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**Title:** COPD Comorbidity Network: Connecting the dots

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**Body:** Comorbidities are frequent in COPD and a known subset of them influences mortality. However, the relations between them are poorly understood. In this study, we describe the COPD comorbidity network in the BODE cohort by exploring co-occurrence clusters using system network graphic analysis. Methods: We included 1659 COPD subjects and comorbidities were recorded systematically. Spearman's coefficient were calculated between comorbidities, and those with significant correlation ( $p < .05$ ) were selected to construct the network: each comorbidity is represented by a node, the size of which relates their prevalence. The edges represent a paired correlation, and the thickness of the edge its strength, which is proportional to  $\rho$  (rho). We calculated the relation between comorbidity connections and prevalence, and also explored the mathematical unbiased clustering of correlated diseases. Results: The network is composed of 79 comorbidities with prevalence ranging from 0.5 to 52% and 568 edges. We found a quadratic relation between prevalence and degree of connection =  $7.5 + 160.3 \cdot \text{prev} - 324.0 \cdot (\text{prev} - 0.06)^2$ ,  $R^2 = 0.75$  ( $p < .0001$ ). Three modules were identified: behavioral/substance abuse, lung cancer and cardiovascular/metabolic modules

**Conclusion:** Certain COPD comorbidities are interconnected and the degree of connection follow a quadratic pattern with their prevalence. In this complex network, particular motifs were identified perhaps amenable to specific interventions.