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References

1. GBD 2015 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;388:1659–1724.
2. Cohen AJ, Brauer M, Burnett R, Anderson HR, Frostad J, Estep K, *et al*. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *Lancet* 2017;389: 1907–1918.
3. McCracken JP, Wellenius GA, Bloomfield GS, Brook RD, Tolunay HE, Dockery DW, *et al*. Household air pollution from solid fuel use: evidence for links to CVD. *Glob Heart* 2012;7:223–234.
4. Fullerton DG, Semple S, Kalambo F, Suseno A, Malamba R, Henderson G, *et al*. Biomass fuel use and indoor air pollution in homes in Malawi. *Occup Environ Med* 2009;66:777–783.
5. Kirwa K, Agarwal A, Bloomfield GS, Alenezi F, Eliot MN, Carter EJ, *et al*. Household air pollution from burning wood is associated with altered cardiac hemodynamics and function among women in western Kenya: results from the Kenya HAP study. Herndon, VA: International Society for Environmental Epidemiology; 2015 [accessed 2017 May 1]. Available from: https://ehp.niehs.nih.gov/isee/2015-2522/.
6. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, *et al*. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010;23:685–713.
7. Burroughs Peña MS, Velazquez EJ, Rivera JD, Alenezi F, Wong C, Grigsby M, *et al*. Biomass fuel smoke exposure was associated with adverse cardiac remodeling and left ventricular dysfunction in Peru. *Indoor Air* 2017;27:737–745.
8. Penney D, Benignus V, Kephalopoulos S, Kotzias D, Kleinman M, Verrier A. WHO guidelines for indoor air quality: selected pollutants. Geneva: World Health Organization; 2010;55–89 [accessed 2017 May 1]. Available from: http://www.euro.who.int/__data/assets/pdf_file/0009/128169/e94535.pdf
9. Mitter SS, Vedanthan R, Islami F, Pourshams A, Khademi H, Kamangar F, *et al*. Household fuel use and cardiovascular disease mortality: Golestan Cohort Study. *Circulation* 2016;133:2360–2369.
10. Klasen EM, Wills B, Naithani N, Gilman RH, Tielsch JM, Chiang M, *et al*; COCINAS Trial Working Group. Low correlation between household carbon monoxide and particulate matter concentrations from biomass-related pollution in three resource-poor settings. *Environ Res* 2015;142:424–431.
11. Allred EN, Bleecker ER, Chaitman BR, Dahms TE, Gottlieb SO, Hackney JD, *et al*. Short-term effects of carbon monoxide exposure on the exercise performance of subjects with coronary artery disease. *N Engl J Med* 1989;321:1426–1432.
12. Stewart S, Wilkinson D, Hansen C, Vaghela V, Mvungi R, McMurray J, *et al*. Predominance of heart failure in the Heart of Soweto Study cohort: emerging challenges for urban African communities. *Circulation* 2008;118:2360–2367.
13. Carter E, Norris C, Dionisio KL, Balakrishnan K, Checkley W, Clark ML, *et al*. Assessing exposure to household air pollution: a systematic review and pooled analysis of carbon monoxide as a surrogate measure of particulate matter. *Environ Health Perspect* 2017; 125:076002.
14. Alexander D, Northcross A, Wilson N, Dutta A, Pandya R, Ibigbami T, *et al*. Randomized controlled ethanol cookstove intervention and blood pressure in pregnant Nigerian women. *Am J Respir Crit Care Med* 2017;195:1629–1639.

The Epworth Sleepiness Scale: Minimum Clinically Important Difference in Obstructive Sleep Apnea

To the Editor:

The Epworth Sleepiness Scale (ESS) is a self-administered questionnaire that quantifies daytime sleepiness, with higher scores indicating increased daytime hypersomnolence (1). Although it is frequently used as an endpoint in intervention trials of patients with obstructive sleep apnea syndrome (2, 3), the minimum clinically important difference (MCID) of the ESS has not been established.

