SLEEP, 2022, 1–2

https://doi.org/10.1093/sleep/zsac174
Advance Access Publication Date: 22 July 2022
Editorial

EDITORIAL

Understanding stability of obstructive sleep apnea endotypes: a step forward

Ulysses J. Magalang[1,*] and Brydon J. B. Grant[2,3]

[1]Division of Pulmonary, Critical Care, and Sleep Medicine, The Ohio State University Wexner Medical Center, Columbus, OH, USA, [2]Division of Pulmonary, Critical Care, and Sleep Medicine and Department of Epidemiology and Environmental Health, University at Buffalo, Buffalo, NY, USA and [3]Public Health Graduate Studies, Baha'i Institute for Higher Education, Iran

*Corresponding author. Ulysses J. Magalang, Division of Pulmonary, Critical Care, and Sleep Medicine, The Ohio State University Wexner Medical Center, 241 West 11th Avenue, Columbus, OH 43201, USA. Email: ulysses.magalang@osumc.edu.

Obesity and certain craniofacial features are known anatomic risk factors for obstructive sleep apnea (OSA) [1–3]. Prior studies also show that several physiological traits (termed endotypes) contribute to the development of the repetitive upper airway obstructions during sleep that characterizes OSA [4]. Four major OSA physiological traits have been identified—increased pharyngeal collapsibility, reduced upper airway dilator muscle compensation, high loop gain, and low arousal threshold [4, 5]. The OSA endotypes have been proposed to guide novel individualized alternative therapies to positive airway pressure for OSA. For example, medications that improve upper airway muscle activity have been used in OSA individuals with low upper airway muscle compensation [6], drugs that increase the respiratory arousal threshold have been tried in those with low arousal threshold [7], and oxygen therapy has been used to decrease ventilatory instability in those with high loop gain [8].

Initially, measurements of the OSA endotypes involved invasive instrumentation not routinely performed during polysomnography [4, 5]. Since then, noninvasive methods to estimate measures of the different physiologic traits have been developed using signals routinely collected during clinical polysomnography [9–11].

Unless these endotypes are shown to be stable throughout the night and reproducible over a period of time, individualized OSA treatment using these endotypes is unlikely to be successful. In this issue of the journal, *Alex et al.* have taken this important step towards the clinical utility of the noninvasive endotype measurements [12]. Using cross-sectional data from the Multi-Ethnic Study of Atherosclerosis (n = 1750), the authors evaluated the within-night repeatability of the physiological endotypes by comparing the estimates obtained between odd and even 30-min periods across the night; data were aggregated to yield two independent measures per individual. The authors also assessed long-term consistency of the physiologic measurements using data from the Osteoporotic Fractures in Men Study (MrOS) at two-time points 6.5 ± 0.7 years apart (n = 595), before and after accounting for body position and sleep state differences. In both datasets, they calculated the Pearson correlation coefficient (R), coefficient of repeatability (CR), and intraclass correlation coefficient (ICC). The CR, also known as the smallest real difference, is closely related to the 95% limits of agreement proposed by Bland and Altman [13]. The authors also categorized the endotypes into both low versus high and low, medium, and high levels. This approach enables an assessment of the level of agreement of the endotypes between categories, which is most important, as decisions about endotype-guided OSA treatments will rely heavily on the stability of the high/low categories.

To understand the results of the recent article, it is crucial to define the metrics being evaluated. *Repeatability* is a measure of precision: how close measurements of the same quantity are to each other. Repeatability is similar to *reliability*, which is the ability to replicate measurements in a consistent manner. *Agreement* occurs when two measurements lie close to a line of identity over a wide range; that is, two measurements have the exact same value. *Consistency* occurs when the measurements follow a linear relation over a range of measurements, but that relation does not follow the line of identity (eg, the measurements are related, but not

© The Author(s) 2022. Published by Oxford University Press on behalf of Sleep Research Society. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com

Downloaded from https://academic.oup.com/sleep/article/45/9/zsac174/6648763 by guest on 09 September 2022

necessarily identical). While agreement is preferable, consistency still has utility because adjustments may be made for underlying biases (e.g. changes in sleep stage and body position). *Pearson's correlation coefficient* tests the linearity between two measurements assuming a normal distribution and uniformity of variance across the range of measurement. Pearson's correlation coefficient does not assess the level of agreement between two measurements. The ICC can provide more insight into the agreement, as it will be further reduced if mean values differ between measurements (whereas Pearson's correlations are independent of mean values). Ultimately, CR and analyses described by Bland and Altman are needed to precisely define agreement between two measurements.

