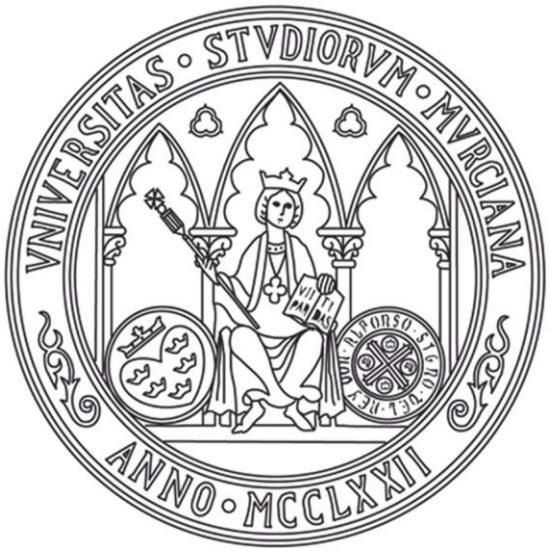


# UNIVERSIDAD DE MURCIA

ESCUELA INTERNACIONAL DE DOCTORADO

Nivel e Influencia de la Actividad Física en Jóvenes y Adultos Españoles con Enfermedades Pulmonares Crónicas

**Dña. Sheila Sánchez Castillo**

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# UNIVERSIDAD DE MURCIA

## ESCUELA INTERNACIONAL DE DOCTORADO

# Nivel e Influencia de la Actividad Física en Jóvenes y Adultos Españoles con Enfermedades Pulmonares Crónicas

Tesis Doctoral Internacional para optar al grado de Doctor Internacional por:

**Dña. Sheila Sánchez Castillo**

Directores:

**Dr. Guillermo Felipe López Sánchez; Dr. Lee Smith;**

**Dr. Arturo Díaz Suárez**

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The presentation of the Doctoral Thesis entitled: **"LEVEL AND IMPACT OF PHYSICAL ACTIVITY IN SPANISH YOUTH AND ADULTS WITH CHRONIC PULMONARY DISEASES",** conducted by Ms. Sheila Sánchez Castillo, under my immediate management and supervision, presented to obtain the Doctoral Degree by the University of Murcia.

Cambridge, September 1st, 2021

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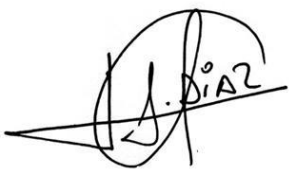
En Murcia, a 1 de septiembre de 2021.

Dº Arturo Díaz Suárez



*“Un camino de mil millas comienza con un paso”*

*Benjamin Franklin*

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# CONTENIDOS [CONTENTS]

## TESIS DOCTORAL COMO COMPENDIO DE PUBLICACIONES

Esta tesis doctoral se presenta como un compendio de seis artículos publicados en revistas científicas de impacto indizadas en el Journal Citation Report (1 Q1, 3 Q2, 1 Q3, 1 Q4):

- Sánchez-Castillo, S., Smith, L., Díaz-Suárez, A. & López-Sánchez, G.F. (2019). Physical Activity Behaviour in People with COPD Residing in Spain: A Cross-Sectional Analysis. *Lung*, *197*(6), 769-775. https://doi.org/10.1007/s00408-019-00287-4 . PMID: 31686208.
- Sánchez-Castillo, S., Smith, L., Díaz-Suárez, A. & López-Sánchez, G.F. (2020). Associations between Physical Activity and Comorbidities in People with COPD Residing in Spain: A Cross-Sectional Analysis. *International Journal of Environmental Research and Public Health, 17*(2), 594. https://doi.org/10.3390/ijerph17020594
- Sánchez-Castillo, S., Smith, L., Díaz-Suárez, A. & López-Sánchez, G.F. (2020). Levels of physical activity in Spanish asthmatics: A cross-sectional study. *Medicina, 56*(12), 643. https://doi.org/10.3390/medicina56120643
- Sánchez-Castillo, S., Smith, L., Díaz-Suárez, A. & López-Sánchez, G.F. (2020). Analysis of physical activity and comorbidities in Spanish asthmatics. *Sustainability*, *12* (13), 5256. https://doi.org/10.3390/su12135256
- Sánchez-Castillo, S., Smith, L., Díaz-Suárez, A. & López-Sánchez, G.F. (2021). Physical activity behavior in people with asthma and COPD overlap residing in Spain: A cross-sectional analysis. *Journal of asthma*. https://doi.org/10.1080/02770903.2021.1888977
- Sánchez-Castillo, S., Smith, L., Díaz-Suárez, A. & López-Sánchez, G.F. (2021). Association between Physical Activity and Comorbidities in Spanish People with Asthma-COPD Overlap. *Sustainability, 13*(14), 7580. https://doi.org/10.3390/su13147580

