La fenotipizzazione della BPCO nell'anziano: nuovi risultati dello studio STORICO

Nicola Scichilone

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The phenotypes of COPD

Symptoms variability in COPD:

Does it really exist?

Does it really matter?

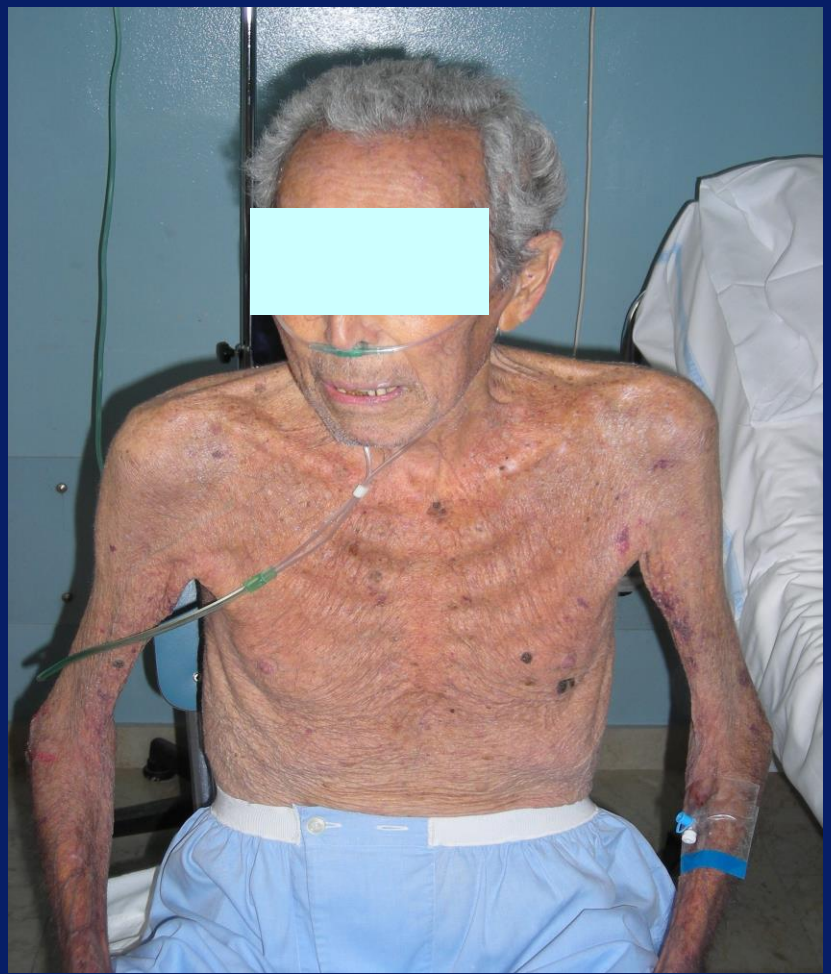
What do (and will) the studies teach us:

From ASSESS to STORICO

The different “natural histories” in COPD

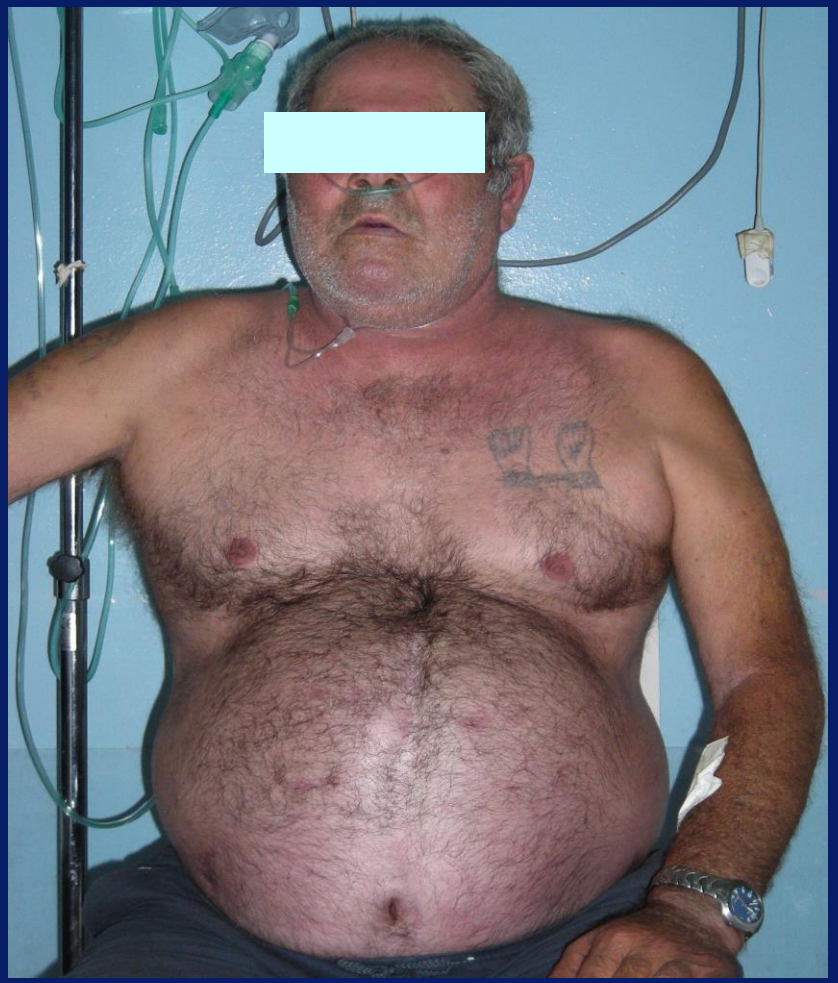
Emphysema

Type A or “pink puffer”

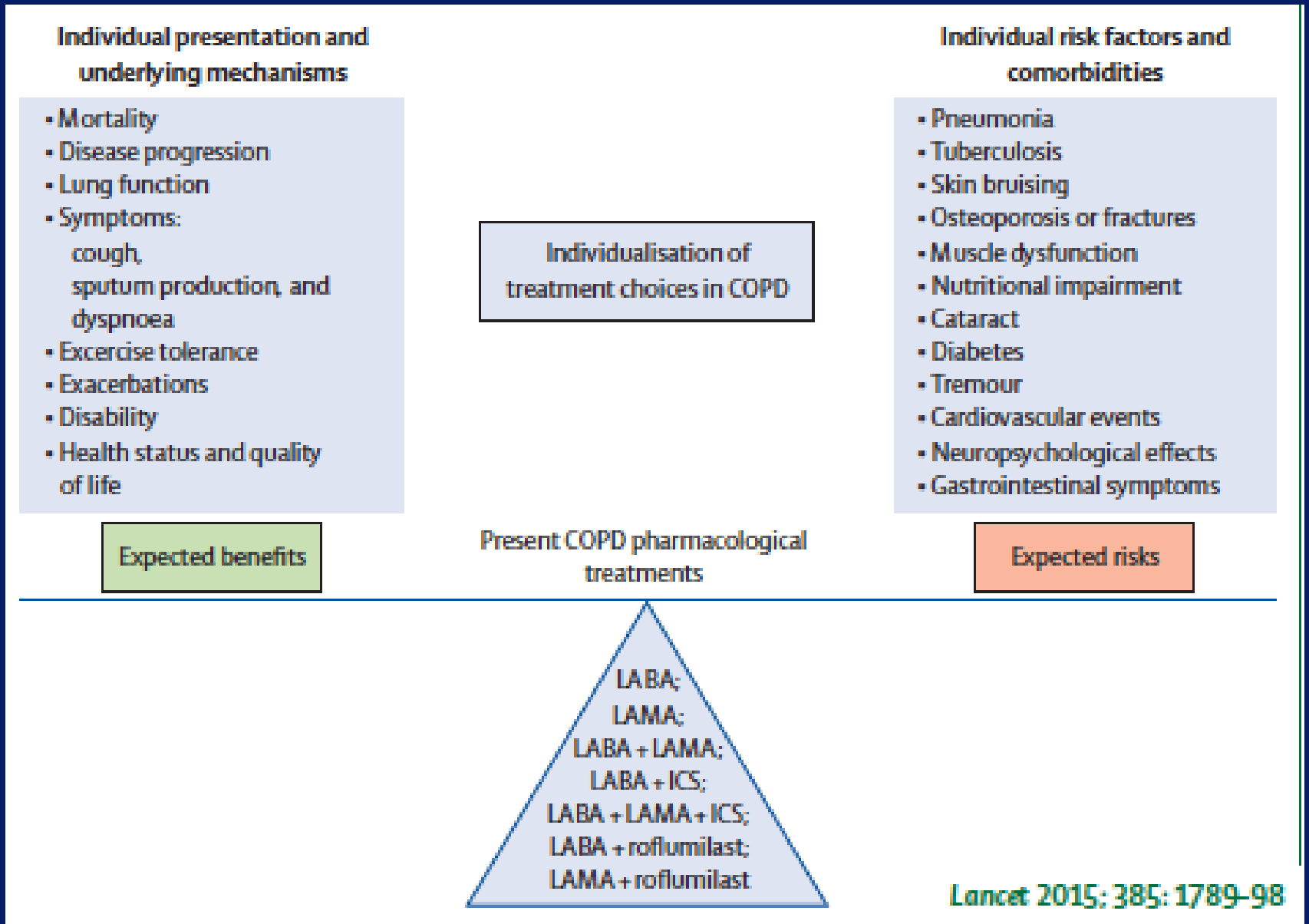


Chronic bronchitis

Type B or “blue bloater”



Current concepts in targeting COPD: making progress towards personalized management