With this context, the results of the work by Alex et al. ultimately support reasonable within-night repeatability and modest long-term consistency of the endotypes. When the recommended amounts of data were available, within-night repeatability was similar for collapsibility, loop gain, and arousal threshold ($R = 0.79–0.83$), but lower for muscle compensation ($R = 0.69$). Importantly, the percentage of individuals who were classified in the same endotype category (low vs. high) in the second measurement as they were in the first ranged from 70% to 79%. All measurements showed lower within-night repeatability than the apnea-hypopnea index (AHI). Long-term consistency of the endotypes was modest ($R = 0.36–0.63$) after accounting for position and sleep state differences. The percentage of individuals who were classified in the same category (low vs. high) at the second time point as they were in the first ranged from 59% to 72%. The consistency of the endotypic measurements across years were comparable with that of the AHI.

While the work by *Alex* et al. is extremely thorough and is a step forward towards the clinical use of OSA endotypes, several unresolved issues remain. The current results tell us that while the within-night repeatability of the endotypes appears reasonable, the long-term consistency is less stellar. In determining the within-night repeatability, the process of aggregating data within each individual likely reduced the variability of the measurements, leading to higher estimates of repeatability. A shorter period between repeat measurements (rather than years) would have provided an evaluation of consistency that is more clinically relevant; this may not require a large number of participants as in the current study. Finally, the results comparing low versus high categorizations tell us that 21%–30% of individuals will not be classified in the same category within the night and 28%–41% will not be classified in the same category with repeat measurements after several years (even after accounting for some biases). These levels of misclassification appear too great to provide sufficient confidence about utilizing endotypes derived from the current noninvasive methodology for individualized treatment of OSA. Thus, while the authors are commended for taking an important step forward, we have not yet reached the point of clinical translation.

Funding

None.

Disclosure Statement

The authors have no conflicts of interest in regard to the subject matter of this editorial.

References

1. Lim DC, *et al*. Obstructive sleep apnea: update and future. *Annu Rev Med*. 2017;**68**:99–112. doi: 10.1146/annurev-med-042915-102623.
2. Wang SH, *et al*. Effect of weight loss on upper airway anatomy and the apnea-hypopnea indeX. The importance of tongue fat. *Am J Respir Crit Care Med*. 2020;**201**(6):718–727. doi: 10.1164/rccm.201903-0692OC.
3. Sutherland K, *et al*. Facial phenotyping by quantitative photography reflects craniofacial morphology measured on magnetic resonance imaging in Icelandic sleep apnea patients. *Sleep*. 2014;**37**(5):959–968. doi: 10.5665/sleep.3670.
4. Wellman A, *et al*. A method for measuring and modeling the physiological traits causing obstructive sleep apnea. *J Appl Physiol*. 2011;**110**(6):1627–1637. doi: 10.1152/japplphysiol.00972.2010.
5. Wellman A, *et al*. A simplified method for determining phenotypic traits in patients with obstructive sleep apnea. *J Appl Physiol*. 2013;**114**(7):911–922. doi: 10.1152/japplphysiol.00747.2012.
6. Taranto-Montemurro L, *et al*. Desipramine improves upper airway collapsibility and reduces OSA severity in patients with minimal muscle compensation. *Eur Respir J*. 2016;**48**(5):1340–1350. doi: 10.1183/13993003.00823-2016.
7. Eckert DJ, *et al*. Eszopiclone increases the respiratory arousal threshold and lowers the apnoea/hypopnoea index in obstructive sleep apnoea patients with a low arousal threshold. *Clin Sci (Lond)*. 2011;**120**(12):505–514. doi: 10.1042/CS20100588.
8. Wellman A, *et al*. Effect of oxygen in obstructive sleep apnea: role of loop gain. *Respir Physiol Neurobiol* 2008;**162**(2):144–151. doi: 10.1016/j.resp.2008.05.019.
9. Sands SA, *et al*. Phenotyping pharyngeal pathophysiology using polysomnography in patients with obstructive sleep apnea. *Am J Respir Crit Care Med*. 2018;**197**(9):1187–1197. doi: 10.1164/rccm.201707-1435OC.
10. Sands SA, *et al*. Quantifying the arousal threshold using polysomnography in obstructive sleep apnea. *Sleep*. 2018;**41**(1). doi: 10.1093/sleep/zsx183.
11. Terrill PI, *et al*. Quantifying the ventilatory control contribution to sleep apnoea using polysomnography. *Eur Respir J*. 2015;**45**(2):408–418. doi: 10.1183/09031936.00062914.
12. Alex RM, *et al*. Within-night repeatability and long-term consistency of sleep apnea endotypes: the multi-ethnic study of atherosclerosis and osteoporotic fractures in men studY. *Sleep*. 2022. doi: 10.1093/sleep/zsac129.
13. Vaz S, *et al*. The case for using the repeatability coefficient when calculating test-retest reliability. *PLoS One*. 2013;**8**(9):e73990. doi: 10.1371/journal.pone.0073990.

Downloaded from https://academic.oup.com/sleep/article/45/9/zsac174/6648763 by guest on 09 September 2022