

Los 10 artículos de mayor factor de impacto del 1er semestre 2014

1. Salas-Salvadó J, Bulló M, Estruch R, Ros E, Covas MI, Ibarrola-Jurado N, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Romaguera D, Lapetra J, Lamuela-Raventós RM, Serra-Majem L, Pintó X, Basora J, Muñoz MA, Sorlí JV, Martínez-González MA. *Prevention of Diabetes With Mediterranean Diets A Subgroup Analysis of a Randomized Trial. ANN INTERN MED* 2014 Jan 7;160(1):1-10. doi: 10.7326/M13-1725.

FACTOR DE IMPACTO: 16,104

Ann Intern Med. 2014;160(1):1-10. doi:10.7326/M13-1725

Original Research | 7 January 2014

Prevention of Diabetes With Mediterranean Diets: A Subgroup Analysis of a Randomized Trial

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Background: Interventions promoting weight loss can reduce the incidence of type 2 diabetes mellitus. Whether dietary changes without calorie restriction also protect from diabetes has not been evaluated.

Objective: To assess the efficacy of Mediterranean diets for the primary prevention of diabetes in the Prevención con Dieta Mediterránea trial, from October 2003 to December 2010 (median follow-up, 4.1 years).

Design: Subgroup analysis of a multicenter, randomized trial. (Current Controlled Trials: ISRCTN35739639)

Setting: Primary care centers in Spain.

Participants: Men and women without diabetes (3541 patients aged 55 to 80 years) at high cardiovascular risk.

Intervention: Participants were randomly assigned and stratified by site, sex, and age but not diabetes status to receive 1 of 3 diets: Mediterranean diet supplemented with extra-virgin olive oil (EVOO), Mediterranean diet supplemented with nuts, or a control diet (advice on a low-fat diet). No intervention to increase physical activity or lose weight was included.

Measurements: Incidence of new-onset type 2 diabetes mellitus (prespecified secondary outcome).

Results: During follow-up, 80, 92, and 101 new-onset cases of diabetes occurred in the Mediterranean diet supplemented with EVOO, Mediterranean diet supplemented with mixed nuts, and control diet groups, respectively, corresponding to rates of 16.0, 18.7, and 23.6 cases per 1000 person-years. Multivariate-adjusted hazard ratios were 0.60 (95% CI, 0.43 to 0.85) for the Mediterranean diet supplemented with EVOO and 0.82 (CI, 0.61 to 1.10) for the Mediterranean diet supplemented with nuts compared with the control diet.

Limitations: Randomization was not stratified by diabetes status. Withdrawals were greater in the control group.

Conclusion: A Mediterranean diet enriched with EVOO but without energy restrictions reduced diabetes risk among persons with high cardiovascular risk.

Primary Funding Source: Instituto de Salud Carlos III.

2. Vestbo J; Agusti A, Wouters EF, Bakke P, Calverley PM, Celli B, Coxson H, Crim C, Edwards LD, Locantore N, Lomas DA, MacNee W, Miller B, Rennard SI, Silverman EK, Yates JC, Tal-Singer R; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints Study Investigators (Bakke P, Coxson H, Edwards L, Tal-Singer R, Lomas D, MacNee W, Silverman E, Crim C, Vestbo J, Yates J, Agusti A, Calverley P, Celli B, Crim C, Miller B, MacNee W, Rennard S, Tal-Singer R, Wouters E, Yates J, Ivanov Y, Kostov K, Bourbeau J, Fitzgerald M, Hernandez P, Killian K, Levy R, Maltais F, O'Donnell D, Krepelka J, Vestbo J, Wouters E, Quinn D, Bakke P, Kosnik M, Agusti A, **Sauleda J**, de Mallorca P, Feschenko Y, Gavrisyuk V, Yashina L, Monogarova N, Calverley P, Lomas D, MacNee W, Singh D, Wedzicha J, Anzueto A, Braman S, Casaburi R, Celli B, Giessel G, Gotfried M, Greenwald G, Mirage R, Hanania N, Mahler D, Make B, Rennard S, Rochester C, Scanlon P, Schuller D, Sciruba F, Sharafkhan A, Siler T, Silverman E, Wanner A, Wise R, ZuWallack R). *Should we view chronic obstructive pulmonary disease differently after ECLIPSE? A clinical perspective from the study team.* **AM J RESP CRIT CARE** 2014 May 1;189(9):1022-30. doi: 10.1164/rccm.201311-2006PP.
- FACTOR DE IMPACTO: 11,986

PULMONARY PERSPECTIVE



Should We View Chronic Obstructive Pulmonary Disease Differently after ECLIPSE?