Para mantener una apariencia homogénea en el documento, los seis artículos se presentan en un mismo formato. En el apartado de anexos se incluye la primera página de cada uno de los trabajos tal y como fueron publicados.

**RESUMEN**

***Introducción:*** La enfermedad pulmonar obstructiva crónica (EPOC) y el asma son dos de las cinco enfermedades respiratorias más significativas. Ambas enfermedades son consideradas como importantes problemas de salud pública debido, no solo a su elevada prevalencia, sino también a su carga socioeconómica y elevada morbimortalidad. En 2019, la herramienta de resultados de Carga Global de Enfermedad (Global Burden of Disease–GBD-), mostró una prevalencia mundial de asma del 3,5% y del 2,8% en EPOC. Además, el 5,8% de las muertes en el mundo se debieron a la EPOC. Asimismo, existen pacientes que muestran características de ambas enfermedades, lo que se conoce como solapamiento de asma y EPOC (ACO). Algunos estudios recientes han sugerido que la actividad física (AF) podría tener un efecto protector en pacientes con EPOC y asma, pues se asocia a una mejor calidad de vida y menor morbimortalidad.

***Objetivos:*** Analizar los niveles de AF y estudiar las relaciones entre estos niveles de AF y la presencia de comorbilidades en jóvenes y adultos españoles con enfermedades pulmonares crónicas como EPOC, asma y ACO.

**Métodos:** Esta tesis doctoral se compone de seis artículos con un diseño transversal. En todos ellos, se analizaron los datos de la Encuesta Nacional de Salud 2017, en la que participaron un total de 23.089 personas residentes en España con al menos 15 años, de las cuales 17.777 respondieron al Cuestionario Internacional de AF versión corta (IPAQ-SF). Aquellos adultos mayores de 69 años fueron excluidos, porque no completaron el IPAQ-SF, pues éste fue desarrollado y testado en personas de entre 15 y 69 años. Según el estudio, se incluyeron como participantes aquellos que respondieron positivamente a la pregunta: "¿Alguna vez ha sido diagnosticado por un médico con EPOC y/o asma?" A nivel de análisis estadístico, se emplean estadísticos descriptivos para definir la muestra, para detallar la cantidad de AF semanal (MET·min/semana) y el nivel de AF (bajo/moderado/alto), y para determinar la prevalencia de las diferentes comorbilidades. Para establecer las diferencias significativas en la cantidad semanal de AF se utilizan los test U Mann-Whitney y H Kruskal-Wallis, mientras que en el nivel de AF se calcula mediante el estadístico chi-cuadrado. La asociación entre el nivel de AF y las comorbilidades se analiza mediante tres modelos distintos de regresión logística multinomial: 1) sin ajustar; 2) ajustado por sexo, índice de masa corporal (IMC), edad,

estado civil, nivel educativo, tabaco y alcohol; 3) ajustado por las mismas variables que el modelo dos, el consumo de medicamentos y la presencia de comorbilidades.

**Resultados y conclusiones:** El 37,8% de españoles con EPOC muestran un nivel bajo de AF, predominando un volumen inferior en mujeres, en mayores de 60 años, en abstemios y en aquellos con obesidad o bajo peso. En asmáticos, el porcentaje de españoles con nivel bajo de AF es ligeramente inferior (31,6%), encontrándose los niveles significativamente más reducidos en mujeres, en aquellos mayores de 30, en aquellos con bajo nivel educativo, en aquellos casados y/o viviendo en pareja, en abstemios y en obesos. En aquellos con ACO, el 35,9% presentan un nivel bajo de AF, estando estos niveles significativamente más reducidos en mayores de 60 años y en obesos. Aunque en valores promedios los españoles con EPOC, asma y ACO muestren un nivel de AF moderado, más del 30% no alcanzan las recomendaciones. Además, un nivel bajo de AF se asocia con un mayor riesgo de comorbilidades, concretamente de incontinencia urinaria, estreñimiento crónico, dolor lumbar crónico, cataratas, ansiedad crónica y osteoporosis. Por ello, se recomienda implementar programas para concienciar sobre la importancia y los beneficios de la AF en personas con EPOC y/o asma, focalizándose en aquellos grupos con niveles más reducidos.

