Influence of Allergy, Asthma Treatment(AT) and Eviction Diet(ED) on Sleep-Disordered Breathing(SDB) in Pediatric Asthma Associated With Osa, Increased Respiratory Effort(RE) During Sleep and Overweight/Obesity: a Study in 78 Children

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Abstract

Pathophysiological mechanisms and allergies in Obstructive Sleep Apnoea-asthma associated are unclear. Apnoea hypopnea Index alone does not seem sufficient to correctly guide for adequate treatment without identification of the specific profile of each patient. Children suffering from allergies and SDB-asthma association are treated with the same recommendations as those suffering from the obstructive type of Obstructive Sleep Apnoea. Obstructive Sleep Apnoea correlates with obesity; however, links between obesity, allergy, and Obstructive Sleep Apnoea remain unexplored. Obesity is considered a risk factor for OSA; however, children with Obstructive Sleep Apnoea increase their Body Mass Index despite being treated adequately for OSA and following adequate weight interventions. Asthma is considered to favor Obstructive Sleep Apnoea; however, it is not explored whether allergies pre-exist and favor Obstructive Sleep Apnoea. Parents often ask questions about the efficacy of adenotonsillectomy/anti-leukotriene treatments/PPC, which are difficult to answer.

We aimed to study the Respiratory Polygraphy/Polysomnography profile of children suffering Obstructive Sleep

Apnoea-asthma associated and the influence of allergies and Asthma Treatment/Eviction Diet upon Apnoea Hypopnea Index/Respiratory Effort/Body Mass Index to diagnose, treat and prevent pediatric Obstructive Sleep Apnoea-asthma associated and related obesity early and accurately.

We effectuated a cross-sectional/case controls diagnostic cohort. We used Receiver Operating Characteristic curves, General Linear Models, regression, and path analysis to evaluate the effect of treatments and allergies on Apnoea Hypopnea Index, Respiratory Effort, Body Mass Index and Polygraphy/Polysomnography parameters such as Respiratory Distress Index, Sleep Fragmentation, Sleep Fragmentation Ventilatory Origin, Oxygen Desaturation Index.

We identified that asthma treatment and specific allergen eviction, along with the co-existence of non-IgE-mediated and respiratory allergies, influence the Apnoea Hypopnea Index, Respiratory Effort during sleep and the Body Mass Index.

Increased Respiratory effort during sleep inherently correlates with SDB/OSA related to allergies, especially the coexistence of RANIgE, and is the origin of the sleep fragmentation in children suffering from OSA-asthma association, even if AHI remains at low levels. It decreases (as AHI) with AT or ED and, if untreated, contributes to AHI increase, thus favoring the persistence of OSA and its comorbidities (hyperactivity, decrease in school performance, behavior/concentration problems), asthma, and obesity.

Consideration of asthma treatment, allergies, and allergen eviction upon interpretation of polygraphy/polysomnography parameters could ameliorate the diagnosis and treatment of Obstructive Sleep Apnoea-asthma associated and possibly avoid, upon their origin, asthma, and obesity.

Keywords: Allergy, Asthma treatment, Eviction diet, Sleep-disordered breathing, Obstructive sleep apnoea, Apnoea hypopnea index, Respiratory polygraphy, Polysomnography, Respiratory effort during sleep, Obesity.

Visual Summary
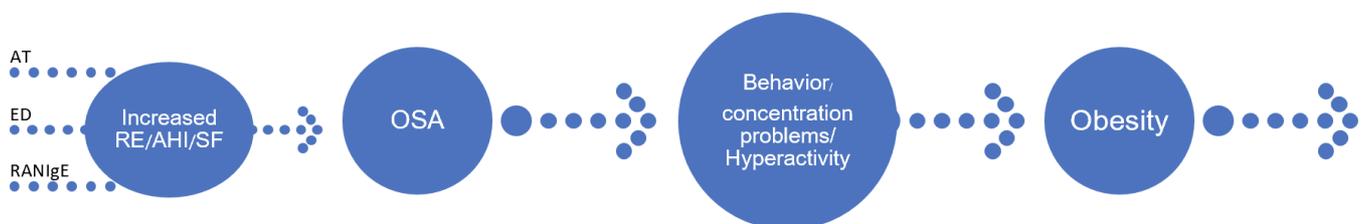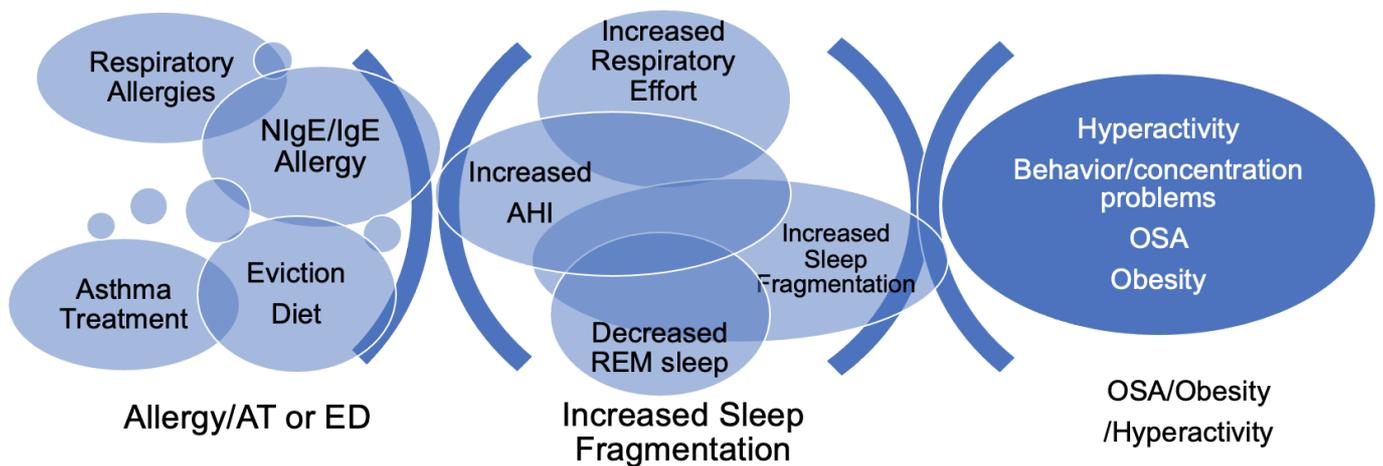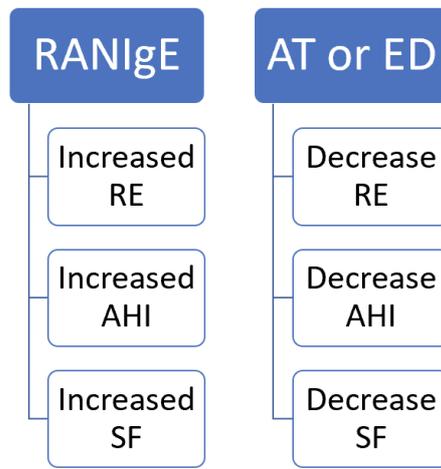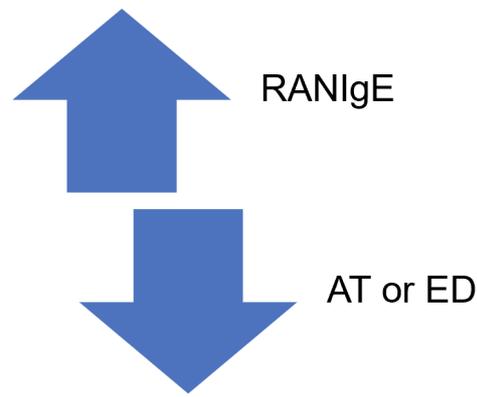
Highlights

1. What is already known about this topic?

- A significant number of children suffering from OSA do not ameliorate with current treatments.

- AHI cannot sufficiently identify OSA and distinguish obstructive and non-obstructive OSA/SDB

- Many children with OSA continue to increase their BMI under CPAP

2. What does this article add to our knowledge?

- Allergic children suffer a significant SF non-explained by associated respiratory events.
- RE during sleep increases in allergic children.
- SF/increased RE contribute to BMI increase.
- Allergy uses sleep disorders/RE increase as mediators for its consequences (asthma/obesity).

3. How does this study impact current management guidelines?

- SF should alert even if AHI is in low values.
- Increased RE should alert for allergy/asthma.
- Allergy diagnosis/treatment in preschool children should be a priority in public health policies to avoid sleep disorders, asthma, and obesity.