A Clinical Perspective from the Study Team

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Abstract

Rationale: Chronic obstructive pulmonary disease (COPD) seems to be a heterogeneous disease with a variable course.

Objectives: We wished to characterize the heterogeneity and variability of COPD longitudinally.

Methods: In the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study of 2,164 patients with clinically stable COPD, 337 smokers with normal lung function, and 245 never-smokers, we measured a large number of clinical parameters, lung function, exercise tolerance, biomarkers, and amount of emphysema by computed tomography. All three groups were followed for 3 years.

Measurements and Main Results: We found a striking heterogeneity among patients with COPD, with poor correlations between FEV₁, symptoms, quality of life, functional outcomes, and biomarkers. Presence of systemic inflammation was found in only a limited proportion of patients, and did not relate to baseline

characteristics or disease progression, but added prognostic value for predicting mortality. Exacerbations tracked over time and added to the concept of the "frequent exacerbator phenotype." Disease course was very variable, with close to a third of patients not progressing at all. Risk factors for 3-year change in both FEV₁ and lung density were assessed. For FEV₁ decline, continued smoking and presence of emphysema were the strongest predictors of progression; club cell protein was found to be a potential biomarker for disease activity. For progression of emphysema, the strongest predictors were continued smoking and female sex.

Conclusions: By following a large, well characterized cohort of patients with COPD over 3 years, we have a clearer picture of a heterogeneous disease with clinically important subtypes ("phenotypes") and a variable and not inherently progressive course. Clinical trial registered with www.clinicaltrials.gov (NCT00292552).

Keywords: chronic obstructive pulmonary disease, exacerbations, computed tomography, lung density, lung function, comorbidities

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- FACTOR DE IMPACTO: 11,248

Preterm birth, infant weight gain, and childhood asthma risk: A meta-analysis of 147,000 European children

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Rotterdam, Groningen, Utrecht, Maastricht, and Bilthoven, The Netherlands, Paris and Villejuif, France, Isle of Wight, Aberdeen, Bristol, and Southampton, United Kingdom, Porto, Portugal, Gijón, Galicia, Barcelona, Valencia, and Balearic Islands, Spain, Copenhagen and Gentofte, Denmark, Crete and Athens, Greece, Bern and Basel, Switzerland, Prague, Czech Republic, Linköping, Sweden, Oslo, Norway, Bologna, Rome, and Turin, Italy, Lodz, Poland, Berlin and Würzburg, Germany, Dublin, Ireland, and Bratislava, Slovakia

Background: Preterm birth, low birth weight, and infant catch-up growth seem associated with an increased risk of respiratory diseases in later life, but individual studies showed conflicting results. **Objectives:** We performed an individual participant data meta-analysis for 147,252 children of 31 birth cohort studies to determine the associations of birth and infant growth characteristics with the risks of preschool wheezing (1-4 years) and school-age asthma (5-10 years). **Methods:** First, we performed an adjusted 1-stage random-effect meta-analysis to assess the combined associations of gestational age, birth weight, and infant weight gain with childhood asthma. Second, we performed an adjusted 2-stage random-effect meta-analysis to assess the associations of preterm birth (gestational age <37 weeks) and low birth weight (<2500 g) with childhood asthma outcomes. **Results:** Younger gestational age at birth and higher infant weight gain were independently associated with higher risks of preschool wheezing and school-age asthma ($P < .05$). The inverse associations of birth weight with childhood asthma were explained by gestational age at birth. Compared with term-born children with normal infant weight gain, we observed the highest risks of school-age asthma in children born preterm with high infant weight gain (odds ratio [OR], 4.47; 95% CI, 2.58-7.76). Preterm birth was positively associated with an increased risk of preschool wheezing (pooled odds ratio [pOR], 1.34; 95% CI, 1.25-1.43) and school-age asthma (pOR, 1.40; 95% CI, 1.18-1.67) independent of birth weight. Weaker effect estimates were observed for the associations of low birth weight adjusted for gestational age at birth with preschool wheezing (pOR, 1.10; 95% CI, 1.00-1.21) and school-age asthma (pOR, 1.13; 95% CI, 1.01-1.27).