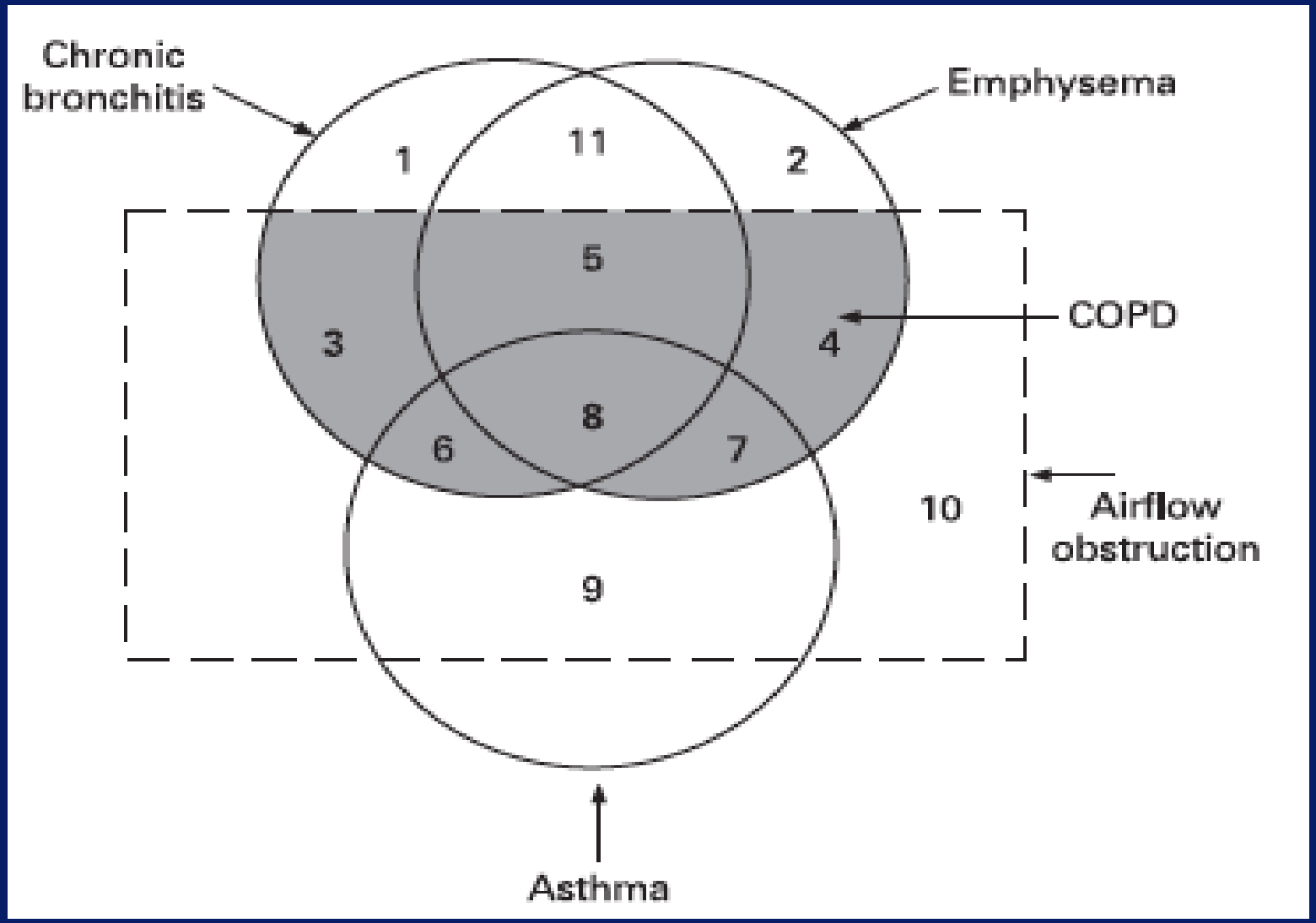


Lancet 2015; 385: 1789–98

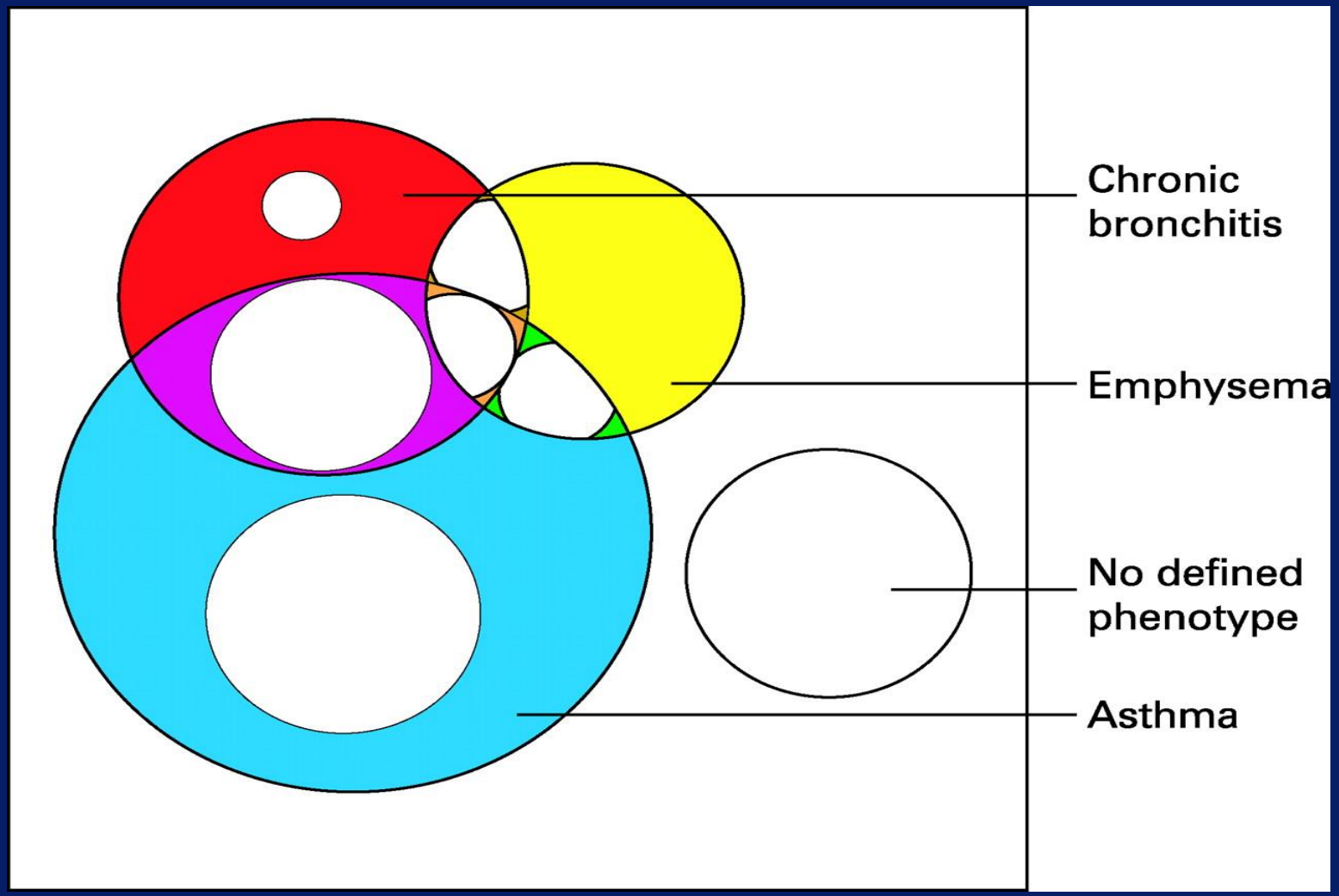
Why do we need a *precision* medicine approach to COPD?

- A complex common disease with difficult definition
- Heterogeneous presentation with different traits
- Variable disease and variable response to drugs
- Incomplete understanding of all phenotypes
- Greater insight into driving mechanisms
- Need for biomarkers

I fenotipi della BPCO: il passato...



...e il presente



Proportional Venn diagram presenting the different phenotypes within the Wellington Respiratory Survey study population.

