bulk transcriptomic data. Although the authors undertook a stringent approach to replicating their results, it is notable that even for the set of 475 persistently altered smoking genes that achieved significance across each study time point, only 41% ($n = 195$) of these genes were also significant in both independent replication cohorts. This level of replication is not surprising for transcriptomic data, which captures many complex signals but can be susceptible to confounding in both cross-sectional and longitudinal study designs. Although multiple stages of replication in this study provide confidence in the 195 fully replicated smoking-associated genes, further studies will be necessary to tease out adaptive versus maladaptive responses to cigarette smoke as well as the lingering consequences of smoke exposure on human health. ■

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PRS-ing Forward to Identify Genetic Risk in Idiopathic Pulmonary Fibrosis

Over the last 2 decades, it has become clear that genetic risk is an important determinant for development of idiopathic pulmonary fibrosis (IPF); however, the genetic architecture underlying IPF is complex and remains incompletely understood. Although a variety of common and rare genetic variants have been associated with IPF, an SNP in the promoter of the of the gene encoding *MUC5B* (Mucin 5B) is the strongest disease risk factor identified to date (1, 2). Across multiple studies, the odds ratio for IPF associated with carrying the T (minor) allele is ~4.5 (3), making it one of the most impactful disease-associated common variants in humans. In addition to the *MUC5B* region, 22 other IPF-associated common variant loci were identified in a recent meta-analysis of genome-wide association studies (GWAS) (4). Given the progress in identifying individual

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genetic variants associated with IPF, a significant question in the field has become whether a predictor of combined genetic risk could be developed that would improve on information obtained by testing for the presence of the *MUC5B* risk allele.

The polygenic risk score (PRS), which was developed in 2007, is increasingly used as a method for analyzing large-scale GWAS data in a variety of diseases (5), including lung diseases such as chronic obstructive pulmonary disease (6) and asthma (7). This approach can combine a large number of common variants, including those below the genome-wide significance threshold for phenotype association, to identify disease risk in individuals. A new study by Moll and colleagues in this issue of the *Journal* (pp. 791–801) is the first comprehensive investigation of this method in IPF (8). The investigators analyzed data from 14,650 study participants, including 1,970 individuals with IPF and 1,068 individuals with interstitial lung abnormalities (ILAs), from a variety of cohorts to develop PRSs for IPF with or without inclusion of the *MUC5B* risk allele. Although the PRS calculated with inclusion of *MUC5B* performed somewhat better than the PRS in the absence of data from the *MUC5B* region, the top quintile in the PRS (excluding *MUC5B*) was associated with an odds ratio of ∼7 compared with the lowest quintile, thereby indicating that common variants outside the *MUC5B* region substantially contribute to risk for IPF. In addition, receiver operating curves for IPF prediction showed that the highest area under the curve was achieved by clinical modeling with a combination of the PRS (excluding *MUC5B*) and genotype information regarding the *MUC5B* risk allele. Furthermore, using linkage disequilibrium score regression, the authors estimated observed-scale heritability in IPF at ∼28%, in the range of prior estimates of the impact of genetic predisposition on the development of IPF (1).

In addition to IPF, the investigators applied the PRS methodology to ILAs, which are abnormal interstitial changes affecting >5% of lung parenchyma on computed tomography scan (9). ILAs are detectable in approximately 7% of individuals >50 years of age and can in some instances precede development of clinical IPF by several years (10). In ILA studies, the PRS model was associated with presence (odds ratio, 1.25) and progression (odds ratio, 1.16) of ILAs; however, this association was only observed in subjects with European ancestry.

Together, the findings in this study reinforce the importance of the *MUC5B* risk allele in IPF and strongly support the idea that a wide variety of common variants throughout the genome influence disease risk. Although testing for the *MUC5B* risk allele is the most efficacious single measurement for risk assessment, prediction is modestly improved by adding the PRS generated from the rest of the genome. Therefore, combining the PRS with testing for the *MUC5B* risk allele and clinical information could be useful in future studies for identification of individuals at the highest risk for development of IPF. An important question is whether genetic risk assessment tools can be used to stratify risk before the onset of disease, particularly to determine which ILAs are most likely to progress to clinical disease, because ILAs are much more frequent than IPF. Although the presence of the *MUC5B* risk allele has been associated with ILAs (11), the results of this study are somewhat disappointing in this regard, because the association of the PRS with the presence and progression of ILAs was modest at best.