Abbreviations

List of Medical Abbreviations used in the article:

(*Scientific Style and Format* by the Council of Science Editors or the AMA's *Manual of Style)*

- **M:** male
- **F:** female
- **BMI:** Body Mass Index,
- **Wt:** Weight
- **Jan:** January
- **Aug:** august
- **Hyper:** in excess
- **Approx:** approximately
- **FH:** Family history
- **Ped:** pediatric
- **GP:** General practitioner
- **ENT:** otorhinolaryngologist
- **Obst:** obstruction
- **OSA:** Obstructive Sleep Apnoea
- **assoc.:** associated
- **SDB:** Sleep Disordered Breathing,
- **ex; exer:** exercise
- **Diag:** diagnosis
- **Exam:** examine; examination
- **Tx:** treatment
- **CBC:** Complete blood count,
- **SPT:** Skin Prick Tests
- **d1:** dermatophagoides pteronyssinus
- **d2:** dermatophagoides farina
- **sIgE:** specific IgE determinations
- **PT:** Patch Tests
- **SLIT:** Sublingual Immunotherapy
- **PG:** Respiratory Polygraphy
- **PSG:** Polysomnography
- **CPAP:** Continuous positive airway pressure
- **T&A:** Tonsillectomy and adenotonsillectomy
- **AHI:** Apnoea Hypopnea Index **ODI:** Oxygen Desaturation

AHI: Apnoea Hypopnea Index **ODI:** Oxygen Desaturation Index

- **RDI**: Respiratory Distress Index
- **SF**: Sleep Fragmentation
- **SFVO:** Sleep Fragmentation Ventilatory Origin
- **TST**: Total Sleep Time (min)
- **Min:** minimum
- **Max:** maximum
- *M:* Mean
- *SD:* Standard Deviation
- *SE:* Standard Error
- *p:* probability value
- *x^2:* Chi-square value
- **ANOVA:** Analysis of variance
- **CC:** Contingency Coefficient
- **Risk:** Risk Estimate
- **MH OR:** Mantel-Haenszel Odds Ratio Estimate
- **N**: Number of Patients/children
- **NN:** Number Needed
- **NNT:** Number Needed To Treat
- **NNH:** Number Needed to be exposed to Harm
- **ROC curve:** Receiver Operating Characteristic Curve
- **UGLM:** Univariate General Linear Model
- **β:** Beta regression coefficients
- **B:** Beta weight of the constant
- **R^2**: R-squared
- **adjusted R^2:** adjusted R-squared
- **VIF:** Variance Inflation Factor
- *SPSS:* Statistical package for the Social Sciences
- **AMOS:** Analysis of a Moment Structure
- **IV:** Indirect Variable
- **DV:** Dependent Variable
- **MV:** mediating variable
- **AIC:** Akaike's Information Criterion
- **BIC:** Bayesian Information Criterion
- **RMSEA:** root mean square error of approximation
- **SRMR:** standardized root mean squared residual
- **CFI:** comparative fit index
- **FMIN:** Index of Model Fit
- **NFI:** Normed Fit Index
- **IFI:** Incremental Fit Index
- **CMIN:** Chi-square
- **df:** degrees of freedom
- *p***CLOSE:** *p* of Close Fit
- **c.r**.: critical ration

Supplementary Abbreviations used in the article:

A: Allergy/Allergies, **AT:** Asthma treatment, **ED:** Eviction diet, **AE:** Allergen eviction, **ATAE:** Asthma treatment or allergen eviction, **AT or ED:** Asthma treatment or eviction diet, **ATED:** Asthma treatment or eviction diet, **OSA-asthma assoc.:** Obstructive Sleep Apnoea-asthma associated, **pedOSA-asthma:** pediatric Obstructive Sleep Apnoea-asthma associated, **RE:** Respiratory effort during sleep,**TS:** Total Analysis Time (min), **RA:** Respiratory allergies, **MA:** Dust mites' allergies, **AA**: Alternaria Alternata,**RANIgE:** Co-existence of Respiratory and non-IgE mediated allergies,**MANIgE:** Co-existence of dust mites' allergies and non-IgE mediated allergies**, FA:** Food Allergy, **IgEFA:** IgE-mediated Food Allergy,**NIgEFA:** non-IgE-mediated Food Allergy,**RANIGE.ATAE subgroups:** subgroups according to the presence of RANIgE and initiation of AT or ED, **RANIgENoATED:** Group with RANIgE and No AT or ED,**NoRANIgE.ATED:** Group negative for RANIGE and under asthma treatment or Eviction Diet, **obesity/overw VsHW:** obesity and overweight versus healthy weight,*HWoverw/ Vsobesity:* healthy weight and overweight versus obesity**, Group:** G, **TRUST IT ALL STUDY:** Treatment of pediatric Sleep-disordered breathing associated with Allergies and obesity STUDY.

Introduction

The prospective, observational, and diagnostic nature of our study helped to reach useful conclusions, as we correlated the polygraphy (PG)/polysomnography (PSG) parameters and the clinical/allergology profile. The study responded to the needs of the patients who came for expert allergology advice due to unresolved Sleep Disordered Breathing (SDB)/OSA. Thus, it helped to identify the real burden of pediatric Obstructive Sleep Apnoea (OSA)-asthma associated.

The exploration was effectuated in primary care centres, and no exam was effectuated apart from those necessary for each child. Therefore, we overcame bias related to a) the selection of severe patients if the study had been effectuated in a tertiary hospital following-up patients with severe asthma, b) social class, and c) non-necessary exams/treatment.

In OSA-asthma assoc., asthma nocturnal symptoms may relate to sleep fragmentation(SF).[1] SF disrupts nocturnal hormonal secretion.[2] Stress and secretion of hormones increase appetite.[3] Sleep deprivation links to obesity[4]. Sleep deprivation alters the metabolic rate and increases hunger[5], leading weight maintenance or weight loss interventions to fail[2][6].

The significant sleep splitting and the increase in Respiratory Effort(RE) decrease REM sleep, the mentally restorative sleep.[7] The REM sleep decrease correlates to obesity[8], as it may alter the energy balance, increasing food intake and decreasing energy use[9]. Th1 inflammation is incriminated in obesity[10].

Obese children with normal spirometry (case 4, Onl.Rep.) and negative SPT do not follow AT; they do not have Th2 asthma. The term "allergic rhinitis «cannot explain the obstruction induced by allergic inflammation only through AHI; apnoea in obstructive OSA is mainly retrolingual[11].

Adequate treatment, favoring factors and ped-OSA-asthma-allergy(A)-obesity subgroups are not well identified.

We distinguished that: a) the adequate treatment differs in SDB/OSA-asthma/allergy-associated and in obstructive OSA[12][13][14] b) the obesity could be a consequence of an inadequately treated OSA-allergy associated[15] c) the RE could help to the correct identification of the OSA subgroup and the evolution to obesity[16][17][18] d) the evaluation of concurrent treatments [Asthma Treatment(AT) or Eviction Diet(ED)] and supplementary PG parameters, as RE and SF could help to the correct interpretation of PG/PSG.[15][17][19]

Evaluation of the main allergies leading to mild/severe pedOSA-asthma along with the effect of treatments on Apnoea Hypopnea Index (AHI)/RE/Body Mass Index (BMI) could give useful and easily applicable guidelines for paediatricians and GPs. We aimed to identify the PG/PSG profile of the allergic children suffering from OSA-asthma along with the effect of treatments and concomitant allergies on AHI/RE/BMI, which could help explore the pathophysiology of pedOSA-asthma.

Methods

We effectuated a cross-sectional/case-control diagnostic cohort study (TRUST IT ALL STUDY) to evaluate the origin of SDB/OSA and the effect of AT/ED on PG/PSG parameters in 2-16-year-old children(N) who proceeded for allergology

advice & concomitant SDB mostly spontaneously (initiative of parents) either addressed by GPs/specialists (ENT, dentists). Recruitment in a consecutive way: Jan 2018-Aug 2019 in 2 primary care centres & one outpatient clinic.

The patients decided if they would have more appointments after the initial exploration and advice. As the classification was upon recruitment, loss of follow-up was not a problem. A non-opposition contentment was obtained from the parents. N° IORG-IRB: IORG0009085. N° IRB: COS-RGDS-2018-06-030.