Marsh et al. Thorax 2008

Eterogeneità dei fenotipi della BPCO

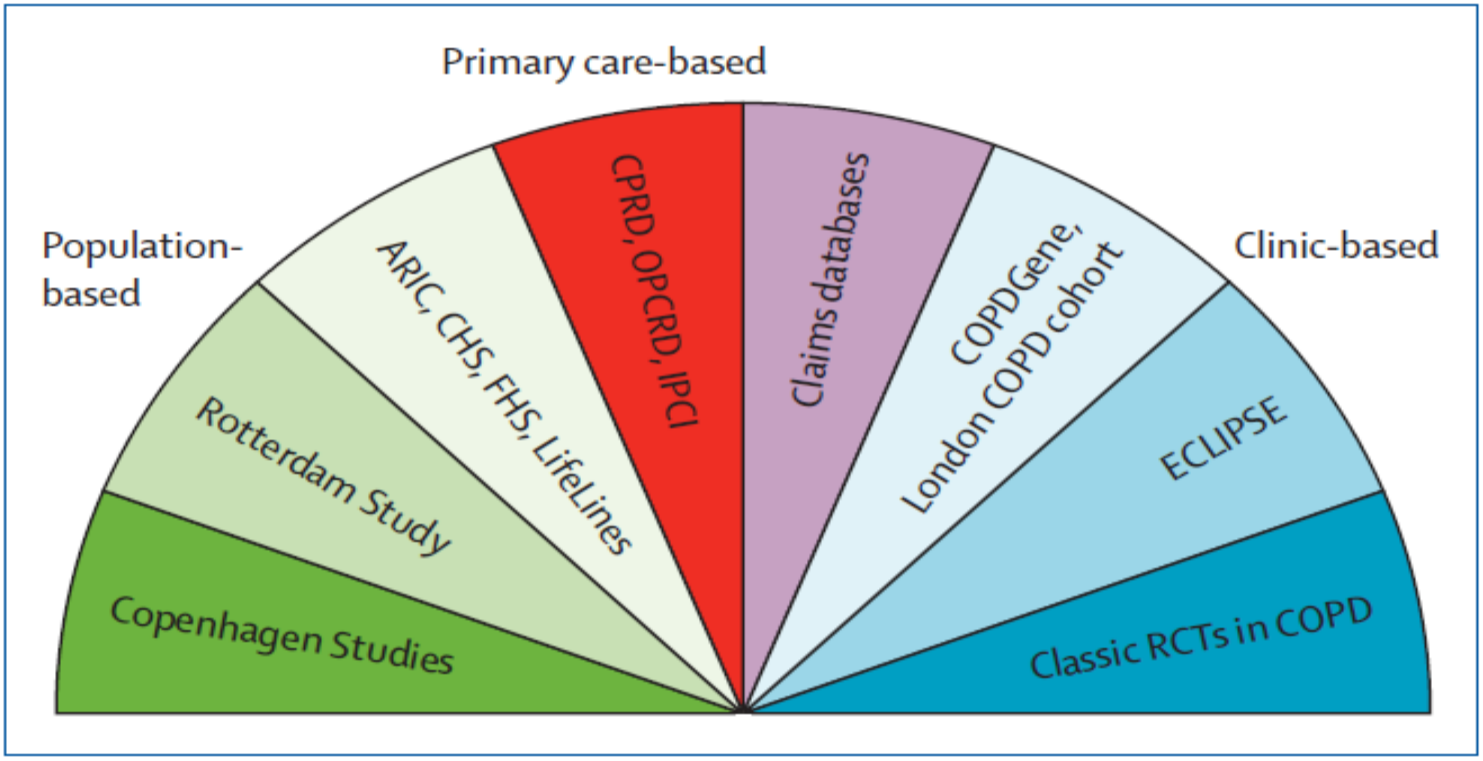


Figure: Examples of the heterogeneity of chronic obstructive pulmonary disease (COPD) cohort studies

Brusselle G., Lancet RM, 2014

The phenotypes of COPD

Symptoms variability in COPD:

Does it really exist?

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What do (and will) the studies teach us:

From ASSESS to STORICO

In the textbooks…

- **COPD** is a chronic disease with daily symptoms especially during physical activity, and some have acute severe worsenings.

- **Asthma** is a disease that varies in degree of obstruction and symptoms during the day, the seasons and specific and non-specific exposures.

In real life...

- **COPD may have rather large changes in FEV_1 after bronchodilators, react to cold air and pollution/irritants with wheeze and cough, and often have morning symptoms or disturbed sleep because of cough and wheeze.**

- **COPD may show features of airway hyperresponsiveness**

Eur Respir J 2008; 31: 742–750
DOI: 10.1183/09031936.00129607

Bronchodilator responsiveness in patients with COPD

D.P. Tashkin*, B. Celli#, M. Decramer¶, D. Liu+, D. Burkhart+, C. Cassino+ and S. Kesten§

Clinical implications of airway hyper-responsiveness in COPD

Nicola Scichilone
Salvatore Battaglia
Alba La Sala
Vincenzo Bellia

Istituto di Medicina Generale e Pneumologia, Cattedra di Malattie dell'Apparato Respiratorio, Università di Palermo, Palermo, Italy

Abstract: COPD represents one of the leading causes of mortality in the general population. This study aimed at evaluating the relationship between airway hyperresponsiveness (AHR) and COPD and its relevance for clinical practice. We performed a MEDLINE search that yielded a total of 1919 articles. Eligible studies were defined as articles that addressed specific aspects of AHR in COPD, such as prevalence, pathogenesis, or prognosis. AHR appears to be present in at least one out of two individuals with COPD. The occurrence of AHR in COPD is influenced by multiple mechanisms, among which impairment of factors that oppose airway narrowing plays an important role. The main determinants of AHR are reduction in lung function and smoking status. We envision a dual role of AHR: in suspected COPD, specific

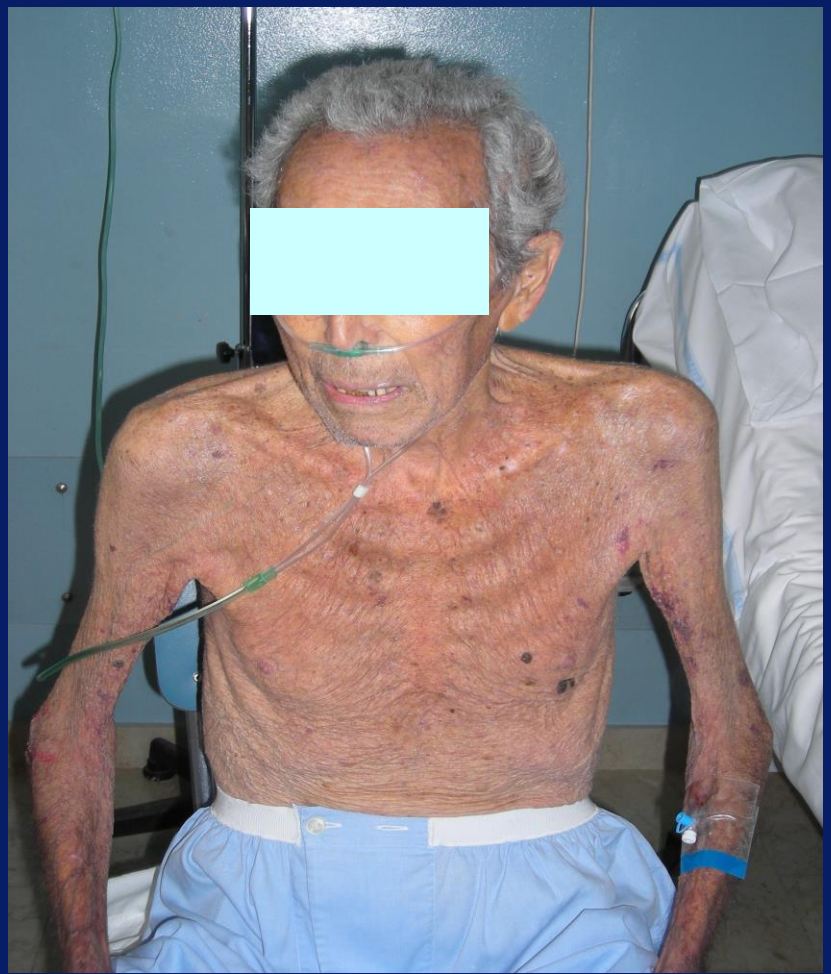
BPCO 1958

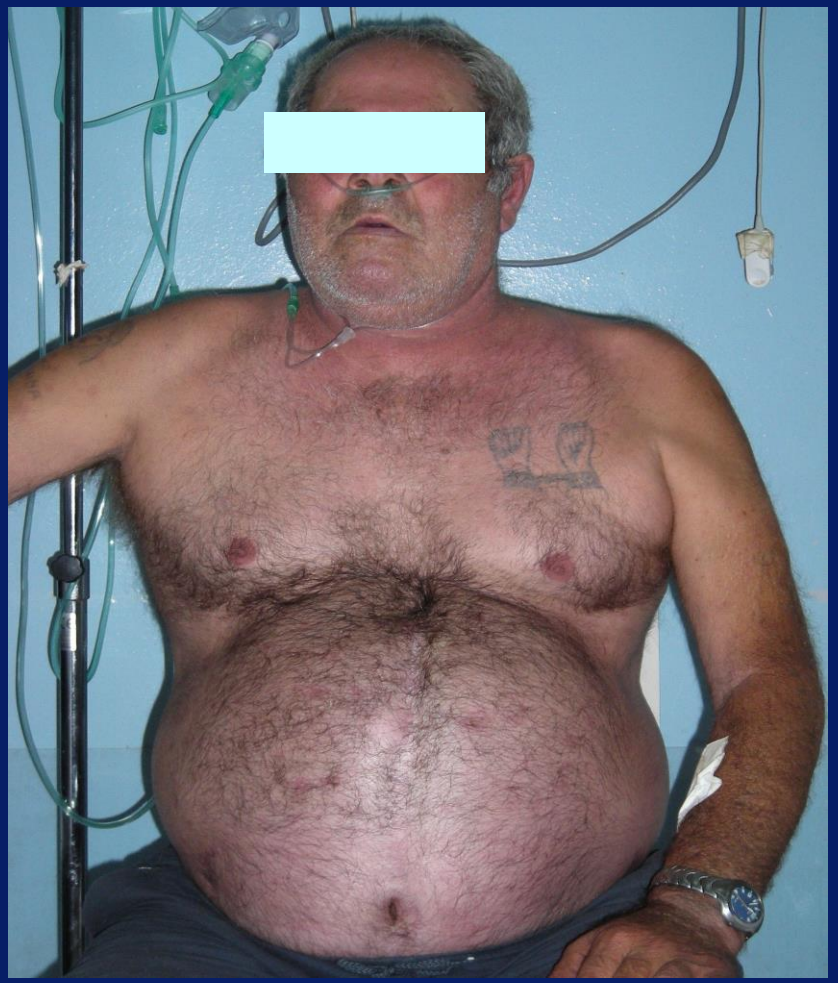
"... a group of diseases with **persistent** or irreversible obstructive lung disease"

CIBA Foundation Guest Symposium.

