Prevalence of cardiac comorbidities, and their underdetection and contribution to exertional symptoms in COPD: Results from the COSYCONET cohort

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Supplementary Methods

We used data of the baseline visit (enrollment) of the German COPD cohort COSYCONET (*COPD and Systemic Consequences - Comorbidities Network*), a prospective, multi-center cohort study in patients with stable COPD of spirometric GOLD grades 0 to 4.[1-3]

For the present analysis, we excluded patients with more than moderate heart valve disease, heart valve replacement, or other cardiac devices such as pacemakers/cardioverter-defibrillators. The reason for this was to focus on lung-heart interactions and thus to exclude patients with major primary cardiac disease, that is associated with strong effects on heart function, rendering it more difficult to detect influences of lung function on cardiac parameters. The analysis was restricted to patients with full and plausible echocardiographic and spirometric data, as well as the cardiac history and medication. Details of the selection process are mentioned elsewhere.[4] The association analysis was further restricted to patients with complete data of bodyplethysmographic parameters and carbon monoxide (CO) diffusing capacity, as well as the SGRQ, CAT™ and mMRC questionnaire.

In COSYCONET, medical history and the presence of all medication were assessed by detailed questionnaires and standard procedures.[1] For the present analysis, we used the patients' reports of doctors' diagnoses of ischemic heart disease, myocardial infarction and heart failure. Medication was categorized according to ATC codes (Anatomical Therapeutic Chemical Classification System) as done previously.[5]

Data analysis

In the association cohort, we used multiple linear and logistic regression analyses to examine relationships between lung function, echocardiographic parameters, medical history, medication and COPD symptoms in terms of the three questionnaires mentioned above. All regression analyses were performed with age, sex and body mass index (BMI) as covariates; further covariates turned out to be unnecessary (insignificant) for the variables analyzed. A multitude of relations became apparent. For the sake of brevity, the results are not shown, but they were used as starting point to employ structural equation modelling (SEM) for the identification of multiple, intricate relationships.[4,6,7]

We built the model (SEM) in several steps, following the principle of parsimony and using the hints given by the regressions analyses as well as clinical/pathophysiological plausibility considerations. For a more clear visualization, the statistically mandatory but uninformative error terms of dependent variables, as well as the correlations (undirected relationships) between some variables are not shown in Figure 4.

Supplementary Discussion 1

The regression analyses revealed a multitude of relationships, both among the predictors and to the symptoms. In order to obtain a parsimonious, understandable description of these relationships, taking into account direct and indirect links between them, we used the statistical technique of structural equation modelling (SEM), which we had employed previously in several analyses of COSYCONET data.[4,6-8] This requires a careful selection of the most informative variables in order to avoid redundancy, ill-defined and non-robust relationships, and unnecessary complications. If the redundancy is high, the respective variables can be collected into a common, latent variable. This turned out to be adequate for mMRC and the activity component of the SGRQ, due to their high correlation and the fact that they had a common set of predictors. Thus, they were practically equivalent within the context of the present analysis. Noteworthy enough, this was not appropriate for the three lung function variables, which were highly correlated with each other but showed specific sets of variables to which they were

linked in the regression analyses; this was also reflected in the SEM (Figure 4). These relationships would have been obscured by the use of a latent variable, in contrast to a previous analysis, in which lung function variables indeed could be comprised into such a latent variable [4]. This underlines the fact that, depending on the measures chosen to be dependent, lung function can have parallel or different effects.

Supplementary Discussion 2

It appears plausible that cardiac history was associated with both LVEDD and LVEF, taken as continuous variables without cut-off in the SEM. Cardiovascular medication had no separate, additional effect on these measures, probably owing to its high correlation with history. History had a direct effect on symptoms, which was smaller than the combined direct effects from lung function and about as large as that of RV/TLC (see standardized estimates in Figure 4 and Supplemental Table 1). Medication had a small additional effect, possibly reflecting the severity of the cardiac disorder and the fact that we had patients with medication but not a report. This finding underlines that it might be of advantage to include comorbidities into the analysis in terms of both patients' reports and specific medication.[5] In the present analysis, however, we took the history as reported and did not include medication in order to separate their contributions.