**[SUMMARY]**

**Introduction:** Chronic Obstructive Pulmonary Disease (COPD) and asthma are two of the major five respiratory diseases. Both conditions are important public health problems not only because their increasing prevalence, but also because their socioeconomic burden and high morbimortality. In 2019, the Global Burden of Disease (GBD) showed a worldwide prevalence of asthma and COPD of 3.5% and 2.8%, respectively. Moreover, COPD was accountable for 5.8% of global deaths. Additionally, some patients have clinical feature of both asthma and COPD, which is known as Asthma-COPD Overlap (ACO). Several studies suggested PA could have a protective effect among patients with COPD and asthma, since it is related with a better quality of life and lower morbimortality.

**Objectives:** To analyse PA levels and to study the associations between those PA levels and the presence of comorbidities in Spanish youth and adults with chronic pulmonary diseases like COPD, asthma and ACO.

**Methods:** This doctoral thesis is composed of six observational papers with a cross-sectional design. Data from the Spanish National Health Survey 2017 were analysed in all papers. A total of 23 089 people residing in Spain and aged 15 years and over participated in the survey, of which 17 777 answered the International Physical Activity Questionnaire Short Form (IPAQ-SF). Those aged over 69 years were excluded, since they did not complete IPAQ-SF, because it was developed and tested in people aged from 15 to 69 years. Depending on the paper, those who answered positively to the following question: Have you ever been diagnosed with COPD/asthma/both by a physician? were included in the analyses. Considering the statistical analysis, descriptive statistics were used to define the sample, to establish weekly amount of PA (MET·min/week) and PA level (low/moderate/high), and to determine the prevalence of the different comorbidities. To establish significant differences in weekly amount of PA, Mann-Whitney U test and Kruskal-Wallis H test were used. In case of PA level, chi-squared test were employed to determine the significant differences. Associations between PA level and comorbidities were analysed using the multivariable logistic regression analyses in three different models: 1) not adjusted; 2) adjusted for sex, body mass index (BMI), age, marital status, education level, smoking and alcohol consumption; 3) adjusted for the same variables as model 2 adding the variables medication intake and presence of comorbidities.

**Results and conclusions:** 37.8% of Spanish with COPD showed a low level of PA. Weekly volume was lower in women, those older than 60 years, those abstemious, and those obese or underweight. Considering asthmatics, the percentage of Spanish with low PA level was slightly lower (31.6%). PA levels were significantly reduced in women, those older than 30 years, those with low education level, those married and/or living together, those abstemious and those with obesity. Meanwhile, 35.9% of those with ACO showed a low level of PA, being significantly reduced in those older than 60 years and those with obesity. Although, on average, Spanish with COPD, asthma and ACO showed a moderate PA level, more than 30% did not achieve PA recommendations. Moreover, a low level of PA is related with a higher risk of comorbidities, specifically urinary incontinence, chronic constipation, chronic lumbar pain, cataracts, chronic anxiety and osteoporosis. Therefore, it is recommended to implement programs that promote the importance and benefits of PA among those with COPD and/or asthma, focusing in those groups with reduced PA levels.

# *INTRODUCCIÓN*

La enfermedad pulmonar obstructiva crónica (EPOC) y el asma son dos de las cinco enfermedades respiratorias más importantes según el Foro de Sociedades Respiratorias Internacionales (FIRS, 2017). Ambas enfermedades son consideradas importantes problemas de salud pública debido a su elevada prevalencia, a su alta morbimortalidad y a su carga socioeconómica (Global Initiative for Asthma [GINA], 2020 & Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2020). En 2019, la herramienta de carga global de enfermedad mostró una prevalencia mundial de asma y EPOC de 3.5% y 2.8%, respectivamente (Institute for Health, Metrics and Evaluation [IHME], 2019). Además, la EPOC fue la tercera causa de muerte en 2019, siendo responsable de aproximadamente el 5,8% del total de fallecimientos (IHME, 2019; World Heatlh Organization [WHO], 2020)