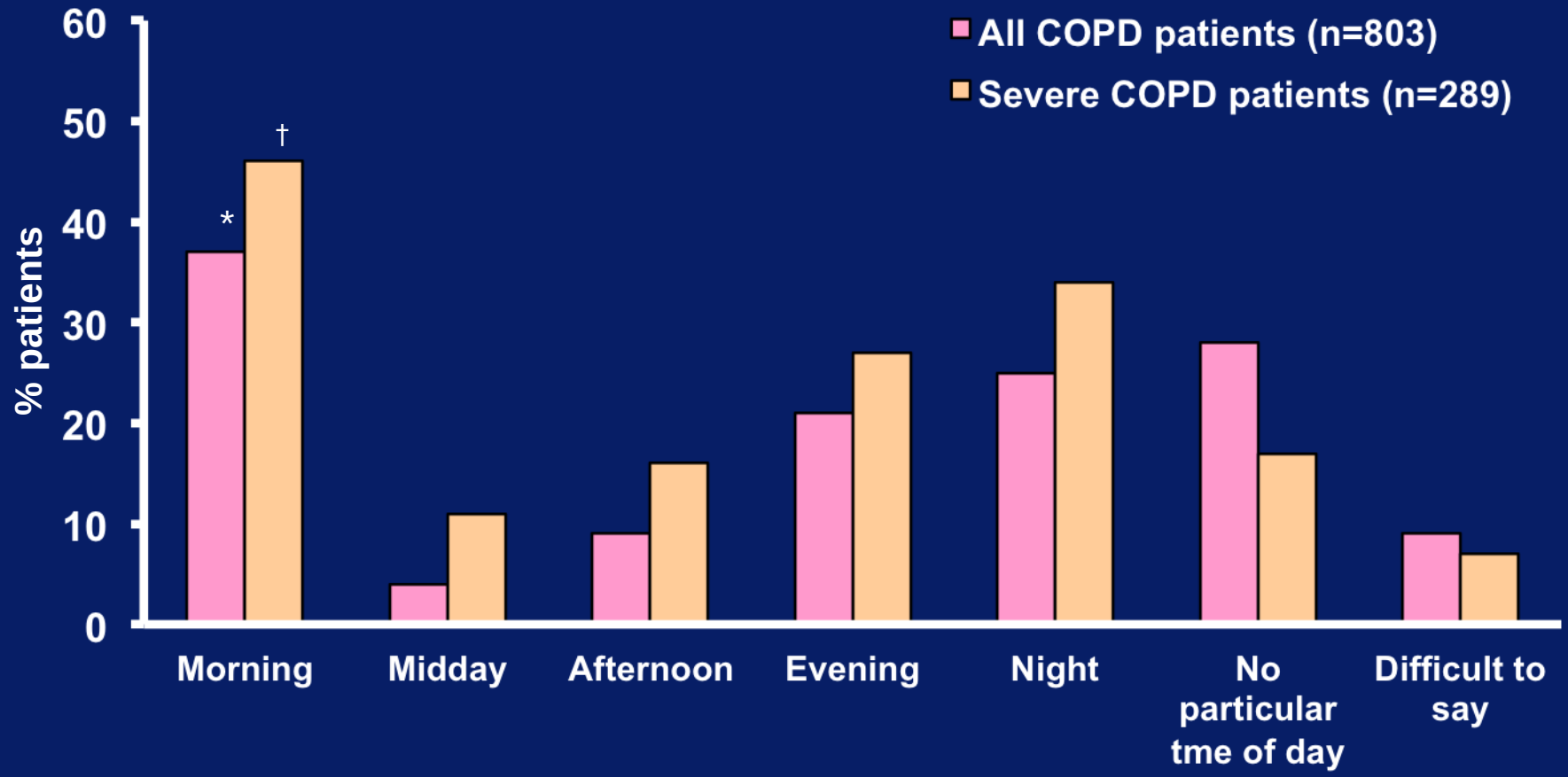
Thorax 1959

Persistent symptoms…but…do they vary during the day?





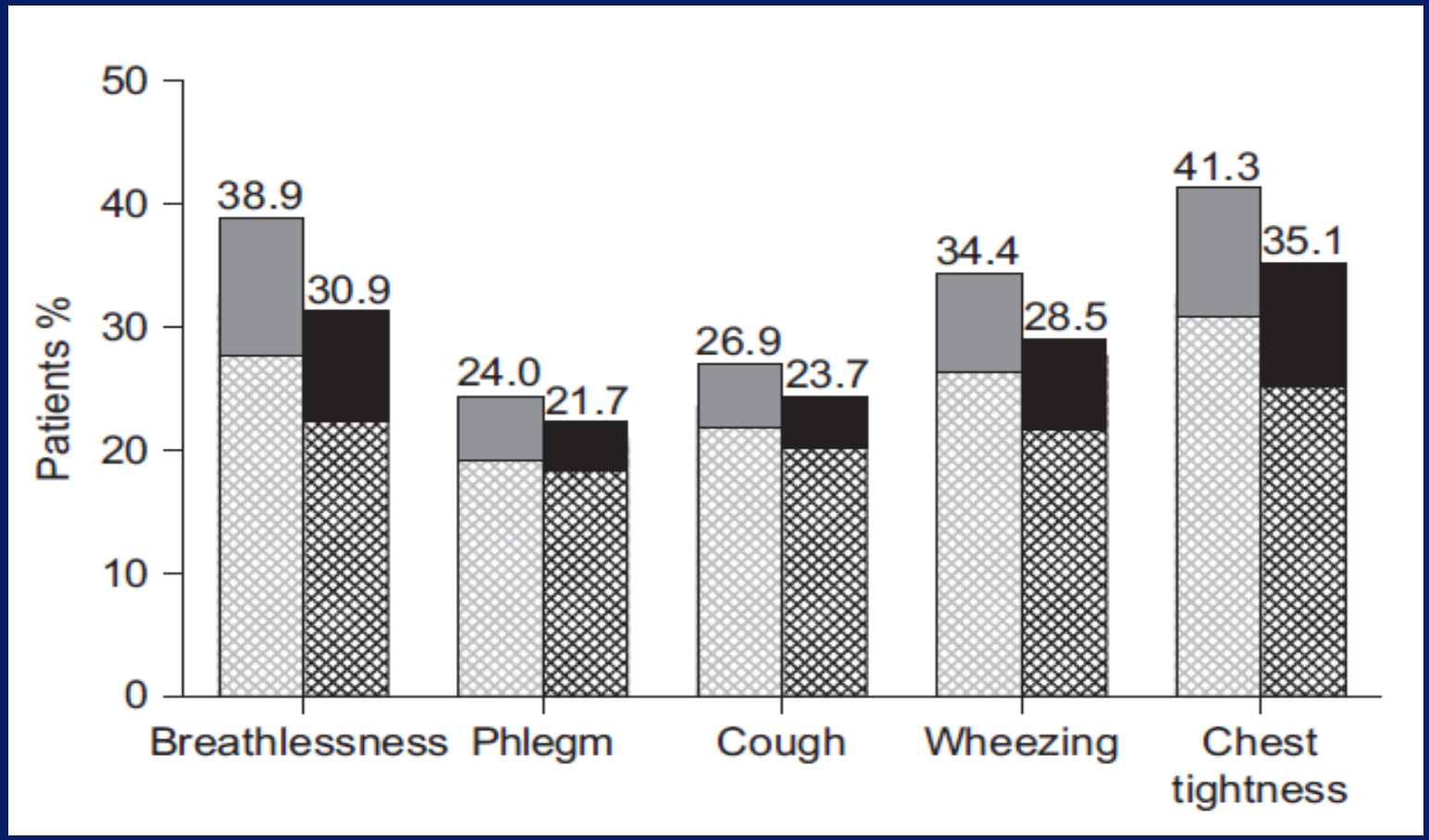
Circadian symptom variability: European and American survey



*p<0.001 vs all other times of day; †p<0.001 vs midday

Partridge et al, Curr Med Res Opin 2009

Weekly and daily variability in COPD symptoms



2441 patients with COPD

Kessler R et al. Eur Respir J 2011

Sleep Disorders in the Elderly With and Without Chronic Airflow Obstruction: the SARA Study

Vincenzo Bellia, MD, FCCP[1]; Filippo Catalano, MD[1]; Nicola Scichilone, MD[1]; Raffaele Antonelli Incalzi, MD[2]; Mario Spatafora, MD[1]; Carlo Vergani, MD[3]; Franco Rengo, MD[4]