Conclusion: Younger gestational age at birth and higher infant weight gain were associated with childhood asthma outcomes. The associations of lower birth weight with childhood asthma were largely explained by gestational age at birth. (*J Allergy Clin Immunol* 2014;133:1317-29.)

Key words: Gestational age, low birth weight, infant growth, wheezing, asthma, children, cohort studies, epidemiology

Respiratory diseases have at least part of their origins in early life. It has been hypothesized that adverse exposures in fetal and early postnatal life might influence lung growth and development, which could lead to persistently smaller airways and impaired lung function. These developmental adaptations might predispose the subject to asthma and chronic obstructive pulmonary disease in childhood and adulthood.¹⁻³ This hypothesis is supported by studies showing associations of low birth weight with an increased risk of wheezing and asthma in childhood⁴⁻⁷ and chronic obstructive pulmonary disease and lower pulmonary function in later life.^{8,11} Published findings are not consistent,^{6,7,12,13} which might be due to differences in study populations and in definitions of outcomes. Also, the observed associations of low birth weight with an increased risk of asthma-related outcomes might be confounded by preterm birth or catch-up growth in infancy. The lungs of preterm children have not yet been fully developed, which makes them prone to suboptimal further development.¹⁴⁻¹⁶

Most children with low birth weight show catch-up growth in infancy.¹⁷ Recent studies suggested that catch-up growth is associated with lower pulmonary function and an increased risk of

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 FACTOR DE IMPACTO: 9,916

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Article

A Novel Analgesic Isolated from a Traditional Chinese Medicine

Yan Zhang¹, Chuan Wang², Lin Wang, Gregory Scott Parks, Xuli Zhang, Zhenou Guo, Yanoung Ke, Kang-Wu Li, Mi-Kyoung Kim, Benjamin Vo, Emilee Borrelli, Guangbo Ge, Ling Yang, Zhen Wang, M. Julo Garcia-Fuster, Z. David Luo, Xinmiao Liang, O. Civelli^{1,2}

¹These authors contributed equally to this work.

DOI: 10.1016/j.cub.2013.11.039

Abstract 222 

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Highlights

- DHC B is isolated from *C. yanzhusuo*, a plant used for centuries for pain relief
- DHC B is an antinociceptive against tactile, inflammatory, and neuropathic pain
- DHC B's antinociception relies on its inhibitory activity at the dopamine D2 receptor
- DHC B administration does not induce antinociceptive tolerance

Summary

Background
 Current pain management is limited, in particular, with regard to chronic pain. In an attempt to discover novel analgesics, we combined the approach developed to characterize traditional Chinese medicine (TCM), as part of the "Herbalome" project, with the reverse pharmacology approach aimed at discovering new endogenous transmitters and hormones.

Results
 In a plant used for centuries for its analgesic properties, we identify a compound, dehydrocorybulbine (DHC B), that is effective at alleviating thermally induced acute pain. We synthesize DHC B and show that it displays moderate dopamine receptor antagonist activities. By using selective pharmacological compounds and dopamine receptor knockout (KO) mice, we show that DHC B antinociceptive effects primarily due to its interaction with D2 receptors, at least at low doses. We further show that DHC B is effective against inflammatory pain and injury-induced neuropathic pain and furthermore causes no antinociceptive tolerance.

Conclusions
 Our study casts DHC B as a different type of analgesic compound and as a promising lead in pain management.



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- FACTOR DE IMPACTO: 9,379



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Original Article

Leukemia (27 September 2013) | doi:10.1038/leu.2013.281

MicroRNA expression at diagnosis adds relevant prognostic information to molecular categorization in patients with intermediate-risk cytogenetic acute myeloid leukemia

M Díaz-Beyá, S Brunet, J Nomdedéu, R Tejero, T Díaz, M Pratcorona, M Tormo, J M Ribera, L Escoda, R Duarte, D Gallardo, I Heras, M P Queipo de Llano, J Bargay, M Monzo, J Sierra, A Navarro, J Esteve and on behalf of the Cooperative AML group CETLAM (Grupo Cooperativo Para el Estudio y Tratamiento de las Leucemias Agudas y Mielodisplasias)