To date, PRS methodology has not had a substantial impact on clinical practice, and pitfalls of PRSs in predicting risk of age-related traits have been documented (12). Other issues related to maximizing the power and utility of PRS include limitations in the size of GWAS datasets available for relatively rare diseases, difficulties in extrapolation to ethnicities underrepresented in GWAS datasets, and underlying assumptions of lack of specific gene-by-environment interactions (13, 14), all of which may have implications for application in IPF. Also, PRS methodology does not account for rare genetic variants, which can have a major impact on disease risk in the ∼8.5% of individuals with sporadic IPF who harbor loss-of-function rare variants in telomere maintenance genes (15). Despite these issues, this study represents substantial progress in genetic risk assessment in IPF. Further refinement of PRS calculations is likely in the future as larger and more ethnically diverse genetic data in subjects with IPF become available. ■

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The Influence of Physiologic Burdens Related to Obstructive Sleep Apnea on Cardiovascular Outcomes

It is impossible to ignore the impact of cardiovascular disease (CVD), as it claims more than 800,000 lives each year and accounts for 32% of all deaths (1). Diving into the complex etiology of CVD, the increasing role of sleep disorders has become evident, thus shaping this nationwide health crisis and propelling the American Heart Association to include healthy sleep in its Life's Essential 8 guidelines (2).

Obstructive sleep apnea (OSA) is arguably foremost among sleep disorders augmenting cardiovascular risk, with its diagnosis and severity typically gleaned from the apnea–hypopnea index (AHI), measured on polysomnography (PSG) or home sleep apnea tests. Although patients with OSA are at increased cardiovascular risk, there is lingering obscurity regarding the AHI metric and questions as to its precision, how accurately it reflects the salient biologic aspects of OSA, and its utility as a defining metric potentially explaining negative clinical trials involving intervention with continuous positive airway pressure (3, 4).

Although there are other traditional metrics besides AHI in PSG reports, such as oxygen saturation (Sp_{O_2}) nadir and the percentage of sleep time spent under 90% Sp_{O_2}, these provide only a partial reflection of the true biophysiological sleep landscape. They fail, for instance, to delve into the depth and duration of physiological signal desaturations during events. This limitation of current standard reporting of metrics, combined with the richness of the data captured during the examination, serves as a major impetus for researchers to explore other ideas for PSG metrics, including those derived from event-based physiological burdens.

In this issue of the *Journal*, Labarca and colleagues (pp. 802–813) examine in depth the association of hypoxic burden (OSA-related total area under the desaturation curve) with incident CVD, coronary heart disease (CHD), and mortality compared with the ventilatory burden (the event-specific area under the ventilation signal identified by amplitude changes in the nasal pressure signal) and arousal burden (the total duration of all arousals divided by the total sleep time) (5). Their study provides information on the strength of predicting CVD-related outcomes even when accounting for confounding. Of note, some measures of sleep disturbance physiological burden, such as the sleep apnea–specific hypoxic burden in association with CVD, have been reported and in of itself does not represent a novel finding (6–8). Rather, the novelty of the present work resides in providing key insights into the interrelatedness of sleep-specific physiological burden metrics reflecting different pathophysiologic aspects.

To perform the study, Labarca and colleagues (5) analyzed PSGs from the community-based cohort of MESA (Multi-Ethnic Study of Atherosclerosis) ($n = 2{,}035$, 917 men) and the MrOS (Osteoporotic Fractures in Men) cohort ($n = 2{,}896$, all men). In MESA, outcomes were based on regular follow-up calls, and in MrOS, participants were contacted every 4 months after the sleep study. In both cohorts, medical records and death certificates were also evaluated. Fortunately, both cohorts are publicly available in the National Sleep Research Resource, a valuable, accessible, and extensive collection of deidentified physiological signals and clinical data elements.

In their primary analysis, the authors address the associations of hypoxic, arousal, and ventilatory burdens with longitudinal outcomes. They used Cox regression and four different models, each with an increasing number of covariates for adjustment from demographics to comorbidities. Also, for model 4, they added the variable desaturation sensitivity, defined as the ratio of hypoxic burden to ventilatory burden, aiming to adjust for the tendency toward desaturation of the individual. For the MESA dataset, every 1 SD increase in hypoxic burden was significantly associated with a 21% increase in the risk of all-cause mortality and a 33% increase in the risk of all CVD. The ventilatory burden was significantly associated with a 24% increased risk of all-cause mortality and a 32% increased risk of all CVD. The statistical significance of the results persisted even when attempting to more rigorously take into account visceral adiposity (i.e., replacing body mass index with waist

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