The impact of CFTR modulator therapy on lower airway microbiota in people with cystic fibrosis: A systematic review and meta-analysis.

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Background and aims

In people with cystic fibrosis (CF), over the years, chronic bacterial infections will lead to decreasing lung function and bronchiectasis. Over the past decade, pharmaceutical agents capable of restoring the function of the cystic fibrosis transmembrane conductance regulator (CFTR) protein (CFTR modulators) were developed. **CFTR modulator therapy** has resulted in marked improvements in pulmonary exacerbations, lung function, body weight, and quality of life. However, it remains unclear how restoring CFTR function modifies existing airway infection and inflammation. Understanding the dynamics of **airway microbiome changes in response to modulator therapy** plays an essential role in developing strategies for managing airway infections. Our aim was to conduct a systematic review and meta-analysis of all available studies.

Methods

We conducted a **systematic search** on the 26th January, 2024 in MEDLINE, Embase, Web of Science, Scopus and CENTRAL. We performed a random-effects meta-analysis of any provided data pertaining to **lower airway microbiota composition before versus after the initiation of CFTR modulator therapy.** Meta-analysis was possible in case of: Shannon index, Simpson index, Pielou's evenness and the relative abundance of more than 10 genera of bacteria (see below). We calculated mean difference (MD) and standardized MD (SMD) with 95% confidence intervals (CI) and visualized the results on forest plots. Chi-squared tests were performed and I^2 values calculated to assess statistical heterogeneity. RevMan 5.4.1 was used to carry out meta-analytical calculations.

Conclusion

Our results demonstrate a clear and statistically significant association between the initiation of CFTR modulator therapy and the stabilization of lower airway microbiota in terms of increased biodiversity, more balanced distribution of microbial species and reduction in the abundance of potentially pathogenic species, all of which contribute to a lower risk of respiratory tract infections. These changes are mostly observed during ETI therapy.

Results

30 studies were eligible for inclusion, with most prospectively examining people with CF before and 4-12 months after the initiation of CFTR modulator therapy. The initiation of CFTR modulator therapy was associated with an **increase in lower airway alpha-diversity** (**Shannon index**; SMD: +0.43 (95% CI: +0.24 - +0.61), p<0.001 (**Figure 1**); Simpson index; SMD: +0.37 (95% CI: +0.14 - +0.60, p=0.001) **and evenness** (Pielou index; SMD: +0.84 (95% CI: +0.55 - +1.12), p<0.00001).