Acute myeloid leukemia (AML) is a heterogeneous disease, and optimal treatment varies according to cytogenetic risk factors and molecular markers. Several studies have demonstrated the prognostic importance of microRNAs (miRNAs) in AML. Here we report a potential association between miRNA expression and clinical outcome in 238 intermediate-risk cytogenetic AML (IR-AML) patients from 16 institutions in the CETLAM cooperative group. We first profiled 670 miRNAs in a subset of 85 IR-AML patients from a single institution and identified 10 outcome-related miRNAs. We then validated these 10 miRNAs by individual assays in the total cohort and confirmed the prognostic impact of 4 miRNAs. High levels of miR-196b and miR-644 were independently associated with shorter overall survival, and low levels of miR-135a and miR-409-3p with a higher risk of relapse. Interestingly, miR-135a and miR-409-3p maintained their independent prognostic value within the unfavorable molecular subcategory (wild-type NPM1 and CEBPA and/or FLT3-ITD), and miR-644 retained its value within the favorable molecular subcategory. miR-409-3p, miR-135a, miR-196b and miR-644 arose as prognostic markers for IR-AML, both overall and within specific molecular subgroups.

ARTICLE TOOLS

SEARCH PUBMED FOR

- M Díaz-Beyá
- S Brunet
- J Nomdedéu
- R Tejero
- T Díaz
- M Pratcorona
- [more authors of this article](#)

6. **Vicens C**, Bejarano F, Sempere E, Mateu C, Fiol F, **Socias I**, Aragonès E, Palop V, Beltran JL, Piñol JL, Lera G, Folch S, Mengual M, Basora J, **Esteva M**, **Llobera J**, **Roca M**, **Gili M**, **Leiva A**. *Comparative efficacy of two interventions to discontinue long-term benzodiazepine use: cluster randomised controlled trial in primary care*. **BRIT J PSYCHIAT** 2014 Jun;204(6):471-9. doi: 10.1192/bjp.bp.113.134650. Epub 2014 Feb 13.
- FACTOR DE IMPACTO: 7,343

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PAPERS 

Comparative efficacy of two interventions to discontinue long-term benzodiazepine use: cluster randomised controlled trial in primary care

C. Vicens, F. Bejarano, E. Sempere, C. Mateu, F. Fiol, I. Socias, E. Aragonès, V. Palop, J. L. Beltran, J. L. Piñol, G. Lera, S. Folch, M. Mengual, J. Basora, M. Esteva, J. Llobera, M. Roca, M. Gili and A. Leiva

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7. Guasch-Ferré M; Hu FB; Martínez-González MA; Fitó M; Bulló M; Estruch R; Ros E; Corella D; Recondo J; Gómez-Gracia E; **Fiol M**; Lapetra J; Serra-Majem L; Muñoz MA; Pintó X; Lamuela-Raventós RM; Basora J; Buil-Cosiales P; Sorlí JV; Ruiz-Gutiérrez V; Martínez JA; Salas-Salvadó J. *Olive oil intake and risk of cardiovascular disease and mortality in the PREDIMED Study*. **BMC MED** 2014 May 13;12:78. doi: 10.1186/1741-7015-12-78.

FACTOR DE IMPACTO: 7,276

Guasch-Ferré et al. *BMC Medicine* 2014, 12:78
<http://www.biomedcentral.com/1741-7015/12/78>



RESEARCH ARTICLE

Open Access

Olive oil intake and risk of cardiovascular disease and mortality in the PREDIMED Study

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Abstract

Background: It is unknown whether individuals at high cardiovascular risk sustain a benefit in cardiovascular disease from increased olive oil consumption. The aim was to assess the association between total olive oil intake, its varieties (extra virgin and common olive oil) and the risk of cardiovascular disease and mortality in a Mediterranean population at high cardiovascular risk.

Methods: We included 7216 men and women at high cardiovascular risk, aged 55 to 80 years, from the PREVENCIÓN con Dieta MEDiterránea (PREDIMED) study, a multicenter, randomized, controlled, clinical trial. Participants were randomized to one of three interventions: Mediterranean Diets supplemented with nuts or extra-virgin olive oil, or a control low-fat diet. The present analysis was conducted as an observational prospective cohort study. The median follow-up was 4.8 years. Cardiovascular disease (stroke, myocardial infarction and cardiovascular death) and mortality were ascertained by medical records and National Death Index. Olive oil consumption was evaluated with validated food frequency questionnaires. Multivariate Cox proportional hazards and generalized estimating equations were used to assess the association between baseline and yearly repeated measurements of olive oil intake, cardiovascular disease and mortality.