The sample was collected in a consecutive manner in primary care centers accepting children from the broader area around Paris and from nearby towns; therefore, it included children positive for SDB-asthma/allergy association, representative of the population which incorporates children from various ethnicities and various continents.

As the study was conducted in primary care allergology centers, we avoided the bias of including severe asthma patients already diagnosed and followed up in tertiary centers. Moreover, in this way, we explored the question of whether allergy accompanied SDB from its origin and favored its evolution before severe asthma was established.

We used a questionnaire (eSupplement) for clinical signs, domestic exposures, personal/FH, and demographic data. Percentages were calculated based on a) the number of parents who answered the specific questions, b) non-answered questions (usually non-bothersome); [missing in Onl.Rep] b) supplementary recorded clinical signs not included in the questionnaire; [missing corresponded to those who did not record these supplementary signs].

Therefore, the children were characterized as being positive for the disease (SDB) as they all had recurrent/chronic clinical signs, including snoring (98.4%), further verified through a detailed history/questionnaire. They were seen in allergology primary care centers as they suffered from allergic signs (Onl.Suppl.). Therefore, they were considered allergic patients suffering from SDB.

We can see that the patients reported asthma signs (90.4%) with an atopic profile [atopic profile (eczema, recurrent rhinitis/conjunctivitis, asthma)] (94.3%) (Onl.Suppl.) and 71% had confirmed allergies (RA/FA). Therefore, they were positive for atopic asthma. Thus, they could be considered positive for SDB-asthma/allergy association.

As we explored a population positive for atopic asthma/SDB in pediatrics, we explored the diagnostic sensitivity and specificity of PG as a screening test in a population positive for the disease, and not as a diagnostic study in the general population with no associated clinical signs of the disease[20]. Anyway, PG/PSG could only be recommended and conducted in patients already suffering from clinical signs of SDB to screen for OSA[20]. We would not conduct PG/PSG in children not already suffering from SDB clinical signs, as this would not have any clinical relevance for the patients.

However, current recommendations exist for children suffering from obstructive-type OSA (premature babies, congenital malformations). Children suffering from asthma/allergy seem to be a distinct population, and there are no existing separate recommendations for this population due to a lack of conclusive studies in this specific type of population. Therefore, existing recommendations for obstructive OSA are also applied to asthmatic/allergic children suffering from OSA, with inconsistent efficacy. Therefore, we tried to focus on the needs of this population by conducting a cohort study to clarify the PG/PSG and clinical characteristics of this specific population. Our study would help provide personalized

treatment/recommendations to this specific population.

We only conducted PG/PSG in children suffering from SDB/OSA whose problems had not been addressed by other specialists already consulted according to current recommendations.

We based our study on the requirements for the minimal sample size for sensitivity and specificity analysis[20]. As we would only explore children suffering from SDB coexistent with allergy/asthma signs, we based our evaluation of the sample size on positive disease. We set a 95% Confidence Interval, with a 5% margin of error and 0.8 the power of the analysis.

For a prevalence of 50%, the minimum sample size for sensitivity and specificity was 20, for a prevalence of 70%, the minimum sample size for sensitivity was 20, and for specificity, it was 4720. Therefore, the minimum sample size for positive disease was estimated to be 20N[20]. We confirmed the initially evaluated sample size at the end of the study, once we confirmed the prevalence of asthma signs, allergies, and snoring signs. We verified that the estimated prevalence of the positive disease corresponded to the initially calculated[20].

Likewise, we initially estimated a sample size of 50N to reach conclusions. We used the rule of thumb (5-10N per parameter estimated; we had 5 main parameters estimated). We included 78N, as we were confronted with a real need from the patients, and we did not intend to leave out eligible children from the study (to avoid bias in the selection of patients).

We performed at home: a) cidelec LX with the tracheal sound sensor: 24N, b) somnolter with the captor Jawac, which records mandibular movements, RE/SF: 50N, c) PSG (reference) (cidelec LXe), on consecutive days, if PG was inconclusive: 3N.

In the reports of PG with somnolter and Cidelec, AHI in the supine and non-supine position was recorded and differentiated. We verified that there was no significant difference recorded in the AHI in the supine and non-supine positions, meaning that the patient avoided sleeping in the supine position. Moreover, we advised the parents to verify the sleep position of their children and favor the non-supine position if this was not already respected, especially in adolescents and obese children[21].

Clinical information and reference standard results (normal: AHI ≤ 1/hrTST, 1 < AHI ≤ 5: mild OSA, 5 < AHI ≤ 10: moderate OSA, AHI > 10/hrTST: severe OSA[22]) were available to the performers/readers of PG/PSG. We followed guidelines about AHI,[22] OSA diagnosis/treatment.[23]

We recorded: 1) AT, 2) ED, 3) spirometry in asthma suspicion, and post-effort if exercise-induced asthma signs, 4) clinical signs, 5) ENT exam/T&A, 6) CBC, 7) Skin Prick Tests (SPT) & Specific IgE determinations (sIgE) for common aeroallergens/ IgE mediated Food Allergies (IgEFA) if clinical signs, 8) Patch Tests (PT) to milk/wheat +/- soja/other allergens if Non-IgE mediated FA (NIgEFA) signs (gastroesophageal Reflux/diarrhoea/constipation/abdominal pain/eczema) +/- ED. PT read according to International Contact Dermatitis Research Group criteria (ICDRG).[24][25] NIgEFA diagnosed if positive PT and clinical amelioration after a 2-month ED.

40N followed-up for >2 months: a) 3N for >6 months, b) 19N for 1-2 years, c) 18N up to now (Aug 2023) (4-5,5 years). Through e-mail/telephone, we understood that the children who did not follow up a) ameliorated and did not need a follow-up. & b) their parents were reluctant to treat their children's allergies. One moved to Dubai and proceeded to report it.

We used the rule of thumb to evaluate the N according to the variables examined: (5-10N for each of the principal variables examined: ATED, RANIgE, AHI, RE, BMI, obesity/overweight), revealed by the initial statistical analysis (correlations, exploratory factor analysis, principal component analysis, regression analysis). The supplementary variables (RDI, ODI, SF, SFVO) were not applied in all subsequent statistical studies.

To evaluate the influence of AT/ED and allergies on AHI/RE, we grouped AT+ED (ATED) and Respiratory allergies (RA)+NIgE (RANIgE).

The variables examined:

1. AHI, Oxygen Desaturation Index (ODI) [PSG/PG (Cidelec/Somnolter)]
2. RE, SF, Sleep Fragmentation Ventilatory Origin (SFVO), Respiratory Distress Index(RDI) (only somnolter)
3. microarousals, intra-sleep arousals >30 sec (only PSG)
4. AT, ED, ATED
5. A, RA, MA, RANIgE, MANIgE
6. a combined (dummy) variable (ATED.RANIgE) for both AT/ED & RANIgE.
7. BMI, obesity
8. two dichotomous variables (BMI adjusted for age/sex):

    1. "obesity group" **(obesity/overw Vs HW)**:

        Group(G) 0: Healthy weight (HW) (BMI 5th-85th percentile)

        G1: overweight(overw) (BMI >85th - <95th percentile) +obese (BMI>/=95th percentile).
    2. "obesity versus non-obesity" *(HWoverw/ Vs obesity)*:

        G0: HW (BMI 5th-85th percentile) +overweight (BMI >85th - <95th percentile)

        G1: obesity (BMI>/=95th percentile).

RE/AHI categorized to: RE>20%, RE>28%, AHI>6,8n/h, upon mean/median values, to evaluate max effect of ATED/RANIgE on RE/AHI.

Outcomes: obesity, obesity/overweight, AHI, RE, AHI>6,8, RE>20, RE>28

Exposures: AT, ED, ATED, A, NIgE, RA, RANIgE, obesity, obesity/overweight

Potential confounders /Effect modifiers: ATED, RANIgE, RE, obesity, obesity/overweight (when the one among them was measured and adjusted to the other one).

SPSS evaluated: a) percentages, mean and median values, correlations, t-test, effect sizes [*Eta, Eta-squared, Epsilon-squared, Omega-squared, Cohen's d, Hedge's correction, Glass's delta)*], **ANOVA,** crosstabs tabulations (Table 2), Risk

estimate, NNT, NNH, ROC curves, regression analysis, Univariate General Linear Model (UGLM), Poisson regression, binary logistic regression, exact *Sig.* 2-sided, b) Profile Plots to reveal interactions.