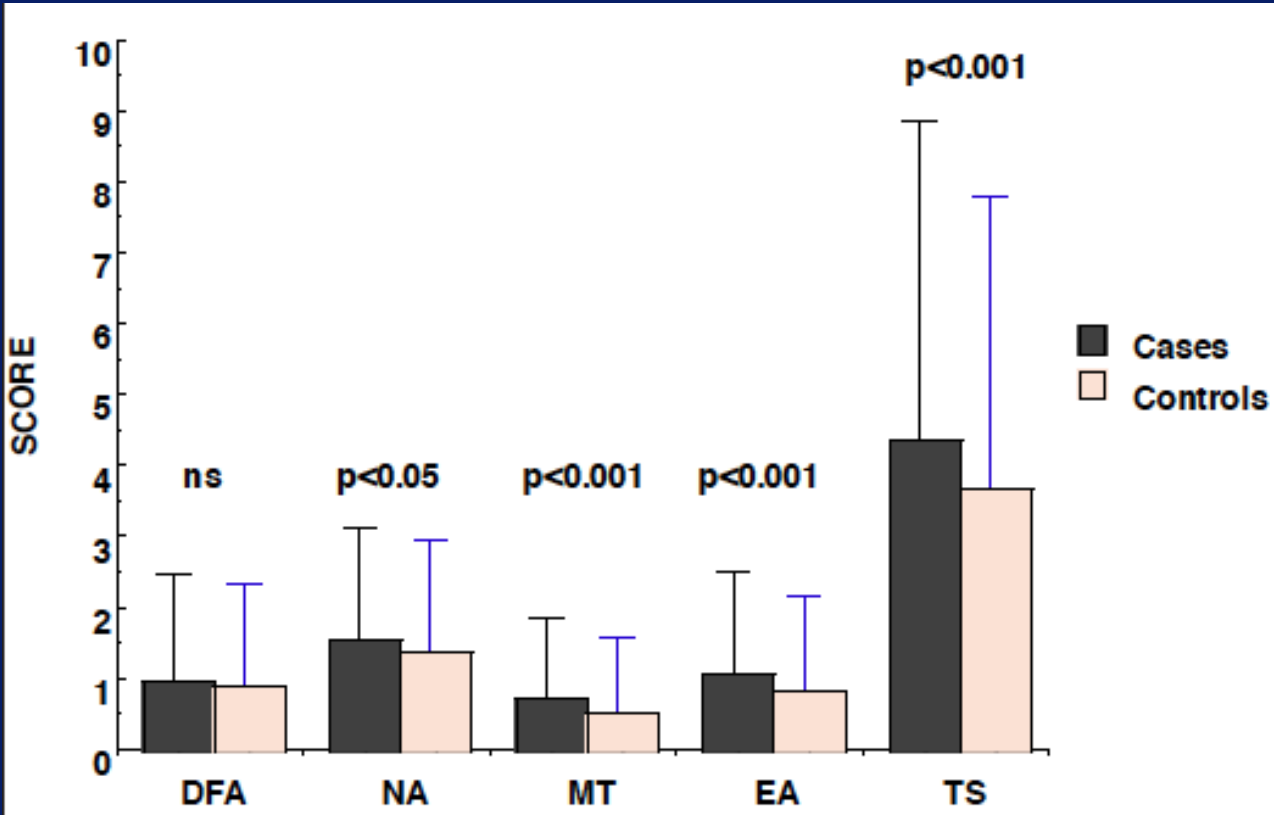


Figure 1—Differences in sleep disturbances between cases and controls. DFA = Difficult Falling Asleep; NA = Nocturnal Awakenings; MT = Morning Tiredness; EA = Early Awakenings; TS = Total Score.

The phenotypes of COPD

Symptoms variability in COPD:

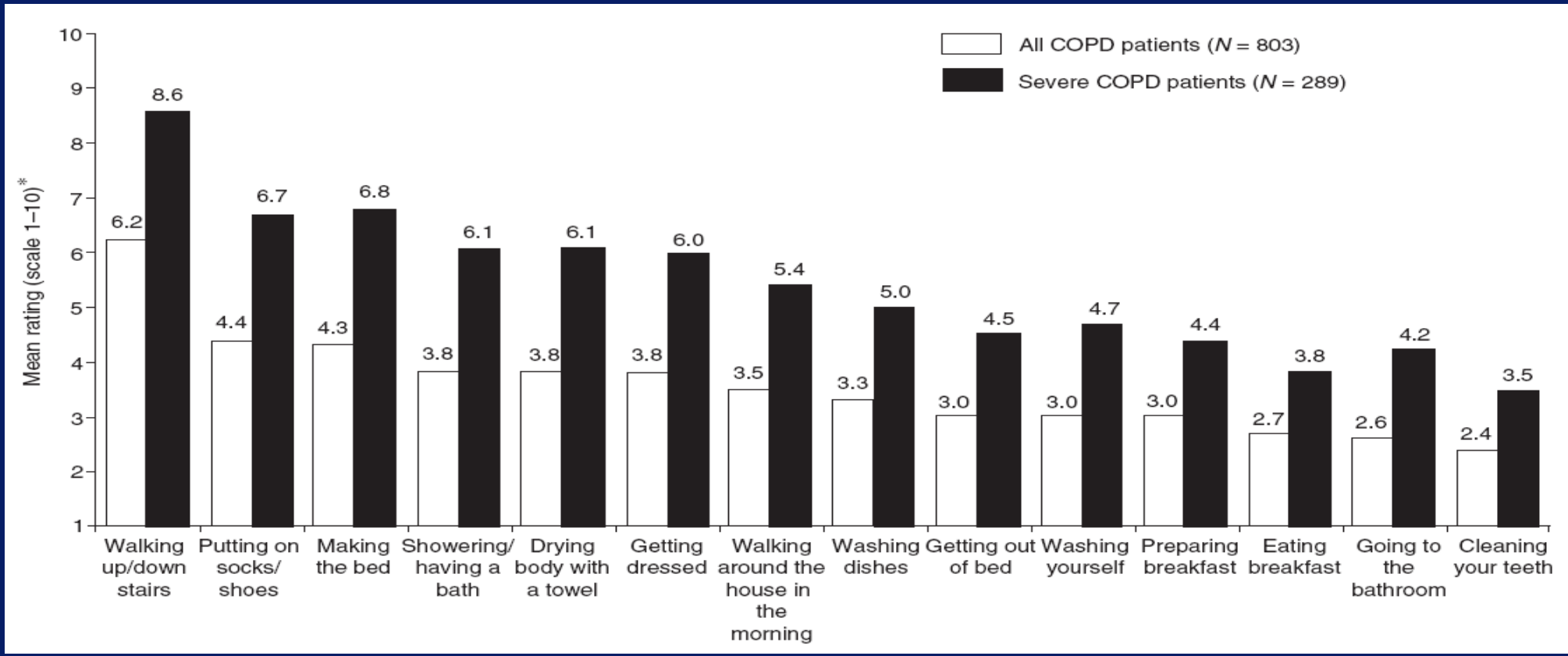
Does it really exist?

Does it really matter?

What do (and will) the studies teach us:

From ASSESS to STORICO

Activities most affected by nocturnal and morning symptoms in COPD



Partridge et al. Curr Med Res Opin 2009

Sleep Medicine 13 (2012) 476–483

Contents lists available at SciVerse ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Disturbed sleep among COPD patients is longitudinally associated with mortality and adverse COPD outcomes

Theodore A. Omachi [a,*], Paul D. Blanc [b], David M. Claman [a], Hubert Chen [a], Edward H. Yelin [c,d], Laura Julian [d], Patricia P. Katz [c,d]

Table 4
Longitudinal analyses: Multivariable analyses of the association between sleep disturbance at baseline and subsequent health outcomes.

	COPD exacerbations[a] OR (95% CI) *p*-value	Respiratory-related emergency utilization[a] OR (95% CI) *p*-value	All-cause mortality[b] HR (95% CI) *p*-value
Model 1: Controlling for Sociodemographics + BMI	4.7 (1.3–17) $p = 0.018$	11.5 (2.1–62) $p = 0.004$	5.0 (1.4–18) $p = 0.013$
Model 2: Model 1 + FEV_1	6.3 (1.6–25) $p = 0.008$	15.2 (2.5–91) $p = 0.003$	9.5 (2.1–44) $p = 0.004$
Model 3: Model 1 + FEV_1 + COPD Severity Score	4.0 (1.1–15) $p = 0.042$	9.7 (1.5–63) $p = 0.017$	8.8 (1.8–43) $p = 0.007$

The phenotypes of COPD

Symptoms variability in COPD:

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What do (and will) the studies teach us:

From ASSESS to STORICO

Miravitlles et al. Respiratory Research 2014, 15:122
http://respiratory-research.com/content/15/1/122