A nivel nacional, el estudio EPI-SCAN (EPIdemiologic Study of COPD in SpAiN) mostró una prevalencia de EPOC del 10,2% en adultos de entre 40 y 80 años (Miravitlles et al., 2009). Anteriormente, el estudio IBERPOC (Estudio Epidemiológico de la EPOC en España) determinó una prevalencia de EPOC del 9,1% en adultos de 40 a 69 años (Sobradillo et al., 1999). Sin embargo, siguiendo los datos de la Encuesta Nacional de Salud 2017, se encontró una prevalencia de EPOC en españoles de entre 15 y 69 años del 3,2% con distribución similar entre sexos (3,3% hombres vs 3,2% mujeres), mientras que la prevalencia de asma era ligeramente superior con un 4,6%, siendo mayor en mujeres (5.6%) (Ministerio de Sanidad, Consumo y Bienestar Social, 2018).

Ambas enfermedades se caracterizan por una limitación del flujo aéreo y la presencia de síntomas respiratorios, pero existen ciertas diferencias entre ellas que se deben tener en cuenta. La EPOC se describe como una limitación persistente del flujo aéreo espiratorio, con una proporción entre el volumen espiratorio forzado en el primer segundo ($VEF_1$) y la capacidad vital forzada (CVF) inferior a 0,70 tras el uso del broncodilatador (GOLD, 2020). En asmáticos, la limitación del flujo aéreo y los síntomas como sibilancias, tos, dificultad respiratoria y presión en el pecho varían en intensidad y mejoran con el uso de broncodilatadores o incluso espontáneamente (GINA, 2020). El asma se suele diagnosticar antes de los 40 años mientras que la EPOC suele ocurrir a partir de los 40 y generalmente en aquellos que han estado expuestos al humo del tabaco u otras partículas nocivas (GINA, 2020). No obstante, encontramos algunos pacientes que presentan características clínicas de ambas enfermedades. Estudios previos utilizaban el término síndrome de solapamiento de asma y EPOC (ACOS) para referirse a estos

pacientes (Alshabat et al., 2015; Tommola et al., 2017), pero las últimas actualizaciones de las guías GOLD (2020) y GINA (2020) utilizan el término solapamiento asma-EPOC (ACO) o asma+EPOC para referirse a estos fenotipos clínicos, pues no se trata de una enfermedad propia, sino de la combinación de ambas enfermedades.

Los costes sanitarios derivados de estas enfermedades no pasan inadvertidos. En España, la EPOC origina aproximadamente el 10% de consultas de atención primaria, el 40% de consultas externas de neumología y el 7% de hospitalizaciones anuales (Álvarez-Sala et al., 2001). Asimismo, una parte importante del coste del asma se asocia a admisiones de urgencia, hospitalizaciones y mortalidad (Barnes et al., 1996). La falta de control del asma supone costes elevados (Doz et al., 2013), que podrían reducirse mejorando el control de la misma.

En pacientes con ACO, a pesar de su dificultad de diagnóstico, especialmente en fumadores y adultos mayores, la literatura previa sugiere que éstos tienen mayor probabilidad de presentar síntomas respiratorios (Menezes et al., 2014; Miravitlles et al., 2013), peor función pulmonar (Menezes et al., 2014), mayor uso de los recursos sanitarios y hospitalizaciones (Andersen et al., 2013; Hardin et al., 2014; Menezes et al., 2014), calidad de vida pobre (Alshabanat et al., 2015; Kauppi, 2011), exacerbaciones frecuentes (Alshabanat et al., 2015) y una mayor mortalidad (Kendzerska et al., 2011), en comparación con aquellos que presentan solo EPOC o asma.

**Actividad física y enfermedades pulmonares crónicas**

La realización de AF de manera regular y mantenida ayuda en la prevención, tanto primaria como secundaria, de diversas enfermedades crónicas (Haskell et al., 2007; Marques et al., 2018; Warburton et al., 2006). A pesar de ello, investigaciones previas encontraron limitada la práctica de AF en personas con EPOC (Troosters et al., 2013), incluso en etapas tempranas (Van Helvoort et al., 2016; Van Remoortel et al., 2016), lo que se relaciona con un mayor riesgo de hospitalización y readmisión (Garcia-Aymerich et al., 2006) e incluso la muerte (García-Río et al., 2012; Waschki et al., 2011). De manera similar, en asmáticos, los síntomas del asma junto con el miedo de aparición de broncoconstricción inducida por el ejercicio (BIE), podrían tener un impacto negativo sobre sus niveles de AF (Cordova-Rivera et al., 2018).

