, et al. Panel 1: Epidemiology, natural history, and risk factors. *Otolaryngol Head Neck Surg.* Apr; 2013 148(4 Suppl):E1–E25. [PubMed: 23536527]
8. Casselbrant ML, Mandel EM, Fall PA, Rockette HE, Kurs-Lasky M, Bluestone CD, et al. The heritability of otitis media: a twin and triplet study. *JAMA.* Dec; 1999 282(22):2125–2130. [PubMed: 10591333]
9. Rovers M, Haggard M, Gannon M, Koeppen-Schomerus G, Plomin R. Heritability of symptom domains in otitis media: a longitudinal study of 1373 twin pairs. *Am J Epidemiol.* May; 2002 155(10):958–964. [PubMed: 11994236]
10. Pukander J, Luotonen J, Timonen M, Karma P. Risk factors affecting the occurrence of acute otitis media among 2–3-year-old urban children. *Acta Otolaryngol.* Sep-Oct;1985 100(3–4):260–265. [PubMed: 4061076]
11. Fleming DW, Cochi SL, Hightower AW, Broome CV. Childhood upper respiratory tract infections: to what degree is incidence affected by day-care attendance? *Pediatrics.* Jan; 1987 79(1):55–60. [PubMed: 3797171]
12. Engel J, Anteunis L, Volovics A, Hendriks J, Marres E. Risk factors of otitis media with effusion during infancy. *Int J Pediatr Otorhinolaryngol.* May; 1999 48(3):239–249. [PubMed: 10402121]
13. Kraemer MJ, Richardson MA, Weiss NS, Furukawa CT, Shapiro GG, Pierson WE, et al. Risk factors for persistent middle-ear effusions. Otitis media, catarrh, cigarette smoke exposure, and atopy. *JAMA.* Feb; 1983 249(8):1022–1025. [PubMed: 6681641]
14. Rovers MM, Hofstad EA, Franken-van den Brand KI, Straatman H, Ingels K, van der Wilt GJ, et al. Prognostic factors for otitis media with effusion in infants. *Clin Otolaryngol Allied Sci.* Dec; 1998 23(6):543–546. [PubMed: 9884810]
15. Lubianca Neto JF, Hemb L, Silva DB. Systematic literature review of modifiable risk factors for recurrent acute otitis media in childhood. *J Pediatr (Rio J).* Mar-Apr;2006 82(2):87–96. [PubMed: 16614761]
16. Kotsis GP, Nikolopoulos TP, Yiotakis IE, Papacharalampous GX, Kandiloros DC. Recurrent acute otitis media and gastroesophageal reflux disease in children. Is there an association? *Int J Pediatr Otorhinolaryngol.* Oct; 2009 73(10):1373–1380. [PubMed: 19643505]
17. Zhang Y, Xu M, Zhang J, Zeng L, Wang Y, Zheng QY. Risk factors for chronic and recurrent otitis media—a meta-analysis. *PLOS ONE.* 2014; 9(1):e86397. [PubMed: 24466073]
18. Owen MJ, Baldwin CD, Swank PR, Pannu AK, Johnson DL, Howie VM. Relation of infant feeding practices, cigarette smoke exposure, and group child care to the onset and duration of otitis media with effusion in the first two years of life. *J Pediatr.* Nov; 1993 123(5):702–711. [PubMed: 8229477]
19. Homøe P, Christensen RB, Bretlau P. Acute otitis media and sociomedical risk factors among unselected children in Greenland. *Int J Pediatr Otorhinolaryngol.* Jun; 1999 49(1):37–52. [PubMed: 10428404]
20. Lasisi AO, Olaniyan FA, Muibi SA, Azeez IA, Abdulwasiiu KG, Lasisi TJ, et al. Clinical and demographic risk factors associated with chronic suppurative otitis media. *Int J Pediatr Otorhinolaryngol.* Oct; 2007 71(10):1549–1554. [PubMed: 17643499]
21. Lasisi AO, Olayemi O, Irabor AE. Early onset otitis media: risk factors and effects on the outcome of chronic suppurative otitis media. *Eur Arch Otorhinolaryngol.* Jul; 2008 265(7):765–768. [PubMed: 18046567]
22. Paradise JL, Rockette HE, Colborn DK, Bernard BS, Smith CG, Kurs-Lasky M, et al. Otitis media in 2253 Pittsburgh-area infants: prevalence and risk factors during the first two years of life. *Pediatrics.* Mar; 1997 99(3):318–333. [PubMed: 9041282]
23. Jero J, Kentala E, Karma P. Factors associated with the development of recurrent acute otitis media—the significance of choosing the right and accurate dependent and independent variables in the multivariate analysis. *Acta Otolaryngol Suppl.* 2000; 543:67–69. [PubMed: 10908981]
24. Swarts JD, Casselbrant ML, Teixeira MS, Mandel EM, Richert BC, Banks JM, et al. Eustachian tube function in young children without a history of otitis media evaluated using a pressure chamber protocol. *Acta Otolaryngol.* Jun; 2014 134(6):579–587. [PubMed: 24828350]