Results: During follow-up, 277 cardiovascular events and 323 deaths occurred. Participants in the highest energy-adjusted tertile of baseline total olive oil and extra-virgin olive oil consumption had 35% (HR: 0.65; 95% CI: 0.47 to 0.89) and 39% (HR: 0.61; 95% CI: 0.44 to 0.85) cardiovascular disease risk reduction, respectively, compared to the reference. Higher baseline total olive oil consumption was associated with 48% (HR: 0.52; 95% CI: 0.29 to 0.93) reduced risk of cardiovascular mortality. For each 10 g/d increase in extra-virgin olive oil consumption, cardiovascular disease and mortality risk decreased by 10% and 7%, respectively. No significant associations were found for cancer and all-cause mortality. The associations between cardiovascular events and extra virgin olive oil intake were significant in the Mediterranean diet intervention groups and not in the control group.

Conclusions: Olive oil consumption, specifically the extra-virgin variety, is associated with reduced risks of cardiovascular disease and mortality in individuals at high cardiovascular risk.

Trial registration: This study was registered at [controlled-trials.com](http://www.controlled-trials.com) (<http://www.controlled-trials.com/ISRCTN35739639>). International Standard Randomized Controlled Trial Number (ISRCTN): 35739639. Registration date: 5 October 2005.

Keywords: Olive oil, Cardiovascular, Mortality, Mediterranean Diet, PREDIMED

8. Tresserra-Rimbau A; Rimm EB; Medina-Remón A; Martínez-González MA; López-Sabater MC; Covas MI; Corella D; Salas-Salvadó J; Gómez-Gracia E; Lapetra J; Arós F; **Fiol M**; Ros E; Serra-Majem L; Pintó X; Muñoz MA; Gea A; Ruiz-Gutiérrez V; Estruch R; Lamuela-Raventós RM. *Polyphenol intake and mortality risk: a re-analysis of the PREDIMED trial*. **BMC MED** 2014 May 13;12:77. doi: 10.1186/1741-7015-12-77.
FACTOR DE IMPACTO: 7,276

Tresserra-Rimbau et al. *BMC Medicine* 2014, 12:77
<http://www.biomedcentral.com/1741-7015/12/77>



RESEARCH ARTICLE

Open Access

Polyphenol intake and mortality risk: a re-analysis of the PREDIMED trial

Anna Tresserra-Rimbau^{1,2}, Eric B Rimm³, Alexander Medina-Remón^{2,17}, Miguel A Martínez-González^{2,4}, M Carmen López-Sabater^{1,2}, María I Covas^{2,5}, Dolores Corella^{2,6}, Jordi Salas-Salvadó^{2,7}, Enrique Gómez-Gracia^{2,8}, José Lapetra^{2,9}, Fernando Arós^{2,10}, Miquel Fiol^{2,11}, Emili Ros^{2,12}, Lluís Serra-Majem^{2,13}, Xavier Pintó^{2,14}, Miguel A Muñoz^{2,15}, Alfredo Gea^{2,4}, Valentina Ruiz-Gutiérrez^{2,16}, Ramón Estruch^{2,17}, Rosa M Lamuela-Raventós^{1,2*} and on behalf of the PREDIMED Study Investigators

Abstract

Background: Polyphenols may lower the risk of cardiovascular disease (CVD) and other chronic diseases due to their antioxidant and anti-inflammatory properties, as well as their beneficial effects on blood pressure, lipids and insulin resistance. However, no previous epidemiological studies have evaluated the relationship between the intake of total polyphenols intake and polyphenol subclasses with overall mortality. Our aim was to evaluate whether polyphenol intake is associated with all-cause mortality in subjects at high cardiovascular risk.

Methods: We used data from the PREDIMED study, a 7,447-participant, parallel-group, randomized, multicenter, controlled five-year feeding trial aimed at assessing the effects of the Mediterranean Diet in primary prevention of cardiovascular disease. Polyphenol intake was calculated by matching food consumption data from repeated food frequency questionnaires (FFQ) with the Phenol-Explorer database on the polyphenol content of each reported food. Hazard ratios (HR) and 95% confidence intervals (CI) between polyphenol intake and mortality were estimated using time-dependent Cox proportional hazard models.

Results: Over an average of 4.8 years of follow-up, we observed 327 deaths. After multivariate adjustment, we found a 37% relative reduction in all-cause mortality comparing the highest versus the lowest quintiles of total polyphenol intake (hazard ratio (HR) = 0.63; 95% CI 0.41 to 0.97; *P* for trend = 0.12). Among the polyphenol subclasses, stilbenes and lignans were significantly associated with reduced all-cause mortality (HR = 0.48; 95% CI 0.25 to 0.91; *P* for trend = 0.04 and HR = 0.60; 95% CI 0.37 to 0.97; *P* for trend = 0.03, respectively), with no significant associations apparent in the rest (flavonoids or phenolic acids).