Supplementary Discussion 3

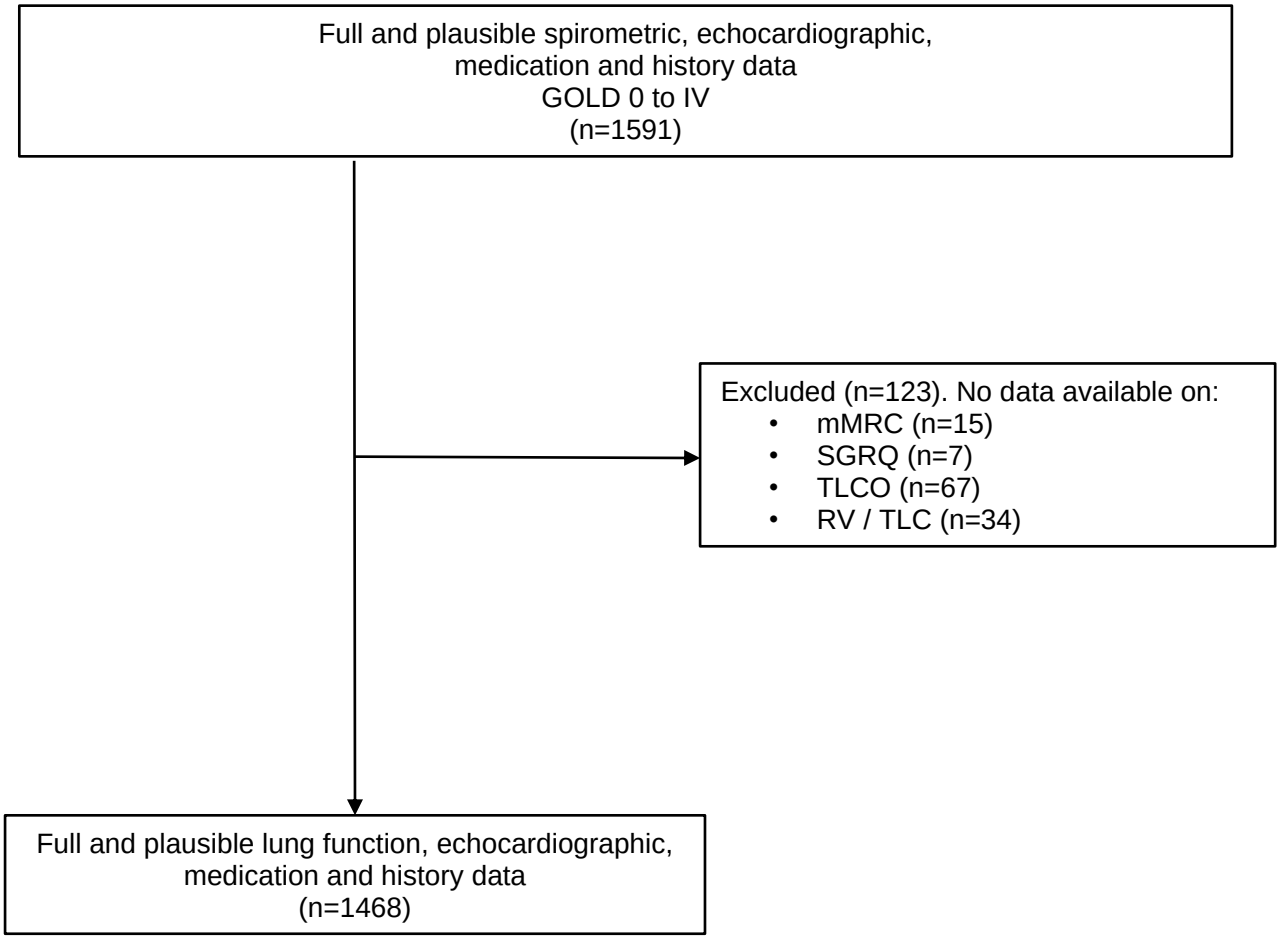
We omitted the CAT score as well as the SGRQ impact and symptoms components from our analysis, as they not did not fit well into the model or contribute additional information that could be clearly and robustly associated with other variables, especially the cardiac ones. The SGRQ components were not equivalent to each other, but the activity component and mMRC. When trying to understand this result, we especially found that the CAT comprised more than one statistical components, one of them represented by the first two questions, which appear to address chronic bronchitis. However, when omitting these two questions and using the remaining six questions for a reduced CAT score, it still did not fit well into the SEM model with

cardiac parameters, probably because the CAT covers a rather heterogeneous range of symptoms. Conversely, our findings suggest that among the standardized COPD scores the mMRC and the SGRQ activity component confer the highest chance to get a hint on a concomitant cardiac disorder.

