

Prioritizing Treatable Traits in Airways Disease



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According to the “treatable traits” paradigm, targeting pulmonary, extrapulmonary, and behavioral traits should enhance patient outcomes in chronic airways diseases.¹ However, delivering a treatable traits approach presents a logistic challenge because more traits have been proposed—greater than 30—than can be comfortably addressed in a typical clinical encounter.

In response, several solutions have been proposed. First, time can be saved by using questionnaires to screen for common traits or electronic templates to guide the consultation.^{2,3} Second, for patients who warrant extensive evaluation because of a high burden of disease, comprehensive approaches with multidisciplinary input have been developed.⁴ Third, if high-yield traits with the greatest clinical impact could be clearly identified, this might help busy clinicians prioritize a smaller, more manageable group of traits.

For a trait to be considered impactful in this manner, the following characteristics are desirable; it should be prevalent enough to warrant attention, easily detected using available clinical tools, and responsive to existing interventions. Crucially, its successful detection and treatment should lead directly to improvements in airways disease outcomes.

High-yield traits may differ in different populations. Variations in demographic characteristics, disease manifestation and severity, and previous therapies already used are all likely to be highly influential. In its original proposal, the treatable traits paradigm embraced a “label-free” approach, with no differentiation between patients diagnosed with chronic obstructive pulmonary disease (COPD) and asthma. However, patients currently grouped according to these diagnostic labels may—by their distinct definitions and demographic characteristics—exhibit different high-yield traits.

High-yield traits may also vary depending on the disease outcomes under consideration. For example, traits that impact exacerbation rates in difficult-to-treat asthma appear different from those that impair symptom control or quality of life.⁵

A final challenge to identifying high-yield traits lies in the observation that many individuals with airways diseases possess multiple traits.⁵ Although the impact of individual traits can be studied with relative ease, it is likely that clusters of traits and their treatments may interact in a complex and unpredictable fashion, complicating their analysis.

This issue of the journal presents the results of a novel and meticulous effort to identify high-yield traits.⁶ Hiles et al⁶ used data from 2 published randomized trials, 1 in COPD (36 participants, 3-month duration) and 1 in severe asthma (55 participants, 4-month duration). Numerous pulmonary, extrapulmonary, and behavioral traits were assessed. Participants in the active arms received the relevant trait interventions, guided by a case manager according to prespecified protocols. Control participants were offered usual care at the discretion of their physician, who were unaware of the trait assessment results. Using Bayesian model averaging (BMA), 22 specific traits and their interventions were studied, of which 7 were excluded from the final analysis, either because there were too few observations for traits or treatments, or because treatments were universally offered to all participants.

Two outcomes were examined. The first was the relationship between the *presence* of a trait (in both active and control arm participants) and the participants’ *baseline* quality of life as measured by the St Georges Respiratory Questionnaire. The second and perhaps more intriguing outcome was the relationship between *treatment* for a trait (whether received in the active arm or the control arm) and *improvements* in participants’ quality of life at the end of the respective study.

For the first outcome, the analysis showed that the presence of frequent chest infections, breathing pattern disorder, inadequate inhaler technique, systemic inflammation measured by C-reactive protein, and depression was most closely associated with baseline quality-of-life impairment. These results build on what is known regarding such traits in airways diseases.⁵ In a separate BMA analysis of a large severe asthma cohort also performed by Hiles et al, 10 traits were predictive of asthma exacerbations, a different outcome.⁷ Interestingly, the only high-yield traits common to both analyses were anxiety and systemic inflammation. This supports the notion that the specific populations and outcomes under consideration will determine the impact of a particular trait.

For the second outcome, the provision of oral corticosteroids and statins, for eosinophilic airway inflammation and systemic inflammation, respectively, was most associated with improvements in quality of life. There were more modest associations for targeting exercise intolerance, anxiety, and obesity.

The benefits reported from suppressing eosinophilic inflammation with oral corticosteroids align closely with the existing body of evidence. However, in severe asthma, guidelines now recommend the use of antieosinophilic biologics (unavailable to the trialists at the time the primary studies were conducted) for

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this purpose over systemic steroids, due to their superior risk-benefit profile. Indeed, the reduction of corticosteroid use is itself now a key outcome in severe asthma management.⁸

The effects reported in this analysis for statin therapy are surprising both in benefit and in magnitude, and inconsistent with broader COPD and asthma analyses from larger data sets.^{9,10} The true significance of this intervention remains unclear and requires further exploration.

The success of tailored therapy to improve each trait was not specifically reported in the current analysis, but data from the original studies suggest that this was not successful for all traits. Neither arm of the asthma trial showed improvements in body mass index (most likely related to the short trial duration) so the benefits reported for targeting obesity may lie elsewhere.

This analysis has many strengths. The use of trial cohorts allowed interventions to be directly examined. A large number of traits were detected and addressed. The advanced statistical methodology could evaluate multiple interventions delivered simultaneously. The choice of the St Georges Respiratory Questionnaire as the outcome of interest was highly relevant to clinical practice.

The decision to pool participants with COPD and asthma together will divide opinion. It is likely to be considered a strength for generalizability by advocates of the “label-free” approach, but a limitation in validity by skeptics, because some traits relevant to the COPD group might be less important in asthma, and vice versa.

As to be expected when addressing such a multifaceted research question, the investigators encountered considerable challenges. They were unable to account for the effects of previous therapy. Nor could they feasibly estimate treatment effects for several potentially influential traits, when either too few participants received treatments (such as adherence coaching), or all participants received treatments (such as breathing retraining for breathing pattern disorder). Trial duration was short, potentially limiting the impact of trait interventions. Finally, the total number of participants was relatively low, and lower still for each trait and intervention.

Some uncertainty remains around traits for which therapy had no impact on quality-of-life improvement. To understand the cause of such negative results requires data on intermediate outcomes. First, was the trait accurately detected? If so, did the

trait impair quality of life? Next, was the trait itself responsive to the intervention? Finally, could treating the trait enhance quality of life, as measured by the St Georges Respiratory Questionnaire? A single failure at any one of these explanatory levels would have broken the chain linking each trait intervention with airways disease outcomes.

In conclusion, the analysis by Hiles et al is a welcome addition to the body of evidence for a treatable traits approach. With the exception of statins for systemic inflammation, most of the traits and treatments identified in this analysis are ready to be applied to or, regarding eosinophilic inflammation, modified for clinical practice. Many of the remaining questions will require larger, additional studies of treatable trait interventions, assessing both intermediate and final outcomes in carefully characterized cohorts. The results of this article will greatly assist the choice of traits and interventions in such studies.

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