We measured mean and median values, and we verified that the median did not differ substantially from the mean. We used median values for variables with skewed distribution, such as the BMI, as it isn't influenced by extremely large values. We explored correlations, and we found a strong correlation in between BMI and AHI, a moderate to strong correlation in between BMI and RE, and only a moderate correlation in between AHI and RE. Therefore, AHI and RE correlated to BMI to a stronger degree than in between them. We effectuated an exploratory factor analysis, and we evaluated the main variables that would be crucial for our study.

We then evaluated our findings with various statistical analysis (t-test, Crosstabs, ROC curves, regression and poisson analysis, GLM) and we verified that all types of statistical analysis gave us results with the same clinical relevance. To avoid type I error, we effectuated the Bonferroni correction (conservative test, used when the number of comparisons is small, and less prone to Type I mistakes) and the LSD (Least significant difference) (small number of comparisons applied) to apply correction for the number of comparisons performed (where applicated). We also reported adjusted R square as it was adjusted for the number of predictors in the model.

We created dichotomous variables to minimize the multiple comparisons of the groups needed. This helped us to minimize the number of possibly incorrectly rejected null hypothesis through focusing on the core of the questions that needed to be answered. We visualized our findings with box plots and profile marginal plots to explore interactions and confounders.

Moreover, we reached to evaluate effect sizes, which are the adequate way to evaluate quantitative variables.

A path analysis with AMOS 28 tested the model **(Fig.20)**. For the bootstrapping, no missing values to calculate 2-tailed *p* values in the indirect effects, so only 32N included. The model was recursive and overidentified. The data were screened and examined for assumptions of path analysis. There were two multivariate outliers detected, which remained in the study. The assumptions of linearity and homoscedasticity by residual plots suggested that all the assumptions were approximately tenable.

To evaluate that the statistical significance and the associated effect sizes in our findings had a clinical relevance, we evaluated if these were observed in our patients[26]. Therefore, we effectuated a verification in the patients once we had results from our statistical analysis. We evaluated that the statistically significant measured differences in the polygraphy parameters as supported by the measurements of effect sizes were observed in our patients. This gave an internal validation for our study to go on. Therefore, we verified that received information about asthma treatments and allergies helped to interpret more accurately the PG parameters. We also verified that keeping levels of RE lower also helped to keep lower the levels of the BMI.

Results

We explored 78 children. We excluded: a)1 child for no compliance, b) Two siblings (the second one from two brother-

pairs) to respect the rule of independence of the sample, c) One 2-year-old girl due to very severe obstructive OSA and her initial follow-up in a tertiary centre[13]. Seventy-four children were included in the study.

We identified two cases of OSA-obstructive type, which illustrate the importance of the distinction between OSA-obstructive type and non-obstructive/allergic OSA.[13][14]

Percentages

1. Sex: girls (F): 33.8%, boys (M): 66.2%. Age: (M: 6.28 years, SD = 3.18).
2. Addressed by a) parents: 74,3%, b) ENT: 8,1%, c) GP: 14,9%, d) dentist: 1,4%.
3. BMI: a) normal weight: 54.1%, b) stagnation of growth: 8.1%, c) at risk of overweight: 16,2%, d) obese: 21,6%.
4. a) RA:57,1 % b) MA: 52,2 % c) RANIgE: 34% d) IgEFA & NIgEFA: 8,1%.

Characteristics of the study participants, along with exposures and potential confounders, are reported in the Onl.Rep.

Correlations

- 1) BMI/AHI, r (73) =.619, p <.001,
- 1) BMI/RE, r (50) =.457, p<.001,
- 3) AHI/RE, r (49) =.248, p.085,

t-test

Children upon PG who:

1. were under AT or ED experienced lower:

   1. (M) AHI than if they were not, t (70) = -3.079, p =.004 (Fig. 2a, 2b) effect size (d =.662).
   2. RE than if they were not, t (48) = 2,728, p =.009, effect size (d =.788) (Fig. 2a,2b, 4a, 4b).

2. did not suffer RANIgE experienced lower (M) RE than children who did, t (32) = 2.896, p =.002(Fig. 4a, 4b, 5a, 5b), effect size (d = 1.237).

   - The effect of combined treatments (ATED)/allergies(RANIgE) on AHI/RE was superior as compared to the separate effect of AT/ED and RA/NIgE.

ANOVA (Table 1)

1. AT or ED on AHI (Eta:.317 Eta squared:.107) (p.002) (F 7.793).
2. RANIgE on RE (Eta:.523, Eta squared:.274) (p.002) (F 11.694).

Crosstabs (Table 2)

- association obesity/overweight and RANIgE, X^2(1, N = 50) = 7.219, p =.012. (Somer's D.450).

- RANIgE effect upon RE>28%: (Eta.527, Somer's D.569).

NNT with AT or AE to a) AHI<6.8n/h: 4.9.

b. RE<22%: 3.

c. avoid the outcome (obesity/overweight): 3.8.

NNH: RANIGE to RE >20%: 2.2 (**Fig.5b**)

- RE >/=20 % to obese/overweight: 3.7.

- RANIGE to obese/overweight: 3,1.

ROC curves revealed a moderate accuracy

1. to predict obesity/overweight vS normal weight based upon:

    1. RE (AUC =0.769, p=.017)(Fig.6)
    2. AHI (AUC =0.768, p=.004)(Fig.7)
    3. RANIgE (AUC = 0.725, p =.029)(Fig.8.Tabl.3)

2. **based upon** RANIgE to predict

    1. BMI (AUC = 0.755, p =.003)(Fig.10)
    2. RE (AUC = 0.788, p =.007)(Fig.11).

Regression analysis [(UGLM) (Onl.Rep.), Poisson Regression analysis, Binary logistic regression analysis]

A UGLM investigated whether a combined variable for AT or AE and RANIgE predict RE. The overall model was statistically significant F (3, 32) = 12,442 p <.001. R^2=.563, Adjusted R^2=.518. AT or AE. RANIgE significantly independently predicted RE, F (3, 32) = 12,442 p <.001 (**Tables 17, 18.** *Onl.Rep*).

Post hoc comparisons (LSD) showed that the group RANIgENoATED had the highest RE, while NoRANIgE.ATED had the lowest RE [(**Table 19.** *Onl.Rep.*, **Fig.12**, **Fig. 16. Onl.Rep.**, **Fig. 17a and 17b (Onl.Rep)**].

Profile Plots revealed interactions between RE/RANIgE and AHI/AT or ED along with Healthy weight and overweight versus obesity: Fig. 12-15. Onl.Rep.

We used **a Poisson regression analysis** to predict BMI through AT or ED and RE.

The likelihood ratio X^2 test (5,982) indicated that the full model was a marginally significant improvement in fit over a null (no predictors) model (p.050) (**Table 23.** *Onl.Rep.*). Goodness of fit criteria: Deviance/df: 1.082, Log Likelihood: -30.063, BIC: 67.321, AIC: 69.555, CAIC: 70.321 (**Table 24.** *Onl.Rep.*).

RE statistically significantly predicted BMI (B=.009, S.E.=.0035, p.014) (**Table 25.** *Onl.Rep.*). ATED was not a significant

predictor of the BMI (B= -.074, S.E.=.2025, p.715).

A **binary logistic model of regression** through GLM ascertained the effects of RE and ATED on the likelihood that participants develop obesity/overwVsHW. *(Table 26.Onl.Rep.).* The overall model was statistically significant, Likelihood Ratio x^2 (2, N= 50) = 8.000, p=.018 (**Table 27.Onl.Rep.**). The predictor variable, RE, in the binary logistic analysis was found to contribute to the model. The unstandardized Beta weight (B) for the Constant; B= 4.002, SE=1.2468, Wald= 10.301, p.001. The unstandardized B for the predictor variable (RE): B = (-.053), SE=.0261, Wald=4.12, *p*.042. *The results of the binary regression GLM indicated that, all else being equal, subjects having lower RE had less odds of having the outcome "obesity" than subjects having increased RE (OR = 4,120; 95% CI: -.104 to -.002; p = 0.042)* (**Table 28.**Onl.Rep.). *Goodness of fit: BIC: 47.703, AIC: 41.967, CAIC: 50.703 (Table 29, Onl.Rep.).*

A UGLM investigated whether AT or ED and RANIgE predict BMI while controlling AHI and RE as covariates *(Tables 30, 31.Onl.Rep.).*

The overall model was statistically significant F (6, 23) = 6,336 p.001. R^2=.691, Adjusted R^2=.582. We saw that there is a significant interaction: a) in between AT or ED * RANIgE * AHI (**Table 32.Onl.Rep.)** and b) in between the absence of AT or ED and the co-existence of RANIgE to influence AHI [AT or ED= 0] * [RANIgE=1] * AHI(p.001) (**Table 33.Onl.Rep.**). The lines in the profile plot intersect, which indicates that there is an interaction between RANIgE, AT or ED and BMI while evaluating AHI and RE as covariates (**Fig.19**).