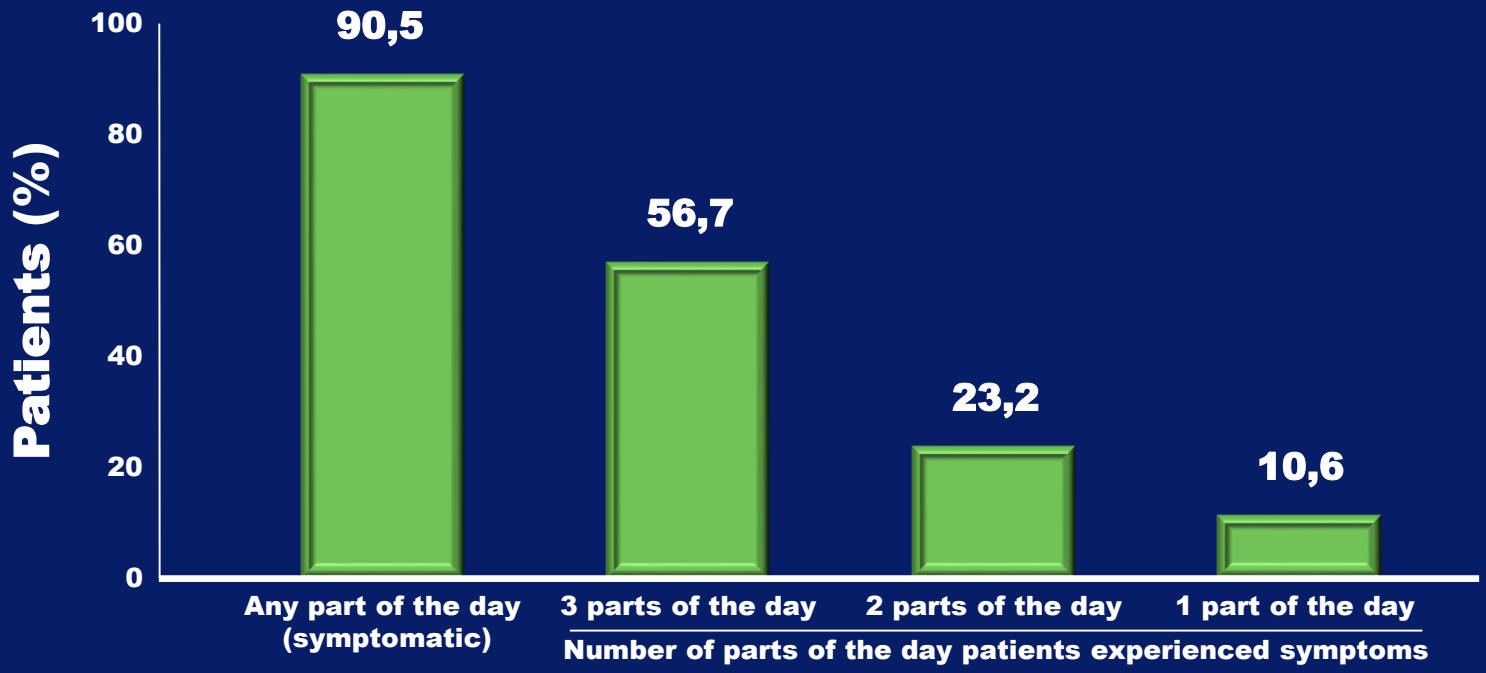
RESPIRATORY RESEARCH

RESEARCH Open Access

Observational study to characterise 24-hour COPD symptoms and their relationship with patient-reported outcomes: results from the ASSESS study

Marc Miravitlles[1*], Heinrich Worth[2], Juan José Soler Cataluña[3], David Price[4], Fernando De Benedetto[5], Nicolas Roche[6], Nina Skavlan Godtfredsen[7], Thys van der Molen[8], Claes-Göran Löfdahl[9], Laura Padullés[10] and Anna Ribera[10]

The ACCESS study: results



In the week before baseline, 90.5% of patients experienced COPD symptoms during at least one part of the 24-hour day and more than half of patients (56,7%) experienced symptoms throughout the whole 24-hour day

Miravitlles et al. Respiratory Research 2014

The ACCESS study: conclusions

Patients with symptoms during any part of the 24-hour period also had significantly worse outcomes across a range of measures that impact on daily living.

Current approaches to managing COPD may not adequately control symptoms, which can impact on a patient's overall well-being.

An accurate differential assessment of COPD symptoms throughout the whole 24-hour period can better highlight the specific required treatment of each individual patient.

Studio Osservazionale sulla caratteRizzazione dei sIntomi delle 24 ore nei pazienti con BPCO

PHENOTYPE 1	SYMPTOMS 1	COPD EVOLUTION 1
PHENOTYPE 2	SYMPTOMS 2	COPD EVOLUTION 2
PHENOTYPE 3	SYMPTOMS 3	COPD EVOLUTION 3

CLINICAL NEED 1:
DESCRIBE THE FREQUENCY OF SYMPTOMS ACCORDING TO PHENOTYPES

CLINICAL NEED 2:
DESCRIBE THE FREQUENCY AND EVOLUTION OF SYMPTOMS ACCORDING TO PHENOTYPES

European Journal of Internal Medicine 43 (2017) 62–68

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

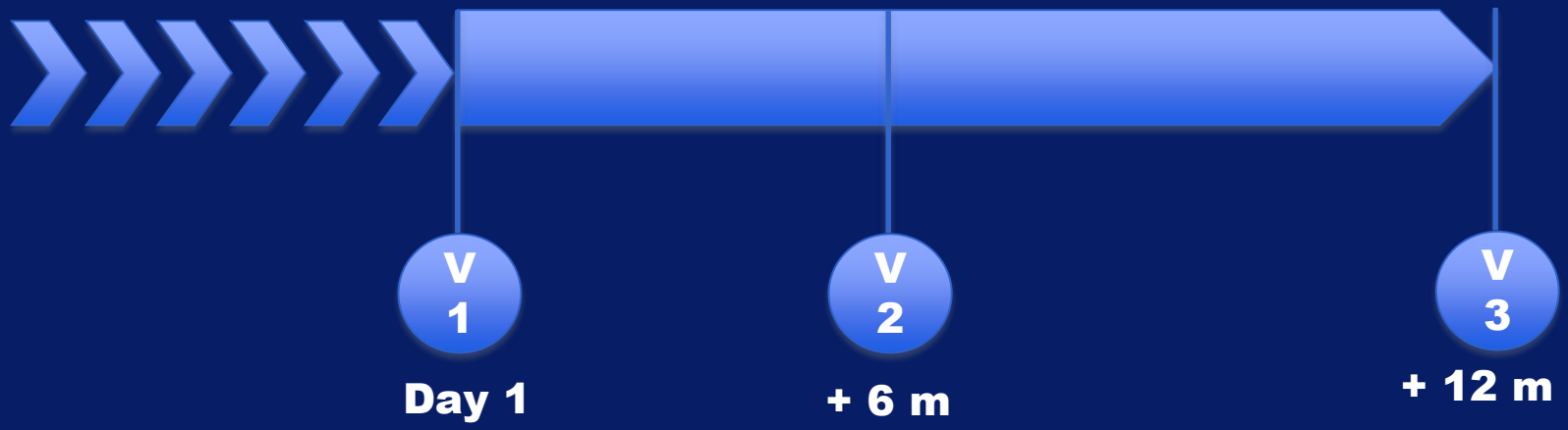
Original Article

Characterization of circadian COPD symptoms by phenotype: Methodology of the STORICO observational study

G.W. Canonica [a,*], F. Blasi [b], N. Scichilone [c], L. Simoni [d], A. Zullo [d], C. Giovannetti [e], C. Briguglio [f], S. Barsanti [e], R. Antonelli Incalzi [g], on behalf of STORICO study group [1]

[a] Personalized Medicine Asthma & Allergy Clinic, Humanitas University, Humanitas Research Hospital, Rozzano, Milan, Italy
[b] Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Cardio-Thoracic Unit and Cystic Fibrosis Adult Center, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico Milano, Milan, Italy
[c] DIBIMIS University of Palermo, Palermo, Italy
[d] Medineos Observational Research, Modena, Italy
[e] Laboratori Guidotti, Pisa, Italy
[f] Malesci, Firenze, Italy
[g] University of Biomedical Campus of Rome, Rome, Italy

The STORICO study: design

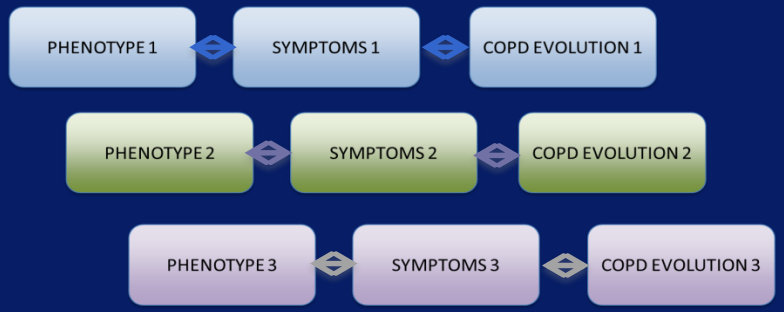


Medical history and demographic data (retrospective)
+
Questionnaires
+
Spirometry

Assess any change in medical condition and medical healthcare resource
+
Questionnaires
+
Spirometry*

Approximately 600 patients consecutively enrolled in 45 centers.

The STORICO study: primary objectives



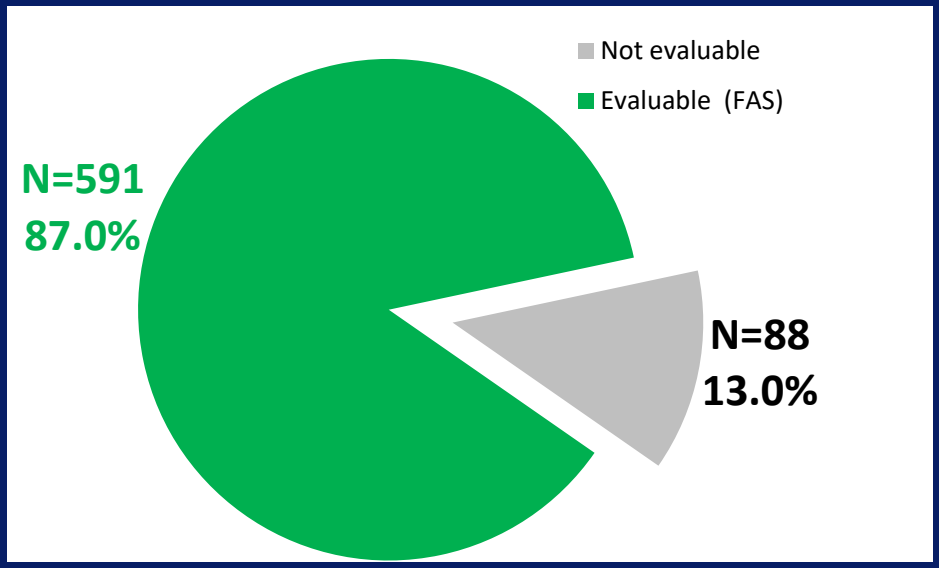
Cross-sectional phase

To describe the *frequency* of early-morning, day- and night-time COPD symptoms *according to phenotypes* in a cohort of Italian patients with stable COPD (GOLD 2014 criteria).