Sin embargo, la literatura sugiere que la práctica regular de AF en personas con EPOC se asocia con una mejor calidad de vida (Cebollero et al., 2018; García-Aymerich

et al., 2003; García-Aymerich et al., 2009) y una menor morbilidad (Benzo et al., 2010; Waschki et al., 2011). Un estudio de cohorte prospectivo llevado a cabo en Barcelona mostró que aquellos que caminaban al menos una hora al día tenían menor riesgo de hospitalización por exacerbación (García-Aymerich et al., 2003). Recientemente, otro estudio prospectivo que analizó la eficacia clínica de un programa de caminata en personas con EPOC encontró mejoras tanto en la calidad de vida como en el número de exacerbaciones (Cebollero et al., 2018).

Igualmente, la práctica regular de AF también favorece el control del asma (Côté et al., 2018; Freitas et al., 2019), reduciendo consecuentemente el riesgo de crisis asmática (GINA, 2020). Diferentes investigaciones sugieren que la realización de AF de manera regular reduce los síntomas del asma (Loponen et al., 2018; Turner et al., 2011), la sensibilidad de las vías aéreas (França-Pinto et al., 2015), la EIB (Côté et al., 2018) y el riesgo de exacerbaciones asmáticas (França-Pinto et al., 2015). También se ha demostrado que la AF mejora la capacidad física (Carson et al., 2013; Eichenberger et al., 2013) y la calidad de vida (Côté et al., 2018; França-Pinto et al., 2015) en personas asmáticas. Respecto a la función pulmonar, existen diferentes puntos de vista sobre los beneficios de la AF. Carson et al. (2013) no encontraron un impacto significativo de la AF sobre la capacidad pulmonar. Por el contrario, Eichenberger et al. (2013) encontraron mejoras en el $VEF_1$ en aquellos asmáticos que realizaban entrenamiento físico. Además, una revisión sistemática determinó que aquellos que realizaban más AF tendrían menor riesgo de desarrollar asma, lo que contribuiría también a reducir los costes sanitarios derivados de la enfermedad (França-Pinto et al., 2015).

Por su parte, en aquellos con solapamiento de asma y EPOC, la literatura sobre los niveles de AF es escasa, pero una investigación reciente en adultos españoles (40-80 años) reveló niveles inferiores de AF en comparación con aquellos que sólo tenían EPOC. Sin embargo, la muestra estaba formada únicamente por 67 adultos con ACO, por lo que la representatividad de los resultados es limitada (Miravitlles et al., 2013).

**Comorbilidades y nivel de actividad física**

La EPOC y el asma son enfermedades heterogéneas que pueden asociarse con otras comorbilidades. El término comorbilidad fue acuñado por Feinstein en 1970 como “cualquier enfermedad adicional coexistente”.

En asmáticos, las comorbilidades pueden ser independientes o estar asociadas a la enfermedad, pero, en cualquier caso, éstas pueden complicar el manejo clínico del asma (Boulet, 2009; Ledford & Lockey, 2013), aumentar el riesgo de exacerbación (Zhang et al., 2009), suponer atención asmática no programada (Steppuhn, Langen, Keil & Scheidt-Nave, 2014), un vago control del asma y deterioro de la calidad de vida (GOLD, 2020) e incluso aumentar la mortalidad (To et al., 2014). Las comorbilidades más comunes en pacientes con asma son la rinosinusitis, las alergias alimentarias, el síndrome de apnea obstructiva del sueño (SAOS), el reflujo gastroesofágico (ERGE) y los problemas de salud mental (Boulet, 2009; Ceylan et al., 2019; GOLD, 2020; Ledford & Lockey, 2013). Además, un estudio reciente mostró también una prevalencia elevada en adultos asmáticos escoceses de hipertensión, depresión, dolor muscular y EPOC (Weatherburn et al., 2017). La literatura existente muestra que los asmáticos presentan significativamente más comorbilidades que los no asmáticos (Gershon et al., 2012; Su et al., 2016). Asimismo, aquellos pacientes obesos muestran mayores dificultades en el control del asma, probablemente debido a un tipo diferente de inflamación de las vías respiratorias, que contribuye a desarrollar otras comorbilidades como SAOS y ERGE, así como por un bajo estado de forma y reducido volumen pulmonar causado por la grasa abdominal, lo que favorece la disnea (GOLD, 2020).