The profile plot of BMI according to both AT or ED and RANIgE visualised in Fig. 19, along with the rest of the profile plots already presented, helped us to create the path analysis that we present in the next part of our statistical analysis.

Path analysis with serial mediation

The Standardized (Fig.**21** and Tabl.**40)** and Unstandardized Estimates (**Fig. 22**, **Tabl.41)** are based on the conceptual model (**Fig. 20. Onl.Rep.).**

Assessment of normality showed that we did not have a strong violation of normality. Multivariate kurtosis: 6.946 and c.r.: 2.348 (**Tabl.34**). There were no multicollinearity problems (**Tabl.35, 36**).

Model Fit Summary

CMIN:.317, **DF:** 1, **p:**.574, **CFI:** 1.0, **RMSEA:**.000, **IFI:** 1.017, **NFI:**.992, **PCLOSE:**.588 (90% CI:.000 to.391), **AIC:** 38.317**.**

Bollen-Stine bootstrap showed that our model fits very well the data:

Testing the null hypothesis that the model is correct, Bollen-Stine bootstrap p =.718

Testing the Model

Path coefficients for direct effects are interpreted like regression coefficients in multiple regression (unstandardized and standardized). The regression weights (**Tabl.38)** and the parameter estimates for the direct effects (Table 40 and Fig.21) are reported below. The squared multiple correlations are shown in **Tabl.37** and the parameter estimates for indirect effects in **Table 41** and in **Fig. 22.**

<u>Moderators' and Mediation Effect</u>

Interpretation of Parameters

We found:

A. a) RANIgE total and direct effect on RE (*p*.002), b) RANIgE total effect on BMI (*p*.022). However, the RANIgE direct and indirect effects on BMI are not significant. We conclude that the significant total effect of RANIgE on BMI is mediated through the significant effect of RANIgE on RE.
B. AT or ED total and direct effect on a) RE (*p*.006) & b) on AHI (*p*.025).
C. the AT or ED total effect on BMI (*p*.021), but the AT or ED direct and indirect effect on BMI are not significant.

Like the RANIgE effect on BMI, the significant AT or ED total effect on BMI is mediated through the significant AT or ED effect on BMI.

Conclusion: We conclude that AT or AE and RANIgE act as moderators as their levels influence the levels of AHI and RE, which influence the BMI. Mediated moderation occurs as the effect of being exposed to RANIgE is greater for high-risk subjects (not being under AT or AE), and the interaction effect of RANIgE exposure and AT or AE may then affect a mediating variable of PG (AHI, RE) that then affects BMI[27][28].

Discussion

The significant sleep fragmentation (SF) in allergic children appeared from the very beginning of the evolution of the RA, related to micro-arousals non-explained by respiratory events, correlated to RE increase, REM decrease[12][29] and BMI increase[15] (cases 5 and 6. Onl.Rep.)[12][29].

PG/PSG under AT and ED diagnosed SF, whereas AHI were at low levels. The PG was inconclusive due to the children being under AT or ED. In our study, PGs/PSGs were effectuated in children free of febrile illness and asthma attacks. The increased RE/AHI could only be attributed to associated allergies/asthma, which could be the origin of subsequent asthma signs.

Our study distinguished that the term "allergic rhinitis" alone does not clearly represent allergies in preschool children. The term rhinitis usually describes viral infections, which provokes confusion in parents.

The measurement of the RE during sleep helped to evaluate the persistent ENT inflammation and induced obstruction,

which had a negative impact on children's neurodevelopment, and the optimum growth of upper airways.

Nearly half of the children in our study suffered from BMI disorders. They also suffered recurrent non-febrile illnesses (otitis, bronchitis, rhinitis), which accompanied SDB and contributed to constant stress, which promoted hypersecretion of cortisol and obesity. Thus, SF/SDB related to allergies promoted another inflammatory disease, obesity.[30][31][32]

The hypothesis that SF impairs the secretion of the growth hormone (GH) and leads to growth stagnation does not explain the facts that many of the allergic children: a) have a normal BMI despite suffering severe persistent SDB, b) become overweight/obese, which is compatible with the fact that sleep deprivation favours obesity[4].

Secretion of GH is impaired after severe sleep deprivation[33][34][35]. However, the lack of secretion of the GH during the night may be decompensated during the day[36], and its secretion is age-dependent[37].

SF leads to imbalances in sleep stages (, which could relate to GH decrease. In our cases(5 & 6. Onl.Rep.)[1][2][29], REM sleep decreased (12.1% - 11.5%).

Stress and low blood sugar levels/nutrition influence GH release, which regulates carbohydrate and lipid metabolism[38][39] Malnutrition increases, whereas obesity decreases GH[40]. GH decrease could relate to a metabolism imbalance that mimics insulin resistance[39]. Therefore, SF could provoke a GH decrease, which could favour obesity through insulin resistance.

The children in our study slept the whole night and had an adequate duration of sleep. TST recorded in the PG/PSG was normal (Mean TST = 8 hours 37 minutes).

Typical adults' sleep deprivation correlates to extreme sleepiness during the day. On the contrary, the children in our study were mostly excited and hyperactive during the day and had difficulties falling asleep; clinical signs are more consistent with the related stress and the increased RE, which impairs children to fall asleep easily, remain asleep and have a restorative sleep physically and mentally.

The fact that the RE decreased in children following a) AT showed that the RE is an effective way to identify the preschool children suffering from OSA-asthma-associated, and b) ED indicated RE as an effective way to measure the efficacy of an ED.

Moreover, the ED had a cumulative effect with AT on RE, AHI and BMI, which indicates that gastroesophageal reflux disease (GERD) aggravates asthma. The effect of ED on asthma through the RE/AHI decrease explains the pathophysiology mechanism and the clinical amelioration that asthmatic children present after an empiric ED.

RE seemed to represent both Th1 and Th2 types of inflammation, as it was most prominent in children who suffered both RA and NIgE. NIgEFA/RA seem to favour OSA-asthma associated via inflammation and the associated ENT signs by increasing the obstructive phenomena.[17]

The effect of RANIgE on BMI increase is more important than the negative effect of AT or ED on BMI, pointing out the necessity of AT and ED adaptation.

Th1 characterizes obese children who increase their BMI under CPAP along with persistently increased RE, which constitutes a risk factor for obesity, arguing that allergic children have a different profile from non-allergic children with OSA[16][30]

We only identified 6/74 (8.1%) children who had an IgEFA, which supports the delayed mechanisms that could intervene in the OSA-asthma associated.

Most children suffered a MA, which could favor SDB. Mites are attracted to humid environments, such as our beds. The nocturnal transpiration that the children experienced favored the SDB vicious circle.

We identified a child (case 10) with a delayed positive SPT to mites along with NIgEFA. After specific mite eviction and ED, the child no longer had a delayed SPT to mites. NIgE allergies favour RA onset, and treatment of Th1 inflammation (NIgEFA) avoids the onset of Th2 inflammation (RA).

We identified milk, wheat, and soy milk as NIgE allergies. Dairy, wheat, and soy additives are the main ingredients of industrialized food and the favourite foods of children who like fast-acting carbohydrates. This was the case in the adolescents in our study who did not even try to follow an ED. These foods represented the major core of their alimentation and were difficult for them to avoid (industrialized foods, school meals, etc.).

We observed that the effect sizes are moderate to large and confirmed in various ways (Somer's D, Eta, Eta-squared, Cohen's D, Hedge's correction, Contingency Coefficient, Phi, Kendall's tau-b). As the effect sizes were large enough, this implicated that we did not need a large sample to reach significant conclusions[26]. The effect sizes calculated revealed that the parameters evaluated were effective in the specific population. Therefore, the large effects identified in this study revealed that the results have a large practical significance and extensive practical applications in the studied population.