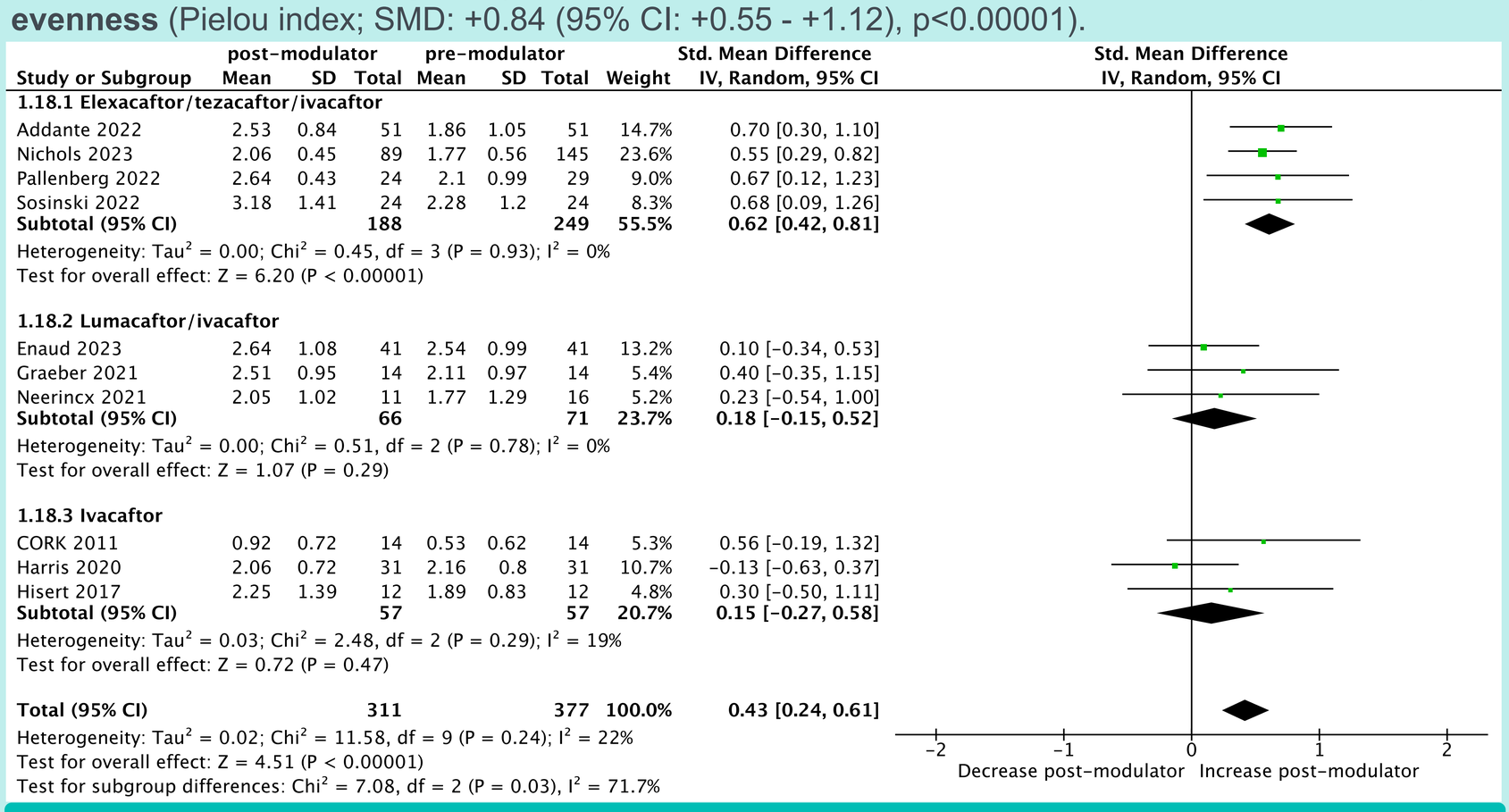

Fig.1. Forest plot of change in Shannon index after initiating CFTR-modulator therapy

Data was availble on **the relative abundance of 13 genera of bacteria (Figure 2)** in lower-airway samples, **before and after the initiation of CFTR modulator therapy**.
We observed a statistically significant **decrease in the relative abundance of the *Pseudomonas*** (MD: -7.12% (95% CI: -13.06% – -1.17%; p=0.02)) and ***Staphylococcus*** genera (MD: -4.31% (95% CI: -6.64% – -1.98%; p<0.01)) which contain species considered **classical pathogens in CF**.
There was a statistically siginificant **increase in case of *Streptococcus*** (MD: +3.36% (95% CI: +0.88% – +5.84%; p<0.01)), ***Fusobacterium*** (MD: +0.86% (95% CI: +0.19% – +1.52%; p=0.01)) and ***Actinomyces*** (MD: +0.60% (95% CI: +0.02% – +1.18%; p=0.04)).