Limitations

It is an inherent limitation of the cross-sectional design that causality cannot be demonstrated. Nevertheless, the SEM approach employed by us allows some inferences on this, particularly by reversing the direction of the arrows. It always turned out that this led to a worse fit and/or loss of statistical significance. A further possible objection is that the association cohort was not identical with the total description cohort. However, the differences were small and explained by the lack of data regarding bodyplethysmography and diffusing capacity, which is plausible since in some patients with severe disease both examinations are sometimes not feasible. Moreover, since the SEM findings were derived from a cohort with slightly less severe COPD, this strengthens our findings. When repeating the SEM without RV/TLC and TLCO in the description cohort, the same structure for all remaining variables was found. This indicates that the loss of some patients did not induce a relevant bias. The strength of our study is the large sample size and the application of a statistical procedure that allows to derive the most compact, parsimonious description of the multiple associations between the variables, particularly regarding the echocardiographic measures and COPD symptoms. One could further argue that the examined subset of 1591 patients of the total COSYCONET cohort of 2741 patients conferred the risk of a selection bias. However, except for a less increased RV/TLC ratio, lung function parameters did not differ among this and the complementary group omitted from the 2741 patients. Reports on ischemic heart disease, heart failure and the presence of cardiovascular medication were less frequent in the selected, which argues against a selection bias towards a higher disease severity in the examined cohort. We cannot exclude the possibility that in the total cohort the associations would be even stronger than in the cohort which we analyzed.

Supplementary Figure 1.



Flow chart showing the selection process of the participants included in the analysis.

Supplementary Table 1. Results of the structural equation model (SEM), n = 1468

Regression weights

Directed Relationships			Estimate	Standardized Estimate	S.E.	C.R.	p value
LVEDD	←	RV/TLC	-5.251	-0.087	1.575	-3.334	<0.001
LVEDD	←	History	0.861	0.053	0.426	2.023	0.043
Exertional COPD symptoms	←	FEV_1	-0.334	-0.305	0.044	-7.624	<0.001
Exertional COPD symptoms	←	TLCO	-0.244	-0.243	0.029	-8.294	<0.001
Exertional COPD symptoms	←	RV/TLC	31.514	0.149	7.597	4.148	<0.001
Exertional COPD symptoms	←	History	6.945	0.122	1.406	4.939	<0.001
Exertional COPD symptoms	←	Medication	2.709	0.058	1.159	2.337	0.019
Exertional COPD symptoms	←	LVEDD	-0.274	-0.078	0.084	-3.251	0.001
LVEF	←	FEV_1	0.039	0.089	0.011	3.443	<0.001
LVEF	←	History	-2.98	-0.131	0.588	-5.066	<0.001
SGRQ activity	←	Exertional COPD symptoms	1	0.87			
mMRC	←	Exertional COPD symptoms	0.031	0.765	0.001	22.674	<0.001

Covariances

Undirected Relationships			Estimate	Correlations	S.E.	C.R.	p value
FEV1	↔	TLCO	234.558	0.559	12.75	18.396	<0.001
FEV2	↔	RV/TLC	-1.474	-0.741	0.065	-22.526	<0.001
RV/TLC	↔	TLCO	-0.841	-0.387	0.062	-13.608	<0.001
History	↔	Medication	0.04	0.23	0.005	8.489	<0.001
LVEF	↔	LVEDD	-9.817	-0.19	1.378	-7.127	<0.001

Regression weights for the SEM in Figure 4. S.E. = standard error, C.R. = critical ratio (estimate/S.E.). p-value of the type-I error according to the Wald statistic. The estimates were derived by generalized least square estimation. FEV_1 and TLCO were evaluated as % predicted (GLI), and the dimensions of all variables are as in Table 1. “Exertional COPD symptoms” denotes a latent variable. FEV_1 = forced expiratory volume in 1 second; RV/TLC = residual volume to total lung capacity ratio; TLCO = transfer factor of carbon monoxide (CO); LVEF = and left ventricular ejection fraction; LVEDD = left ventricular enddiastolic diameter; mMRC = modified British Medical Research Council dyspnoea scale; SGQR activity = Saint Georges Respiratory Questionnaire activity component. The lower panel of the table shows the covariances and correlations that were introduced between related variables in order to improve the model fit. The covariance between LVEDD and LVEF refers to that between the respective error terms. For the sake of clarity these are not shown in Figure 4.

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