We performed path analysis to elucidate causal relationships in between the variables. With the regression analysis, we identified the parameters that were valuable to explain obesity/BMI. However, we reached at a point where we could not go further with our regression analysis. We found that there is an interaction in between RANIgE * AsthmaTreatmentAllergen Eviction* AHI which is statistically significant p <.001. The significant interaction in between RANIgE and AT or ED in the covariance of AHI was on the origin of failing to show significance in a relationship in between the different independent variables and the dependent variable (Tables 21,22). We could not explain which parameters are the most valuable to explain obesity/BMI when all these parameters were set together due to their interactions.

We wanted to clarify if the respiratory effort was only a characteristic (thus a trait) of the already obese children (which it actually is), either the respiratory effort was also the causality for them to be obese. If the respiratory effort only characterized the obese children, then we can only do weight interventions to decrease BMI, AHI and the RE which accompanies the obese children.

On the other hand, if the RE is the causality behind obesity, then it could alert us to identify the high-risk children to become obese, the factors provoking the increase in the RE, thus, to make recommendations and easily applicable health

policies to avoid obesity and all its deleterious consequences on its origin.

The path analysis was crucial to identify ways of causal relationships. We tested with a Bollen-Stine bootstrap, and we verified that our model fits very well to the data. We visualized the causality of the relationships with a graphic model representing the parameter estimates. Not only that, but we thus identified that the AT or ED and the RANIgE inversely affect the BMI through moderating the influence of AHI/RE upon BMI. We thus identified that high-risk subjects for the effect of RANIgE are those not being under AT or ED. Consequently, our hypothesis was clearly developed and effective in the specific population. The results could be probabilistic as there were large effects demonstrated, and the sample was adequate and representative of the population of children suffering from coexistent SDB/allergies/asthma, which is until now called OSA-asthma associated.

Moreover, the prospective nature of our study helped to reach useful conclusions, as we were able to verify that our hypothesis clinically applied to correlate clinical signs and treatments with the polygraphy and allergology profiles of the patients. As soon as we gained knowledge from our study, we confirmed our findings in our patients. We verified that if we gained more information about asthma treatments, eviction diets and allergies, we could interpret the PG/PSG results more effectively, than when we did not have this information. Moreover, we identified children as in Case 1.Onl.Suppl. who became obese after having adenotonsillectomy. He continued to gain weight despite adequate weight interventions and ceasing corticosteroids. He only decreased his weight after starting sublingual immunotherapy for mites.

Increased respiratory effort during sleep inherently correlates with SDB/OSA related to allergies, especially the coexistence of RANIgE, and is the origin of the sleep fragmentation in children suffering from OSA-asthma association, even if AHI remains at low levels. It decreases (as AHI) with AT or ED, and if untreated, contributes to AHI increase, thus favoring the persistence of OSA and its comorbidities (hyperactivity, decrease in school performance, behavior/concentration problems), asthma, and obesity.

Sleep fragmentation (SF) should alert the physician even if AHI is kept at low levels. Allergic children suffer significant SF, which is mediated through the RE increase during sleep. The SF and RE increase are at the origin of the REM sleep disturbance, hyperactivity, behavioural problems, ENT and orthodontic complications and the BMI increase in allergic children through a burst of stress-related mechanisms. The RE decrease under AT or ED could be an indicator of allergy and asthma. An easy guideline for GPs/ENT/paediatricians could be to test for NIgEFA (milk, wheat) and perennial RA (mites/Alternaria Alternata) in preschool children with an allergic profile non-obstructive SDB. The RE could have a role in early detecting the high-risk children prone to develop OSA-asthma association, thereby avoiding unnecessary operations and preventing the loss of precious time required to apply appropriate personalized treatment.

Allergy early diagnosis and treatment should be a priority to avoid sleep disorders, asthma, hyperactivity, behavior problems and obesity. Any alimentation which disturbs the sleep of children and favors stress pathways should be avoided. We should not wait for obese children to start detecting allergies. Public health policies should focus on alerting physicians about early detection of allergies to avoid asthma, OSA, and obesity. Asthma treatment, allergies, and allergen eviction have a significant impact on sleep disordered breathing/OSA and the Body Mass Index and provide valuable insights for more personalized and comprehensive treatment plans for affected children and into potentially mitigating

pediatric asthma and obesity.

Conclusion

Sleep fragmentation (through an increase in AHI/RE) mediates the pathway to asthma, OSA, and obesity, while allergies, asthma treatment, and allergen eviction moderate (increase/decrease) the effect of sleep fragmentation on asthma, OSA, and obesity.

Tables

See *qeios-esupplement-allergy-osa-obesity3.docx* for other tables (Supplementary Data).

Table 2. Crosstabs Chi-square / Pearson chi-square/ Exact *Sig.* 2-sided/ Contingency Coefficient (CC) / Eta/ Somer's D/Kendall's tau-c/Kendall's tau-b/Phi/Cramer's V/ Risk Estimate (Risk) /Mantel-Haenszel Odds Ratio Estimate (MH OR)/ Number Needed to Treat (NTT) Number Needed to be exposed to Harm (NNH)

	X^2, (df, N), p	CC	Eta	Somer's D	Kendall's tau- c	Kendall's tau- b	Phi	Cramer's V	Risk	MH OR, p	NNT	NNH
RANIgE*AHI>6.8	4.76 (1,49),**.04**	.298	.312	.340	.252	.312	.312	.312	4.35	4.356 (**.035**)		2.2
AT*AHI>6,8	4,261 (1,72),**.067**	.236	.243	-.288	-.190	-.243	-.243	.243	.212	.212 (**.054**)	4.9	
AT or AE*AHI>6,8	4,58 (1,72),**.042**	.349	.372	-.247	-.204	-.252	-.252	.252	.241	.241 (**.042**)	4.9	
RANIgE*RE>20	6.63 (1,33),**.014**	**.409**	**.449**	**.433**	**.430**	**.449**	**.449**	**.449**	7.5	7.5 (**.014**)		2.2
RANIgE*RE>22	4.53 (1,33),**.066**	**.348**	**.371**	**.361**	**.353**	**.371**	**.371**	**.371**	5.0	5.0 (**.039**)		2.6
RE>20*obesity/overweight	6.603 (1,50),**.017**	**.342**	**.363**	**.494**	**.266**	**.363**	**.363**	**.363**	11.375	11.375 (**.029**)		3.7
Obesity/overweight*RE>20	6.603 (1,50),**.017**	.342	.363	.267	.266	.363	.363	.363	11.375	11.375 (**.029**)		2
RANIgE*obesity/overweight	7.219 (1,50),**.012**	.355	.380	.450	.288	.380	.380	.380	7	7.0 (**.013**)		3.1
Obesity/overweight*RANIgE	7.219 (1,50),**.012**	.355	.380	.321	.288	.380	.380	.380	7	7.0 (**.013**)		2.2

Table 38. Regression Weights

	Estimate	S.E.	c.r.	p	Label
AHI <--- AT or ED	-2.332	1.247	-1.870	**.061**	PATAEAHI
AHI <--- RANIgE	2.597	1.289	2.014	**.044**	PRAHI
Respiratory Effort <--- RANIgE	15.007	4.645	3.231	**.001**	Pranre
Respiratory Effort <--- AT or ED	-11.931	4.492	-2.656	**.008**	Patedre
BMI <--- AT or ED	-.477	1.308	-.365	.715	Patedbmi
BMI <--- AHI	.432	.163	2.655	**.008**	Pahibmi
BMI <--- RANIgE	1.431	1.415	1.011	.312	pRANBMI
BMI <--- Respiratory Effort	.080	.045	1.766	**.077**	pREBMI

Table 40. Standardized total, direct and indirect effects through path analysis with serial mediation in AMOS.