La presencia de comorbilidades en aquellos con EPOC es bastante alta. Un estudio reciente encontró que el 80% de los pacientes con EPOC presentaban al menos una comorbilidad, aunque generalmente coexisten múltiples comorbilidades (Sieve et al., 2015). Previamente Barr et al. (2009) establecieron una media de nueve comorbilidades en personas con EPOC. Las comorbilidades con mayor prevalencia en pacientes con EPOC son de tipo cardiovascular, metabólicas, musculoesqueléticas y psicológicas (Franssen & Rochester, 2014). Éstas pueden estar presentes en pacientes en cualquier estadio y conlleva una mayor tasa de hospitalización (Mannino et al., 2008) y aumento de la mortalidad (Barnes & Celli, 2009). Además, se encontró que el nivel de AF puede verse deteriorado por la presencia de comorbilidades, con independencia del grado de limitación del flujo aéreo y el tipo de comorbilidad (Miller et al., 2013; Sievi et al., 2015).

Predeciblemente, la presencia de comorbilidades también es bastante común en pacientes con ACO (Barrecheguren et al., 2020; Krishnan et al., 2019; Rubio et al., 2017; van Boven et al., 2016). Investigaciones previas mostraron que la diabetes, la enfermedad cardiovascular, la hipertensión, la dispepsia, la arritmia, la úlcera gástrica, la ansiedad y

la depresión eran las comorbilidades más frecuentes en pacientes con ACO. (Barrecheguren et al., 2020; Krishnan et al., 2019; Rubio et al., 2017).

No hay evidencia sobre cómo los niveles de AF pueden contribuir a reducir el riesgo de comorbilidades en asmáticos y pacientes con ACO, y en pacientes con EPOC es bastante escasa.

# *[INTRODUCTION]*

Chronic obstructive pulmonary disease (COPD) and asthma are two of the five major respiratory diseases, established by the Forum of International Respiratory Societies (FIRS, 2017). Both conditions are important public health problems owing to their increasing prevalence, high morbimortality and socioeconomic burden (GINA, 2020 & GOLD, 2020). In 2019, the Global Burden of Disease tool showed a worldwide prevalence of asthma and COPD of 3.5% and 2.8%, respectively (IHME, 2019). Moreover, COPD was the third leading cause of death, responsible for approximately a 5.8% of total deaths in 2019 (IHME, 2019; WHO, 2020).

Considering national data, the EPI-SCAN study (Epidemiologic Study of COPD in Spain), revealed a national prevalence of COPD of 10.2% in adults aged from 40 to 80 years (Miravitlles et al., 2009). Previously, the IBERPOC (Epidemiological study of COPD in Spain) found a COPD prevalence of 9,1% in people aged from 40 to 69 years (Sobradillo et al., 1999). However, according to data from the Spanish National Health Survey 2017, the prevalence of COPD in Spanish people aged 15 to 69 years was found to be 3.2%, with a similar distribution between sexes (3.3%men vs 3.2% women), while the prevalence of asthma was slightly higher, with a 4.6%, being greater in women (5.6%) (Ministerio de Sanidad, Consumo y Bienestar Social, 2018).

These respiratory conditions are characterized by airflow limitation and respiratory symptoms, but there are some differences between them that need to be considered. COPD is defined by persistent expiratory airflow limitation, with a ratio between forced expiratory volume in the first second ($FEV_1$) and forced vital capacity (FVC) lower than 0.70 post-bronchodilator use (GOLD, 2020). In asthmatics, expiratory airflow limitation and symptoms such as wheeze, cough, shortness of breath and chest tightness vary over time in intensity and improve with the use of bronchodilators or even spontaneously (GINA, 2020). Onset of asthma tends to be before the age of 40 years while COPD tends to occur after 40 years and generally in those who have been exposed to tobacco or any other noxious particles (GINA, 2020). However, some patients have clinical features of both asthma and COPD. Previous studies have used the term Asthma-COPD overlap syndrome (ACOS) to describe these patients (Alshabat et al., 2015; Tommola et al., 2017), but latest updates of GOLD (2020) and GINA (2020) have named these clinical phenotypes Asthma-COPD overlap (ACO) or asthma+COPD, since it is not a definition of a single condition but a combination of both asthma and COPD.