Conclusions: Among high-risk subjects, those who reported a high polyphenol intake, especially of stilbenes and lignans, showed a reduced risk of overall mortality compared to those with lower intakes. These results may be useful to determine optimal polyphenol intake or specific food sources of polyphenols that may reduce the risk of all-cause mortality.

Clinical trial registration: ISRCTN35739639.

Keywords: Polyphenol intake, All-cause mortality, PREDIMED, Mediterranean diet, Stilbenes, Lignans

9. Ramon MA, Gimeno-Santos E, Ferrer J, Balcells E, Rodríguez E, de Batlle J, Gómez FP, **Sauleda J**, Ferrer A, Barberà JA, Agustí A, Gea J, Rodríguez-Roisin R, Antó JM, Garcia-Aymerich J; PAC-COPD Study Group. *Hospital admissions and exercise capacity decline in patients with COPD*. **EUR RESPIR J** 2014 Apr;43(4):1018-27. doi: 10.1183/09031936.00088313. Epub 2014 Jan 3.
FACTOR DE IMPACTO: 7,125

 **EUROPEAN RESPIRATORY journal**
OFFICIAL SCIENTIFIC JOURNAL OF THE ERS

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Hospital admissions and exercise capacity decline in patients with COPD

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Abstract

Exercise capacity declines with time and is an important determinant of health status and prognosis in patients with chronic obstructive pulmonary disease (COPD). We hypothesised that hospital admissions are associated with exercise capacity decline in these patients.

Clinical and functional variables were collected for 342 clinically stable COPD patients. The 6-min walk distance (6MWD) was determined at baseline and after a mean±SD of 1.7±0.3 years. Information on hospitalisations during follow-up was obtained from centralised administrative databases. Linear regression was used to model changes in exercise capacity.

Patients were mostly male (92%), with mean±SD age 67.9±8.6 years, post-bronchodilator forced expiratory volume in 1 s 54±17% predicted and baseline 6MWD 433±93 m. During follow-up, 6MWD decreased by 21.9±51.0 m·year⁻¹ and 153 (45%) patients were hospitalised at least once. Among patients admitted only for COPD-related causes (50% of those ever admitted), the proportion presenting a clinically significant loss of 6MWD was higher than in patients admitted for only nonrespiratory conditions (53% versus 29%, p=0.040). After adjusting for confounders, annual 6MWD decline was greater (26 m·year⁻¹, 95% CI 13-38 m·year⁻¹; p<0.001) in patients with more than one all-cause hospitalisation per year, as compared with those with no hospitalisations.

Hospitalisations are related to a greater decline in exercise capacity in COPD.

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FACTOR DE IMPACTO: 7,125



Target lobe volume reduction and COPD outcome measures after endobronchial valve therapy

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Abstract

Endobronchial valve (EBV) therapy may be associated with improvements in chronic obstructive pulmonary disease-related **outcomes** and may therefore be linked to improvements in the body mass index, airflow obstruction, dyspnoea, exercise capacity (BODE) index.

Data from 416 patients with advanced emphysema and hyperinflation across Europe and USA, who were randomised to EBV (n=284) or conservative **therapy** (n=132) were analysed. Quantitative image analysis was used to compare the **volume** of the **targeted lobe** at baseline and at 6 months to determine **target lobe volume reduction** (TLVR).

44% of patients receiving EBV **therapy** (versus 24.7% of controls) had clinically significant improvements in the BODE index ($p < 0.001$). BODE index was significantly reduced by mean \pm SD 1.4 \pm 1.8, 0.2 \pm 1.3 and 0.1 \pm 1.3 points in patients with TLVR $> 50\%$, 20%-50% and $< 20\%$, respectively (intergroup differences $p < 0.001$), but increased by 0.3 \pm 1.2 points in controls. Changes in BODE were predicted by baseline BODE and correlated significantly with lobar exclusion and lung volumes at 6 months.

A greater proportion of patients in the treatment group than in the control group achieved a clinically meaningful improvement in BODE index; however, the likelihood of benefit was less than half in both groups. Patients in whom TLVR was obtained had greater improvements in clinical **outcomes**.