25. Mandel EM, Swarts JD, Casselbrant ML, Tekely KK, Richert BC, Seroky JT, et al. Eustachian tube function as a predictor of the recurrence of middle ear effusion in children. *Laryngoscope*. Sep; 2013 123(9):2285–2290. [PubMed: 23575552]
26. Casselbrant ML, Swarts JD, Mandel EM, Doyle WJ. The Cephalic Index is not different among groups of children aged 36–48 months with chronic otitis media with effusion, recurrent acute otitis media and controls. *Int J Pediatr Otorhinolaryngol*. Mar; 2013 77(3):334–337. [PubMed: 23280277]
27. Velepici M, Rozmanic V, Bonifacic M. Gastroesophageal reflux, allergy and chronic tubotympanic disorders in children. *Int J Pediatr Otorhinolaryngol*. Oct; 2000 55(3):187–190. [PubMed: 11035175]
28. Bernstein JM. The role of IgE-mediated hypersensitivity in the development of otitis media with effusion. *Otolaryngol Clin N Am*. Feb; 1992 25(1):197–211.
29. Bernstein JM, Lee J, Conboy K, Ellis E, Li P. Further observations on the role of IgE-mediated hypersensitivity in recurrent otitis media with effusion. *Otolaryngol Head Neck Surg*. Oct; 1985 93(5):611–615. [PubMed: 3932928]
30. Miura MS, Mascaro M, Rosenfeld RM. Association between otitis media and gastroesophageal reflux: a systematic review. *Otolaryngol Head Neck Surg*. Mar; 2012 146(3):345–352. [PubMed: 22157391]
31. Uhari M, Mantysaari K, Niemela M. A meta-analytic review of the risk factors for acute otitis media. *Clin Infect Dis*. Jun; 1996 22(6):1079–1083. [PubMed: 8783714]
32. Rovers MM, de Kok IM, Schilder AG. Risk factors for otitis media: an international perspective. *Int J Pediatr Otorhinolaryngol*. Jul; 2006 70(7):1251–1256. [PubMed: 16481051]

Table 1

Sex, race and age distribution of children by group, number (%).

Variable		Group		
		Control	COME	RAOM
Total	Number	45	45	51
Sex	Males	23 (51)	24 (53)	26 (51)
Race	Black	12 (27)	8 (18)	8 (16)
	White	27 (60)	33 (73)	37 (73)
	Other	6 (13)	4 (9)	6 (12)
Age (yrs)	Average	3.52	3.53	3.4
	Standard deviation	0.34	0.33	0.31

Table 2

Percent distribution of children with positive histories for the 17 items by group and the pairwise between-group *P*-values calculated using the Mann-Whitney *U* test.

Variable	Control	COME	RAOM	CvsO ^a	CvsR	OvsR
Runny nose	10.9	37.8	35.3	<0.01	<0.01	
Snoring	41.3	62.2	45.1	0.04		0.09
Mouth breathing	32.6	55.6	43.1	0.02		
Sinusitis	15.2	26.7	27.5			
Frequent colds	17.4	42.2	45.1	<0.01	<0.01	
Sneezing	10.9	20.0	17.6			
Itchy nose	8.7	22.2	17.6	0.04		
Watery runny nose	6.5	17.8	25.5	0.05	<0.01	
Seasonal	10.9	22.2	25.5		0.03	
Asthma	17.4	20.0	23.5			
Night cough	10.9	15.6	21.6			
Hoarseness	4.3	4.4	9.8			
Burps	4.3	4.4	11.8			
Belly-ache	2.2	6.7	15.7		<0.01	
Food in throat	4.3	6.7	13.7		0.04	
Spit-up	6.5	28.9	17.6	<0.01	0.04	
Reflux	6.5	28.9	19.6	<0.01	0.03	

^aPairwise *P*-values for the comparisons between the Control and COME groups (CvsO), the Control and RAOM groups (CvsR) and the COME vs. RAOM groups (OvsR).

Table 3

Factor structure for the 17 items.

Factors	Name	Variables loading on the factor				
		Variable 1	Variable 2	Variable 3	Variable 4	Variable 5
Factor 1	GER (general)	Night cough	Hoarseness	Burps	Belly-ache	Food in throat
Factor 2	Nasal allergy	Sneezing	Itchy nose	Watery runny nose	Seasonal	
Factor 3	Frequent vURI	Sinusitis	Runny nose	Frequent colds		
Factor 4	GER (specific)	Spit-up	Reflux			
Factor 5	Nasal obstruction	Snoring	Mouth breathing			
Factor 6	Asthma	Asthma				

Table 4

Significant factors with *P*-values included in the three discriminant functions that assign children to pairwise groups and the sensitivity, specificity and accuracy of those assignments.

Factors	Name	Control vs. COME	Control vs. RAOM	RAOM vs. COME
1	GER (general)		0.025	
2	Nasal allergy	0.005		
3	vURI	0.009	0.048	
4	GER (specific)	0.001		0.039
5	Nasal obstruction			0.055
Sensitivity		0.84	0.82	0.67
Specificity		0.64	0.55	0.44
Accuracy		74%	68%	61%