Healthcare costs caused by these diseases have not gone unnoticed. Importantly, a total of 10% of primary care consultations, 40% of neumology consultations and 7% of annual hospitalizations in Spain are due to COPD (Álvarez-Sala et al., 2001). Moreover, an important part of the cost of asthma is associated to urgent admissions, hospitalization and mortality (Barnes et al., 1996). Thus, uncontrolled asthma has significantly high costs (Doz et al., 2013), which could be reduced by improving disease control.

In turn, despite the difficulty of diagnosing ACO patients, especially in smokers and older adults, previous literature suggests that patients with ACO are more likely to have respiratory symptoms (Menezes et al., 2014; Miravitlles et al., 2013), worse lung function (Menezes et al., 2014), higher rates of use of health care resources and hospitalizations (Andersen et al., 2013; Hardin et al., 2014; Menezes et al., 2014), poor quality of life (Alshabanat et al., 2015; Kauppi, 2011), experience frequent exacerbations (Alshabanat et al., 2015) and have a higher rate of mortality (Kendzerska et al., 2011), compared with their pairs with asthma or COPD alone.

**Physical activity and chronic respiratory diseases**

Regular and sustained participation in PA aids in both primary and secondary prevention of several chronic diseases (Haskell et al., 2007; Marques et al., 2018; Warburton et al., 2006). However, previous investigations revealed a limitation of PA in people with COPD (Troosters et al., 2013), even in early stages (Van Helvoort et al., 2016; Van Remoortel et al., 2016), which is related with a high risk of hospitalization and readmission (Garcia-Aymerich et al., 2006) and even death (García-Río et al., 2012; Waschki et al., 2011). Similarly, in asthmatics, asthma symptoms together with the fear of having exercise-induced bronchoconstriction (EIB), could have a negative impact on PA levels (Cordova-Rivera et al., 2018).

Even though, previous literature suggests that regular participation in PA is associated with better quality of life (Cebollero et al., 2018; García-Aymerich et al., 2003; García-Aymerich et al., 2009) and fewer morbidities in people with COPD (Benzo et al., 2010; Waschki et al., 2011). A prospective cohort study carried out in Barcelona revealed that those who walked for at least one hour per day had a lower risk of hospitalization by a COPD exacerbation (García-Aymerich et al., 2003). Recently, another prospective study that analysed the clinic efficacy of a walking program in people with COPD showed improvements in both quality of life and exacerbation's number (Cebollero et al., 2018).

In the same way, regular PA aids in the control of asthma (Côté et al., 2018; Freitas et al., 2019) which consequently reduces the risk of asthma crisis (GINA, 2020). Different investigations suggest that a usual amount of PA reduces the symptoms of asthma (Loponen et al., 2018; Turner et al., 2011), airway responsiveness (França-Pinto et al., 2015), EIB (Côté et al., 2018) and the risk of asthma exacerbations (França-Pinto et al., 2015). It has also been demonstrated that PA improves exercise capacity (Carson et al., 2013; Eichenberger et al., 2013) and quality of life (Côté et al., 2018; França-Pinto et al., 2015) in people suffering from asthma. Regarding lung function, there is no agreement about the benefits of PA. Carson et al. (2013) found that PA had no significant impact on lung function, but Eichenberger et al. (2013) found improvements in $FEV_1$ in asthmatics who engaged in exercise training. Moreover, a systematic review proposed that people involved in more PA may have less risk of developing asthma, which will also contribute to reduce health cost (França-Pinto et al., 2015).

In those with ACO, literature about PA level is scarce but a recent investigation in Spanish adults (aged 40-80 years) revealed lower levels of PA in comparison to those with only COPD. However, only 67 adults with ACO participated in the study and thus the representation of the findings is limited (Miravitlles et al., 2013).