Longitudinal phase

To describe the 12-month frequency and *evolution* of early-morning, day- and night-time COPD symptoms *according to phenotypes* measured at enrollment.

Enrolled and Evaluable patients



N enrolled = 683

679 analyzed patients

Criterion	N violators
(2) Diagnosis of stable COPD at least 12 months before enrolment	3
(3) Current or ex-smokers with a smoking history of at least 10 pack-years	2
(9) Without a previous diagnosis of asthma/sleep apnea syndrome/other chronic respiratory disease different from COPD/relevant medical conditions that reduced the life expectancy of less than 3 yrs (Charlson index>3)	5
(10) Not under long-term oxygen therapy	1
(11) Available information about COPD symptoms	81
(12) Available information about clinical phenotype	2
(13) Clinical phenotype not Mixed COPD-asthma+Chronic bronchitis or Other (OVERLAP SYNDROME)	3

COPD Medical history

	OVERALL (N=606)	CB (N=351)	EM (N=215)	MCA (N=32)
COPD duration (yrs) (mean±SD)	7.8±6.5	7.7±6.5	8.0±6.3	8.7±8.9
Age at COPD diagnosis (yrs) (mean±SD)	63.6±9.1	63.9±9.4	63.5±8.1	61.4±11.5
N of COPD exacerbations/year (5 years before baseline) median (25° -75° percentile)	2.0 (1.0-3.0)	2.0 (1.0-4.0)	1.0 (0.0-2.0)	3.0 (1.0-5.0)
COPD assessment (GOLD guidelines) (%)				
group A	25.6%	21.7%	30.7%	37.5%
group B	30.9%	37.9%	20.0%	21.9%
group C	20.8%	16.8%	26.5%	25.0%
group D	22.8%	23.6%	22.8%	15.6%

Comorbidities

	FAS N=591	Chronic bronchitis N=345	Emphysema N=211	Mixed COPD-asthma N=29	Emphysema+ Chronic bronchitis N=6
Patients with at least one comorbidity	**72.1%**	**70.7%**	**74.4%**	**69.0%**	**83.3%**
Arterial Hypertension	**49.2%**	**51.6%**	**44.1%**	**51.7%**	**83.3%**
Atrial fibrillation	5.6%	5.5%	5.7%	6.9%	0.0%
Cardiac ischemic disease	**10.3%**	**9.9%**	**9.5%**	**20.7%**	**16.7%**
Community Acquired Pneumoniae (CAP)	1.0%	0.9%	0.9%	3.4%	0.0%
Depression	2.9%	3.5%	2.4%	0.0%	0.0%
Diabetes	**10.3%**	**11.3%**	**8.5%**	**10.3%**	**16.7%**
Gastroesophageal Reflux Disease	3.7%	3.5%	3.8%	6.9%	0.0%
Heart failure	2.0%	2.3%	0.9%	3.4%	**16.7%**
Kidney Insufficiency	2.5%	2.3%	2.8%	3.4%	0.0%
Lung cancer	0.5%	0.3%	0.5%	3.4%	0.0%
Neoplastic disease	4.9%	2.6%	7.6%	**10.3%**	**16.7%**
Osteoporosis	4.2%	5.8%	2.4%	0.0%	0.0%
Other clinically relevant comorbidities	**31.0%**	**29.9%**	**34.6%**	**20.7%**	**16.7%**

Comorbidities with frequency ≥10% were highlighted.
A patient could have more than one comorbidity.

	FAS N=591	Chronic bronchitis N=345	Emphysema N=211	Mixed COPD-asthma N=29	Emphysema+ Chronic bronchitis N=6
Underweight (BMI<18.5)	2.2%	**1.2%**	**4.3%**	0.0%	0.0%
Normal weight (BMI 18.5-24.9)	30.3%	**25.6%**	**38.1%**	31.0%	16.7%
Overweight/obese (BMI>25)	67.5%	**73.2%**	**57.6%**	69.0%	83.3%

Nicola *et al. BMC Pulmonary Medicine* (2019) 19:171
https://doi.org/10.1186/s12890-019-0935-2

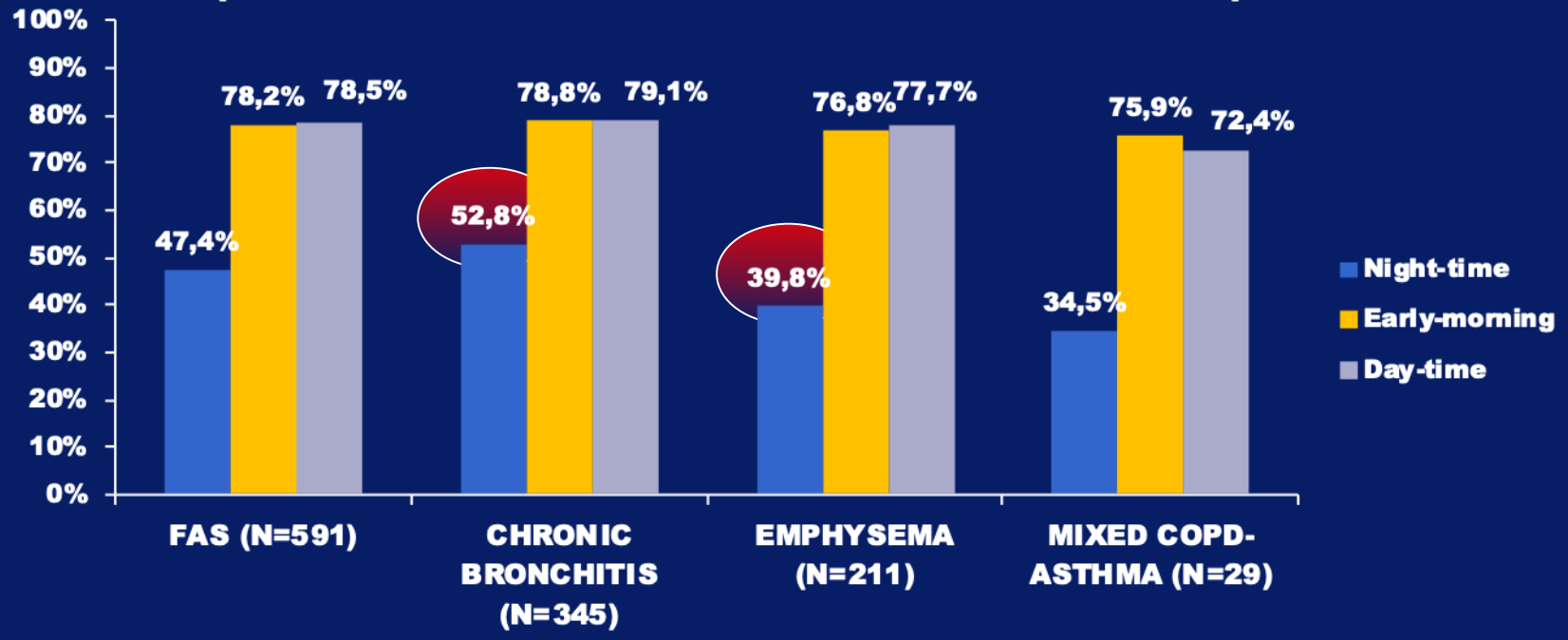
BMC Pulmonary Medicine

RESEARCH ARTICLE Open Access

Circadian rhythm of COPD symptoms in clinically based phenotypes. Results from the STORICO Italian observational study

Scichilone Nicola[1*], Antonelli Incalzi Raffaele[2], Blasi Francesco[3], Schino Pietro[4], Cuttitta Giuseppina[5], Zullo Alessandro[6], Ori Alessandra[6], Canonica Giorgio Walter[7] and on behalf of STORICO study group

Frequency of patients with COPD symptoms (at least one in the week before baseline)



COPD symptoms vs COPD severity, previous exacerbations, mMRC, SGRQ, CASIS, HADS scores (by phenotype)

In Chronic Bronchitis and Emphysema patients

•the frequency of early-morning, day- and night-time symptoms increased with COPD severity (higher frequency observed in stage C-D vs A-B).

The patients with ≥2 previous exacerbations (compared to patients with 0-1 previous exacerbations) had higher frequency of

•night-time and early-morning symptoms (Chronic Bronchitis)

•early-morning symptoms (Emphysema).

Conclusions

- The novelty of the current investigation is the distribution of the respiratory symptoms during each part of the 24-h day according to pre-defined clinical phenotypes.
- Night-time symptoms, alone or in combination with symptoms during other parts of the day, appear to specifically characterize the CB phenotype.
- Similarly in both phenotypes frequency of symptoms during 24-h increases with disease severity.
- The nocturnal component of the respiratory symptoms in the CB phenotype did not specifically affect quality of life, nor quality of sleep when compared to EM subjects.
  The CB phenotype did not differ from the EM phenotype in terms of level of anxiety and/or depression, nor for dyspnea perception.