In a prospective service evaluation of 125 consecutive patients with obstructive sleep apnea syndrome (apnea–hypopnea index [4], or $\geq$4% oxygen desaturation index, $>$7.5 events/h, and symptoms of daytime tiredness and hypersomnolence) offered continuous positive airway pressure (CPAP), ESS was measured at baseline and follow-up (3-months post-CPAP initiation). At follow-up, patients were asked, "Compared with your last visit (before treatment), how would you describe the change in your daytime sleepiness?" Responses were recorded using a seven-point Likert global rating of change in sleepiness questionnaire ("1: Much less sleepy" to "7: Much more sleepy," with "4: No change") (5).

Distribution- and anchor-based methods were used to estimate the MCID of the ESS. For distribution-based methods, we calculated half the SD (0.5SD) (6) and the SE of measurement (7), using the equation:

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SE of measurement = SD $\times \sqrt{1 - (\text{test–retest reliability})}$. Based on previous data, we assumed the test–retest reliability of the ESS to be 0.82 (8). For anchor-based methods, we estimated the MCID to be the mean change in ESS with CPAP for those reporting feeling "3: Little less sleepy." Receiver operating characteristic curves were plotted to determine the ESS change cutoff that best discriminated between those who did or did not report at least a little improvement in sleepiness (global rating of change in sleepiness questionnaire responses 1–3 vs. 4–7), with equal weighting given to sensitivity and specificity (9).

Ninety-nine of 125 patients receiving CPAP returned for follow-up. Baseline characteristics were as follows: 66 men (67%); age [mean (SD)], 55 (12) years; body mass index, 33.8 (7.5) kg/m^2; neck circumference, 43 (12) cm; ESS, 12.7 (5.3); apnea–hypopnea index, 28.9 (23.4); oxygen desaturation index, 28.1 (22.3); and median Mallampati score, 3 (interquartile range, 2–3).

With CPAP, mean change in ESS was −4.5 (95% confidence interval, −5.6 to −3.5), with a mean (SD) self-reported compliance of 4.5 (2.8) hours. Of the participants, 39% reported feeling "much less sleepy," 14% "moderately less sleepy," 13% "little less sleepy," 31% "no change," and 2% "little more sleepy." No patients reported feeling "moderately more sleepy" or "much more sleepy." There was a significant correlation between self-reported CPAP compliance and change in ESS (Spearman rank rho, −0.46; $P < 0.0001$).

Using distribution-based methods, the MCID of the ESS was estimated as −2.65, using 0.5 × SD, and −2.21, using the SE of measurement assuming a test–retest reliability of 0.82. For the anchor-based methods, the mean (SD) change in ESS for those reporting "little less sleepy" was −2.5 (2.1) (Figure 1).

An ESS change of −2 had an area under curve of 0.93 (sensitivity, 91%; specificity, 88%) in identifying those who scored at least feeling "little less sleepy" (Figure 2). An ESS change of −3 had a sensitivity of 80% and specificity of 88%, and an ESS change of −1 had a sensitivity of 94% and specificity of 74%. Assuming the MCID lies somewhere between −2 and −3, responder analysis showed that 58–65% of our cohort noticed clinical improvements in daytime sleepiness after 3 months of CPAP treatment. This is in line with the results of recent randomized controlled trials of CPAP therapy (3).