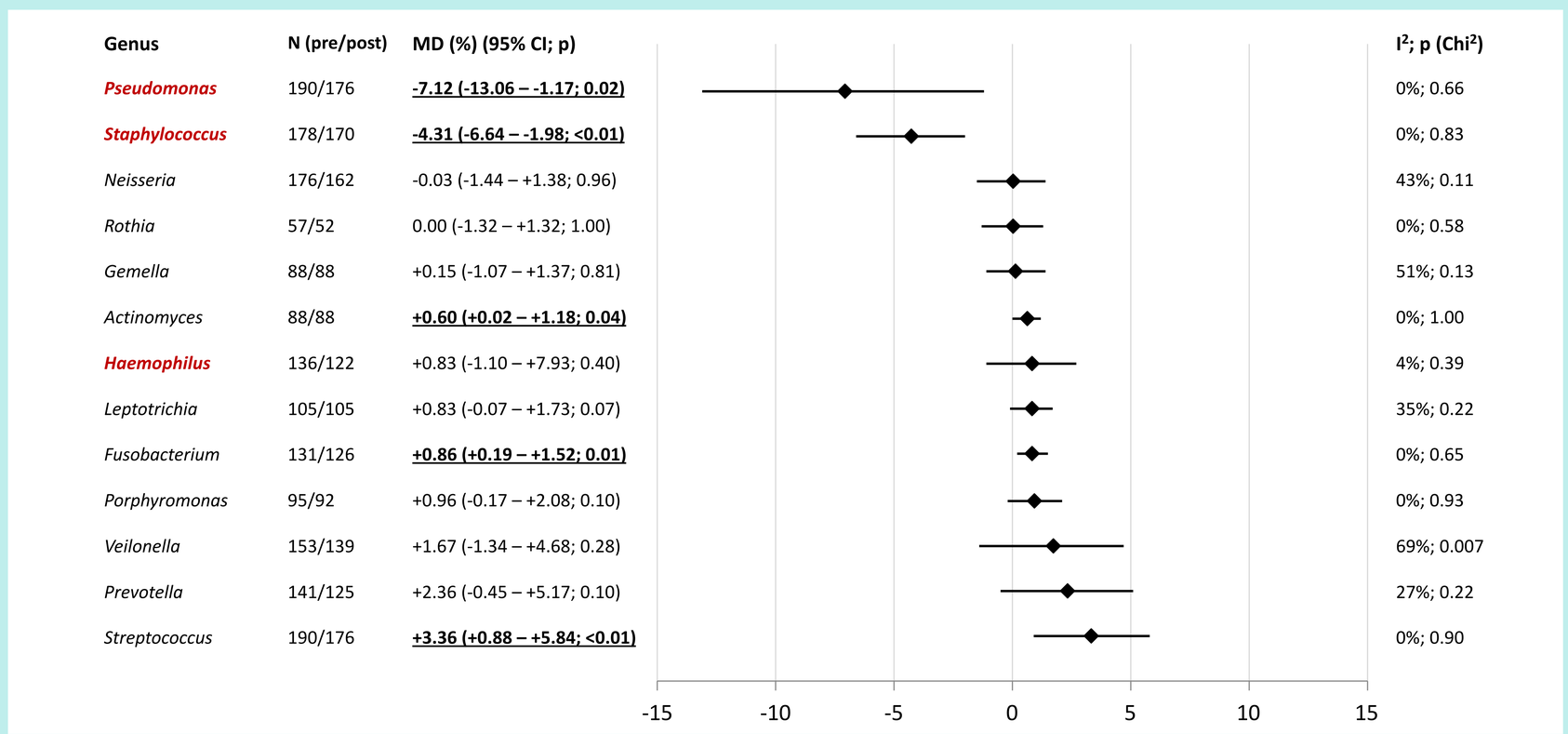

Fig.2. Change in relative abundance of bacteria genera before and after initiation of CFTR-modulators

As visible on Figure 1, we had the chance of conducting **subgroup analyses based on the type of CFTR modulator** therapy. Just as with the significant improvement in Shannon index, a trend was apparent in case of the Simpson index, Pielou's evenness, *Pseudomonas* and *Staphylococcus* relative abundance: **lumacaftor-ivacaftor and ivacaftor** monotherapy subgroups noted **no changes** in said outcomes, **significant changes in the elexacaftor-tezacaftor-ivacaftor (ETI) therapy subgroups** produced the overall significant results. Within-subgroup statistical heterogeneity was low but tests for subgroup differences revealed significant heterogeneity, further suggesting that these improvements are seen only/mostly next to ETI therapy.

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