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Editorial

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Incident cardiovascular disease risk prediction using extensive oximetry patterns

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Obstructive sleep apnea (OSA) has been associated with increased risk of developing cardiovascular disease (CVD) in multiple studies [1–3]. However, the nature of its association requires further investigation, including how to best predict which patients ultimately develop CVD. This is a challenging task, given the heterogeneous information provided by the apnea–hypopnea index (AHI; which may obscure OSA endotypes) [4, 5] on one hand, and the complex nature of polysomnographic signals (with minimal guidance on defining optimal signals) on the other. Identifying an optimal signal or combination of signals that improves the accuracy of CVD risk prediction would improve risk stratification and personalized medicine. Ideally a search across a broad range of candidate signals would also provide insights on potential biological mechanisms and contribute to the design of improved OSA clinical trial measures when appropriately considering the larger biological context that contributes to these signals [6]. Testing dozens of candidate signals among thousands of participants remains technically challenging, even when considering cleaned and harmonized PSG datasets provided by resources such as the National Sleep Research Resource (NSRR) [7].

In this issue, Kate Sutherland and colleagues [8] describe the most comprehensive analysis of oximetry patterns that may help to predict incident CVD among patients with OSA to date. The authors examined a subset of Sleep Heart Health Study participants with OSA (as defined by AHI ≥ 5) and without preexisting CVD. The median follow-up was 11.5 years. Thirty-one candidate signals were examined in primary analyses and further examined in sex-stratified and NREM- and REM-specific analyses. These signals were divided into four domains [9]. In addition to desaturation characteristics that have been explored using the hypoxic burden and similar measures, Sutherland and colleagues examined the time series of saturation values (e.g. the shape of the distribution of SpO_2 values), the power spectral density of the oximetry signal (e.g. the shape of the distribution of the OSA-band portion of the curve), and nonlinear analyses (e.g. the regularity of similar oximetry patterns). The authors did not identify any individual signals that were associated with incident CVD at Bonferroni-adjusted significance in the combined sample or in men, but did identify suggestive associations in women that include the oxygen desaturation index (ODI) at 5%, the nadir SpO_2, the mean of the OSA frequency band of the power spectral density, and the SpO_2 distribution standard deviation (p 0.007–0.014). A suggestive association with the hypoxic burden was present in women ($p = 0.02$) but not in men ($p = 0.91$). Multiple candidate signals were better individual predictors of incident CVD than the AHI ($p \geq 0.26$).

Despite a lack of statistically significant results, this study is nevertheless an important step in identifying candidate predictive signals for CVD that should be continued in future studies. A broad "grid search" that identifies optimal signals associated with clinical outcomes among a range of partially correlated candidate signals is a productive means of moving beyond the AHI to identify more clinically relevant PSG metrics. Sutherland et al. have demonstrated the scalability of their algorithms to thousands of recordings, which is a necessary threshold for practically addressing epidemiological-scale questions. Multiple suggestive associations and a prior study of the same dataset with a broader range of AHI values and broadly similar endpoints [2] indicate that significant associations are possible with improvements in study power. The suggestively significant hypoxic burden associations in women are broadly similar to more significant hypoxic burden associations with CVD in women relative to men in another cohort [3] (albeit with opposite directionality) and highlight heterogeneity that should be examined in future prioritized work. Different point estimates in Sutherland and colleague's sex-stratified analyses were observed for certain desaturation, time series, and power spectral density candidate signals, and could reflect known endotype differences [4], further emphasizing a need for personalized medicine improvements. Identifying a candidate oximetry-derived signal may provide unique practical benefits, including inexpensive data collection and the reuse of underutilized clinical tracings as longitudinally-collected biomarkers.

The authors have also applied ten power spectral density and two nonlinear measures to CVD prediction for the first time, enabling the querying of the frequency content and the regularity of the oximetry signal. While none of these signals predicted CVD with statistical significance, there were notable differences in the

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point estimates in sex-specific analyses with some associations reaching nominal significance. These associations may provide complementary information to more widely analyzed signal measures and may be useful in future studies with larger sample sizes or prediction of specific cardiovascular diseases. The inclusion of a series of understudied oximetry statistics may drive further innovation as the characteristics of the most clinically relevant statistics are applied to derive new signal extractions in the future.

The weaknesses of this study that are notable concern modest sample size and further CVD risk factor adjustment that could be addressed in future work. Generalization of results into other studies could be useful to improve study power and demonstrate the potential clinical utility of candidate signals in a broader range of contexts. A meta-analysis using additional NSRR studies linked with often extensive CVD data housed within BioLINCC would have improved study power and possibly identified significant associations while demonstrating that the findings are robust to different PSG equipment and/or signal filters used to measure participants with more diverse ancestries and other characteristics. Larger studies may be ultimately necessary to distinguish between similar candidate PSG signals with modest differences in hazard ratios. The authors excluded participants with CVD reported within two years of the PSG. Adjustment for cardiovascular risk factors at baseline using the Framingham risk score [10] (and/or other measures such as a polygenic risk score [11]) would have also improved the analysis and potentially demonstrated additional clinical utility for oximetry statistics in CVD prediction beyond traditional risk factors alone [12]. Additional work is needed to understand and replicate the directionality of the ODI 5% hazard ratio in women (0.78; 95% CI [0.64–0.93]; $p = 0.007$) as well as the direction of other results in women, including the remaining desaturation class results with attenuated associations ($p = 0.017$–0.108).

Future studies in this area of research should be prioritized and potentially address larger sample sizes, sex, age- and obesity-stratified group differences [3, 13], OSA endotype-specific signal candidates, and include additional known predictors (e.g. [14]) and potentially predictive non-oximetry signals. The relative importance and independent nature of candidate signals and traditional CVD risk factors could be assessed through machine learning or other methods [15]. Combined candidate signals with orthogonal information may be more predictive than individual signals, and the relative predictive importance of individual signals could differ by OSA endotype. The substantial effort invested in extracting and analyzing dozens of signals in thousands of participants for associations with CVD risk could be efficiently repurposed by examining other OSA comorbidities, which may associate with different signals. Robust predictors of CVD or other comorbidities that generalize to diverse samples may provide some insight on pathophysiology, such as the relative importance of hypoxemia versus arousals, which may differ by disease.

The analyses by Sutherland and colleagues demonstrate a path forward for extracting and applying more meaningful information from the PSG that holds promise for advancing clinically important research in the future.

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