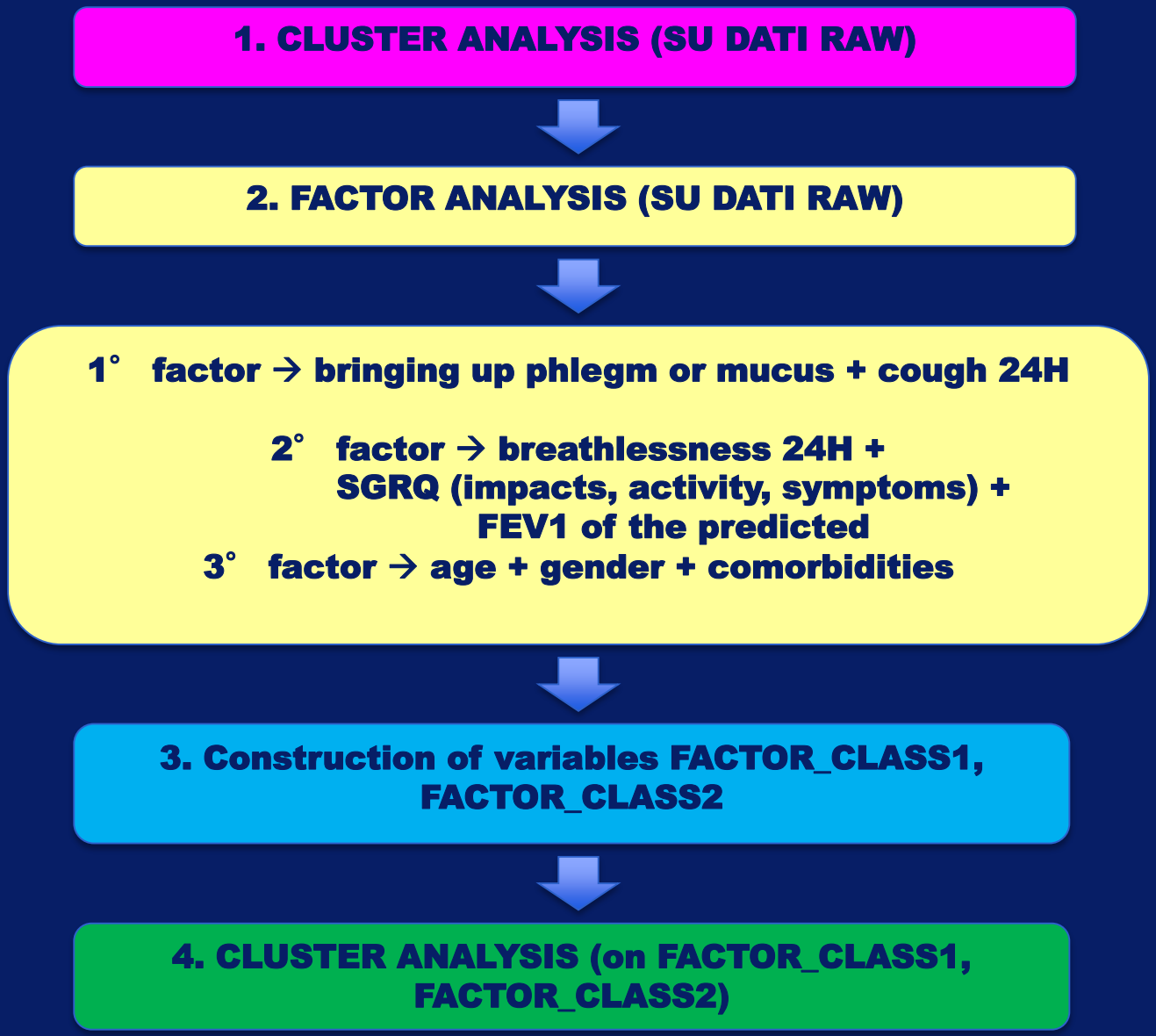
PLOS ONE

RESEARCH ARTICLE

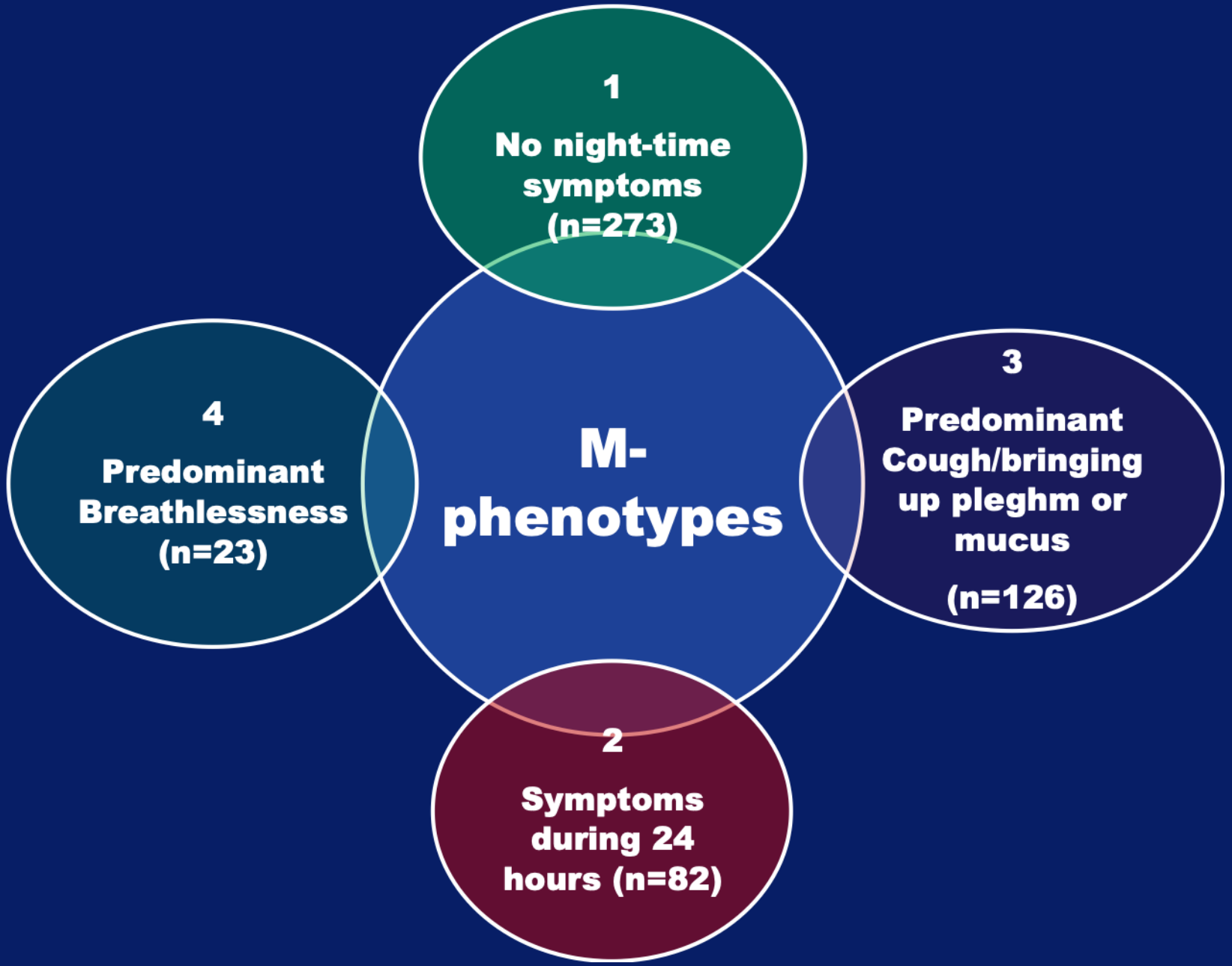
The COPD multi-dimensional phenotype: A new classification from the STORICO Italian observational study

Raffaele Antonelli Incalzi[1]*, Giorgio Walter Canonica[2], Nicola Scichilone[3], Sara Rizzoli[4], Lucia Simoni[4], Francesco Blasi[5], on behalf of STORICO study group[¶]

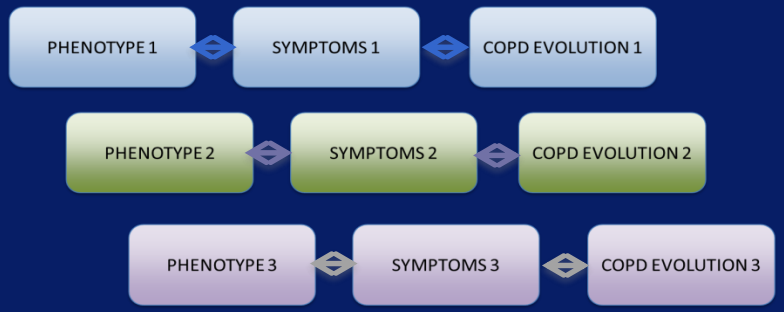
Identification of m-phenotype – work flow



Multi-dimensional phenotypes



The STORICO study: primary objectives



Cross-sectional phase

To describe the *frequency* of early-morning, day- and night-time COPD symptoms *according to phenotypes* in a cohort of Italian patients with stable COPD (GOLD 2014 criteria).

Longitudinal phase

To describe the 12-month frequency and ***evolution*** of early-morning, day- and night-time COPD symptoms ***according to phenotypes*** measured at enrollment.

Clinical evolution and quality of life in clinically-based COPD phenotypes: results from the 1-year follow up of the STORICO Italian observational study.

Blasi Francesco, Antonelli Incalzi Raffaele, Canonica Giorgio Walter, Schino Pietro, Cuttitta Giuseppina, Zullo Alessandro, Ori Alessandra, Scichilone Nicola on behalf of STORICO study group

Conclusions: The STORICO study showed that, in a real-world setting, EM patients seem to suffer from a worse clinical condition and health status compared to CB patients, appearing to have "more treatable" traits.

Under review, Respiratory Medicine

From background to rationale

What do we need to have a better management of COPD symptoms?

→ **DIAGNOSIS**

→ **PHENOTYPES DEFINITION**

→ **ASSOCIATION BETWEEN SYMPTOMS**

NOVEL CLASSIFICATORY PARADIGM BASED ON SYMPTOM VARIABILITY