	Total effects				Direct Effect					Indirect effects					
Hypothesis	B	SE	T	P	B	SE	T	P	Hypothesis	B	SE	T	P	Percentile bootstrap 95% CI	Result
RANIgE→ BMI	.426	.149	2.85	**.022**	.163	.172	0.94	.306	RANIgE→(RE+AHI) →BMI	.263	.165	1.59	.155	-.041	.503
RANIgE→ RE	.459	.121	3.79	**.002**	.459	.121	3.79	**.002**							
RE→ BMI	.296	.255	1.160	.326	.296	.255	1.16	.326							
RANIgE→ AHI	.323	.161	2.00	**.082**	.323	.161	2.00	**.082**							
AHI→ BMI	.395	.290	1.36	.295	.395	.290	1.68	.295							
AT or AE→BMI	-.286	.117	-2.44	**.021**	-.056	.168	-.33	.605	AT or ED→(RE+AHI) →BMI	-.230	.149	-1.54	.212	-.413	.077
AT or AE→RE	-.378	.123	-3.073	**.006**	-.378	.123	-3.07	**.006**							
AT or AE→AHI	-.300	.124	-2.41	**.025**	-.300	.124	-2,41	**.025**							

Note. SE: Standard Error, RANIgE: Respiratory and Non-IgE mediated Allergies, RE: Respiratory Effort, AHI: Apnoea Hypopnea Index, BMI: Body Mass Index, AT, or AE: Asthma treatment or eviction diet, β=Estimate, CI: Confidence Intervals, L: Lower, U: Upper, Bootstrap 5000

Table Legends

- **Table 2.** Statistical comparisons (Crosstabs Chi-square / Pearson chi-square) in between groups (RANIgE, AHI>6.8, AT, obesity/overweight) are reported. Only exact *Sig.* 2-sided are reported.
- Effect sizes are reported through evaluation of: Contingency Coefficient (CC) / Eta/ Somer's D/Kendall's tau-c/Kendall's tau-b/Phi/Cramer's V. To evaluate the risk of the disease, we report Risk Estimate (Risk) /Mantel-Haenszel Odds Ratio Estimate (MH OR).
- The Number Needed to Treat (NTT) to avoid the outcome and the Number Needed to be exposed to Harm (NNH) to have the outcome are also evaluated.

- **Table 38.** Regression Weights

- **Table 40.** Standardized total, direct and indirect effects through path analysis with serial mediation in AMOS.

Figures

See *qeios-esupplement-allergy-osa-obesity3.docx* for other figures (Supplementary Data).

Figure 5b. Clustered Boxplot of RespiratoryEffort by RANIgE by obesity group
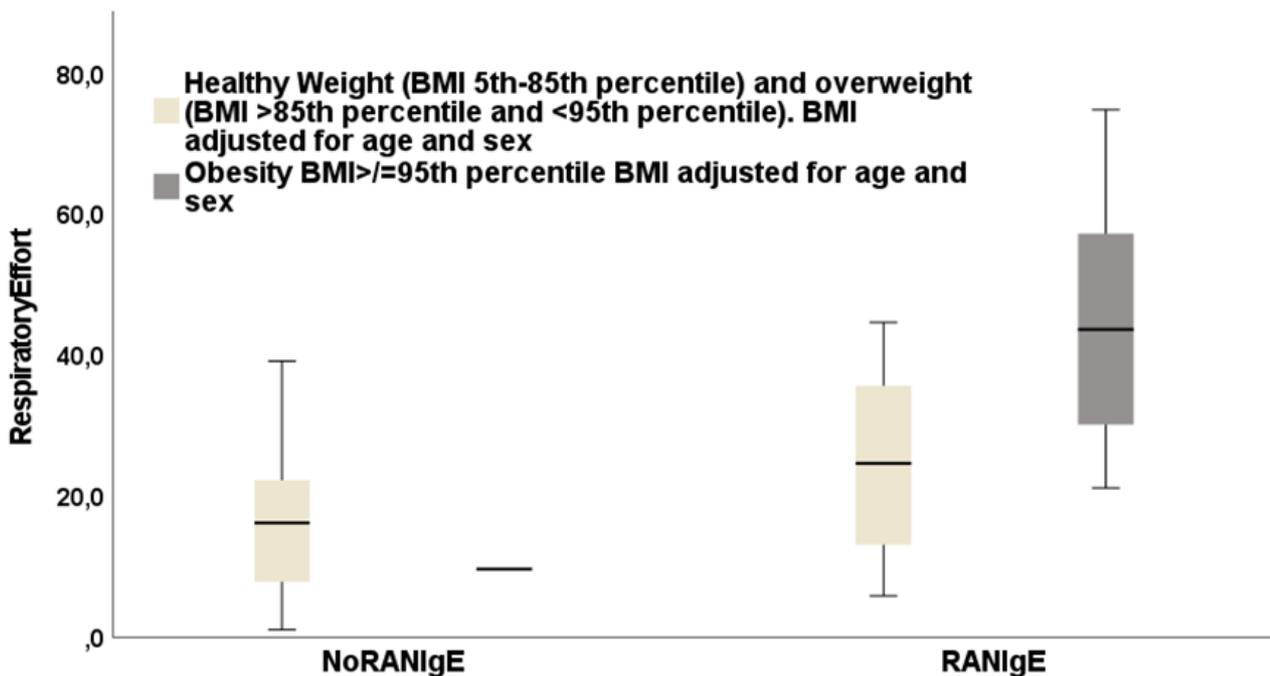
Note. This figure shows that the children who do not suffer the co-existence of respiratory and non-IgE mediated allergies (NoRANIgE) have lower levels of respiratory effort during sleep (RE) than the children who suffer RANIgE. This figure also shows that the children who do not suffer the co-existence of RANIgE also have a healthy weight or overweight whereas the children who suffer RANIgE could either be obese either have healthy weight/overweight. This could indicate that the RANIgE favors increased RE and obesity.

Figure 5b.

Figure 6. ROC Curve of Respiratory effort to predict obesity and overweight versus healthy weight
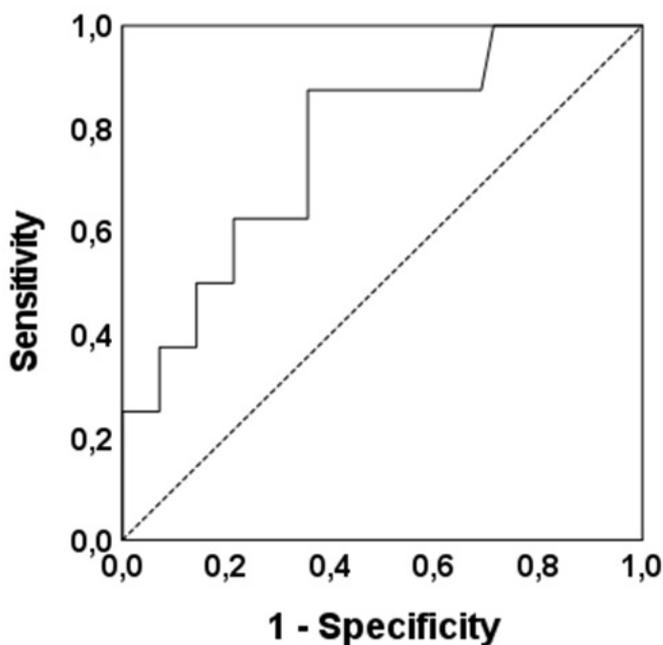
Figure 6.