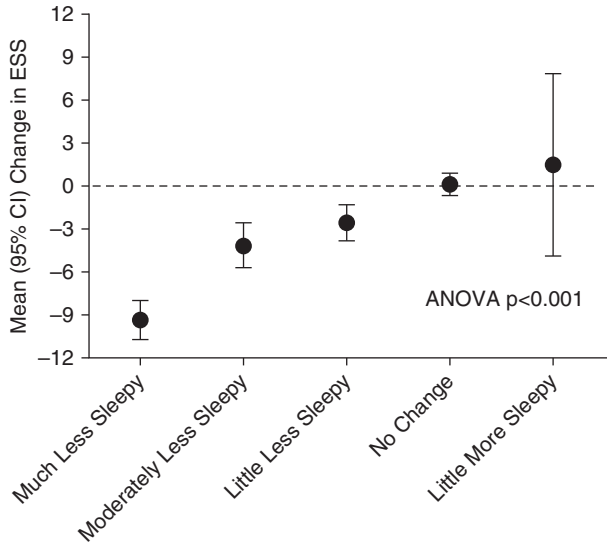

Figure 1. Mean (95% confidence intervals [CIs]) change in Epworth Sleepiness Scale (ESS) according to response to the global rating of change in Sleepiness questionnaire. No patient reported feeling moderately or much more sleepy.

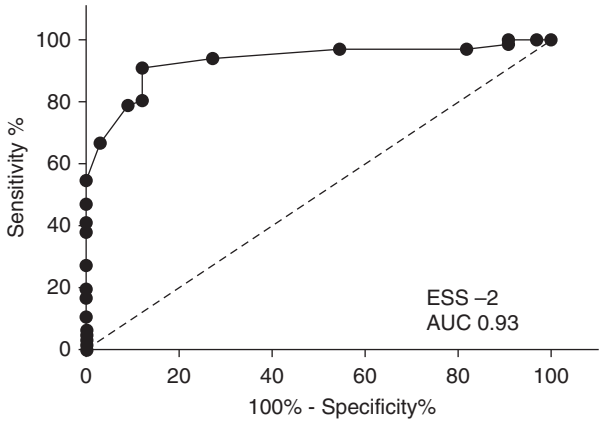

Figure 2. A receiver operating characteristic plot with sensitivity (*y*-axis) plotted against 100% − specificity% (*x*-axis), demonstrating the predictive value of the Epworth Sleepiness Scale (ESS) change in identifying patients who reported at least a little improvement in sleepiness. An ESS change of −2 had an area under the curve (AUC) of 0.93, sensitivity of 81%, and specificity of 88%.

The MCID represents the smallest change considered beneficial or detrimental, and it is useful in interpreting an outcome measure, as it is recognized that not all statistically significant changes are clinically important. Furthermore, the MCID is useful in determining sample size for clinical trials. The determination of the MCID remains controversial with no consensus on methodology (9). Our study used both distribution- and anchor-based methods, with consistent estimates of the MCID irrespective of methodology, providing a degree of reassurance about the validity.

Limitations of our study are that we did not use a validated subjective or objective measure of daytime sleepiness or quality of life as an anchor, as these were not used routinely in our unit's clinical practice. However, we used a global rating of change questionnaire, which is considered an acceptable anchor for determining the MCID of questionnaires in obstructive sleep apnea syndrome and other disorders (5, 9–11). Second, few patients reported deterioration in their daytime sleepiness; hence, our data estimate the minimum clinically important improvement rather than the true MCID of the ESS. Further studies are required to corroborate our data and assess whether patients perceive size of deterioration different to size of improvement in the ESS.

In summary, using distribution- and anchor-based methods, we estimate the minimum clinically important improvement of the ESS to lie between −2 and −3. ■