Figure 17a. Multiple Line Mean of AHI, Mean of BMI, Mean of RespiratoryEffort by a combined (dummy) variable (ATED.RANIgE) representing the treatment (asthma treatment or eviction diet)(AT or ED) and the co-existence of respiratory and non-IgE mediated allergies (RANIgE).Percentages of ATED.RANIgE subgroups are also shown.
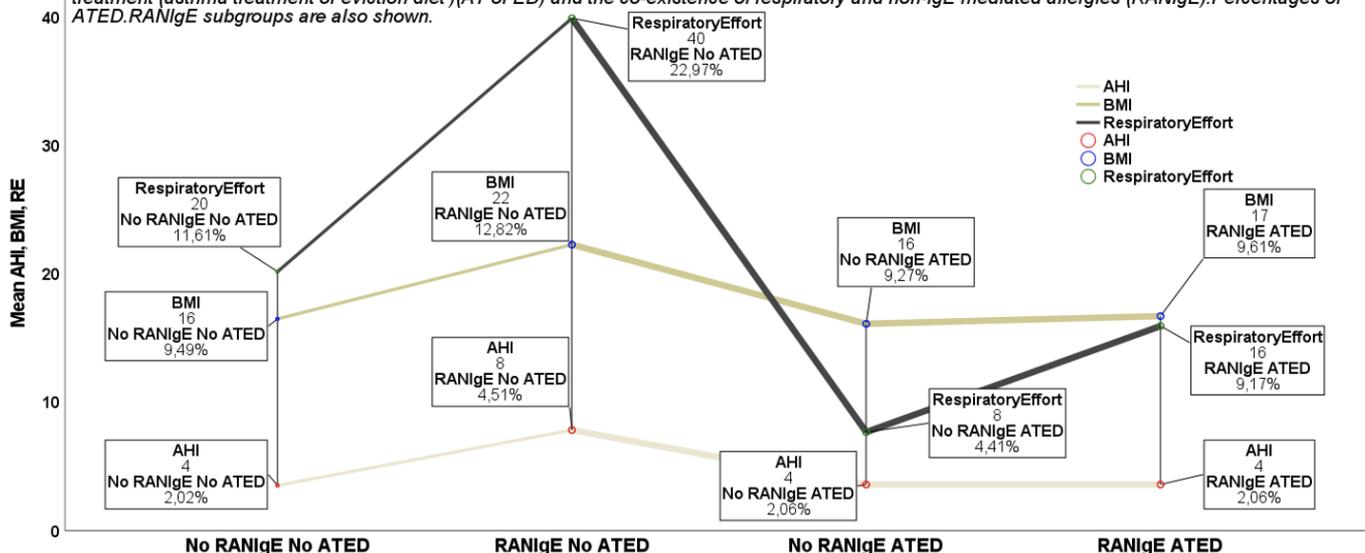
Note.This figure shows that the co-existence of RANIgE and lack of asthma treatment (AT or ED) results to a predominant increase of respiratory effort during sleep (RE) and to a mild increase upon BMI and AHI. AT or ED and non co-existence of RANIgE result to a prominent decrease of RE and a mild decrease upon BMI and AHI. The decrease upon BMI and AHI seems to be mainly result by the non co-existence of RANIgE. That results as the mean values of BMI and AHI are similar in the NoRANIgE No ATED and the No RANIgE ATED groups.

Figure 17a.

Estimated Marginal Means of BMI
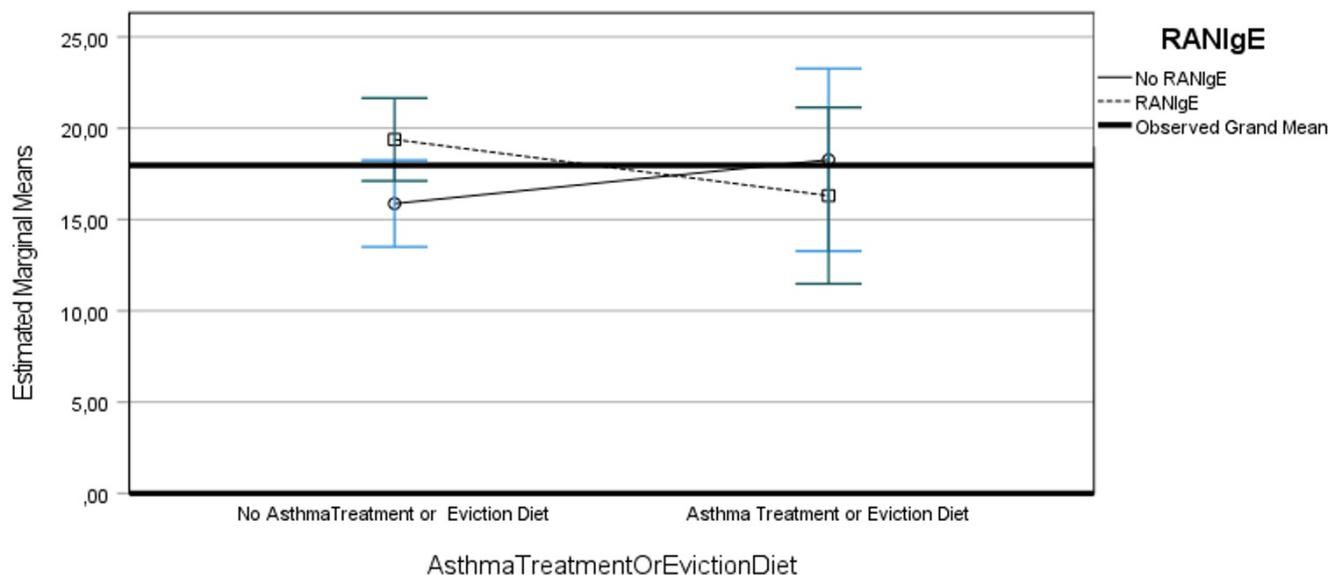
Covariates appearing in the model are evaluated at the following values: AHI = 4,7708, RespiratoryEffort = 23,8542

Error bars: 95% CI

Figure 19.
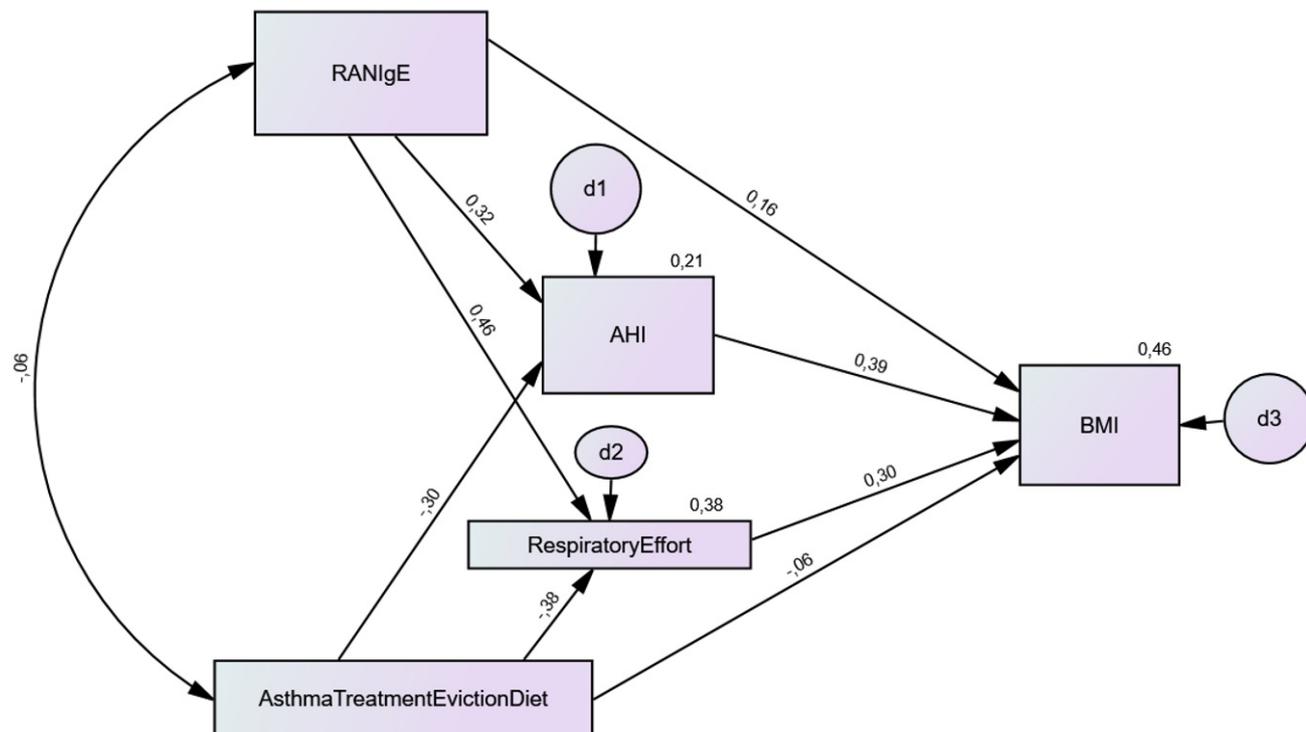
Figure 21. Standardized Estimates

Figure Legends

Figure 5b. Clustered boxplot of the RE by RANIgE by obesity group.

Figure 6. ROC curve (BMI adjusted for age and sex) of the RE to predict obesity (BMI>/=95th percentile) and overweight (BMI >85th percentile and <95th percentile) versus normal weight (BMI 5th-85th percentile).

Figure 17a. Mean values of AHI, BMI, and RE in children under AT or AE, either with no AT or AE, when RANIgE variable has been taken into consideration. The representation of both AT or AE and RANIgE is effectuated through a combined (dummy) variable (ATED.RANIgE) representing both the treatment (AT or ED) and the co-existence of RANIgE.

Figure 19. Profile plot of BMI according to both AT or ED and RANIgE.

Figure 21. Standardized Estimates of the direct effects of the path analysis.

Acknowledgments

Declarations

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