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References

1. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14:540–545.
2. Giles TL, Lasserson TJ, Smith BH, White J, Wright J, Cates CJ. Continuous positive airways pressure for obstructive sleep apnoea in adults. *Cochrane Database Syst Rev* 2006;(3): CD001106.
3. McMillan A, Bratton DJ, Faria R, Laskawiec-Szkonter M, Griffin S, Davies RJ, *et al*. A multicentre randomised controlled trial and economic evaluation of continuous positive airway pressure for the treatment of obstructive sleep apnoea syndrome in older people: PREDICT. *Health Technol Assess* 2015;19:1–188.
4. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, *et al*. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine.*J Clin Sleep Med* 2012;8:597–619.
5. Fischer D, Stewart AL, Bloch DA, Lorig K, Laurent D, Holman H. Capturing the patient's view of change as a clinical outcome measure. *JAMA* 1999;282:1157–1162.
6. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care* 2003;41:582–592.
7. Wyrwich KW, Tierney WM, Wolinsky FD. Further evidence supporting an SEM-based criterion for identifying meaningful intra-individual changes in health-related quality of life. *J Clin Epidemiol* 1999;52: 861–873.
8. Kendzerska TB, Smith PM, Brignardello-Petersen R, Leung RS, Tomlinson GA. Evaluation of the measurement properties of the Epworth sleepiness scale: a systematic review. *Sleep Med Rev* 2014;18:321–331.
9. Kon SS, Canavan JL, Jones SE, Nolan CM, Clark AL, Dickson MJ, *et al*. Minimum clinically important difference for the COPD Assessment Test: a prospective analysis. *Lancet Respir Med* 2014;2:195–203.
10. Copay AG, Subach BR, Glassman SD, Polly DW Jr, Schuler TC. Understanding the minimum clinically important difference: a review of concepts and methods. *Spine J* 2007;7:541–546.
11. Lacasse Y, Godbout C, Sériès F. Independent validation of the Sleep Apnoea Quality of Life Index. *Thorax* 2002;57:483–488.

Spirometry-based Diagnostic Criteria That Are Not Age-Appropriate Lack Clinical Relevance

To the Editor:

To have broad generalizability in clinical practice, it is imperative that spirometry-based diagnostic criteria are age-appropriate across the continuum of lung function. Despite advances in developing age-appropriate criteria for defining normal spirometry and spirometry-confirmed respiratory disease (1, 2), clinical research continues to use the seriously flawed fixed ratio for FEV_1/FVC and the seriously limited percentage predicted (%Pred) for FEV_1 (3).

We therefore raise concerns regarding an article by Tejero and colleagues (3), which included a study sample aged 40 years or older and a diagnosis of airflow limitation based on a dual threshold for FEV_1/FVC of <0.70 and below the lower limit of normal (LLN). This approach is highly problematic when applied across the continuum of lung function and across the lifespan. For example, the dual threshold will underdiagnose airflow limitation in persons younger than 45–50 years (as the FEV_1/FVC can be <LLN but >0.70) and will lead to an indeterminate spirometric classification in persons older than 45–50 years (as many will have an FEV_1/FVC <0.70 but $\geq$LLN) (1, 2). Notably, the inclusion of a fixed-ratio threshold of 0.70 for FEV_1/FVC also precludes the establishment of an age-appropriate definition of normal spirometry that would be uniformly applicable across the lifespan (4).

Tejero and colleagues (3) also defined chronic obstructive pulmonary disease (COPD) severity based on %Pred thresholds for FEV_1 that do not apply across the lifespan. This is because %Pred assumes incorrectly that a given value is equivalently low or high for all persons (5). To illustrate the effect of age in a white male of average height, a given value of 80%Pred for FEV_1 will correspond to the sixth and 14th percentile distribution of the reference population at ages 40 and 70 years, respectively (5). Stated differently, at a given percentile distribution (e.g., fifth percentile [LLN]), the %Pred value for FEV_1 will decrease with advancing age (1, 2, 4–6). Given these limitations, Tejero and colleagues may have overestimated the relative risk for death when using $FEV_{1\%}$Pred thresholds for at least two reasons. First, the reference group of mild COPD, which was the basis for calculating relative risk, was likely younger (and healthier) when defined by FEV_1 $\geq$70–80%Pred. Second, the comparison groups of severe and very severe COPD were likely older (and less healthy) when defined by FEV_1 <50%Pred. Importantly, prior work has shown that defining COPD severity based on %Pred for FEV_1 (with or without

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