**Comorbidities and physical activity level**

Both asthma and COPD are heterogeneous diseases that can be associated with several comorbidities. The term comorbidity was coined by Feinstein in 1970 and it refers to “any additional co-existing ailment”.

In asthmatics, comorbidities could be independent or associated with the disease, but they could complicate the clinical management of asthma (Boulet, 2009; Ledford & Lockey, 2013), increasing the risk for exacerbation (Zhang et al., 2009), unscheduled asthma care (Steppuhn et al., 2014), poor asthma control and impaired of life quality (GOLD, 2020) and mortality (To et al., 2014). The most frequent conditions are rhinosinusitis, food allergy, obstructive sleep apnoea syndrome (OSAS), gastroesophageal reflux (GER) and mental health disorders (Boulet, 2009; Ceylan et al., 2019; GOLD, 2020; Ledford & Lockey, 2013). Moreover, a recent study showed a high prevalence of hypertension, depression, pain and COPD among Scottish adults with asthma (Weatherburn et al., 2017). Previous literature found that asthmatics have significantly more comorbid conditions than non-asthmatics (Gershon et al., 2012; Su et

al., 2016). Besides, obese patients show more difficulties in the control of asthma, probably because of a different type of airway inflammation that contributes to other comorbidities like OSAS and GER and due to a poor shape and a decrease in lung volume caused by abdominal fat, which contributes to dyspnoea (GOLD, 2020).

The presence of comorbidities among patients with COPD is pretty high. It was found that 80% of COPD patients had at least one comorbidity (Sieve et al., 2015), but generally multiple comorbidities coexist. Previously, Barr et al. (2009) found an average of nine comorbidities in people with COPD. The most prevalent comorbidities among patients with COPD are cardiovascular, metabolic, musculoskeletal and psychological diseases (Franssen & Rochester, 2014). Comorbidities can occur in patients with any degree of COPD and they could drive to a high hospitalization rate (Mannino et al., 2008) and increased mortality (Barnes & Celli, 2009). Furthermore, PA level was found to be impaired by the presence of comorbidities independent of the degree of airflow limitation and the type of comorbidity (Miller et al., 2013; Sievi et al., 2015).

Unsurprisingly, the presence of comorbidities is very common among patients with ACO too (Barrecheguren et al., 2020; Krishnan et al., 2019; Rubio et al., 2017; Van Boven et al., 2016). The most frequent comorbid conditions found among ACO patients in previous investigations were diabetes, cardiovascular disease, hypertension, eczema, rhinitis, musculoskeletal diseases, dyspepsia, arrhythmia, gastric ulcers, anxiety and depression (Barrecheguren et al., 2020; Krishnan et al., 2019; Rubio et al., 2017).

To author’s knowledge, there is no evidence about how PA levels can contribute to reduce the risk of comorbidities in asthmatics nor in ACO adults, and literature among COPD is very scarce.

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# *OBJETIVOS*

## Objetivo general

El objetivo general de esta tesis doctoral es analizar los niveles de actividad física y estudiar la relación de éstos con la presencia de diferentes comorbilidades en jóvenes y adultos con EPOC, asma o ACO residentes en España

## Objetivos específicos

I. Determinar la cantidad de AF física semanal que practican jóvenes y adultos españoles con EPOC, asma y ACO, analizando las diferencias según sexo, edad, nivel educativo, estado civil, convivencia en pareja, hábito tabáquico, consumo de alcohol e índice de masa corporal. (Artículos I, III y V)
II. Analizar los niveles de AF (bajo, moderado, alto) de jóvenes y adultos españoles con EPOC, asma y ACO según sexo, edad, nivel educativo, estado civil, convivencia en pareja, hábito tabáquico, consumo de alcohol e índice de masa corporal. (Artículos I, III y V)
III. Determinar la prevalencia de 31 comorbilidades diferentes en jóvenes y adultos españoles con EPOC, asma y ACO (Artículos II, IV y VI)
IV. Evaluar la influencia del nivel de AF sobre la presencia de comorbilidades en jóvenes y adultos españoles con EPOC, asma y ACO (Artículos II, IV y VI)

# [AIMS]

## General aim

The general aim of this doctoral thesis is to analyze physical activity levels and to evaluate their influence on the presence of different comorbidities among youth and adults with COPD, asthma or ACO residing in Spain.

## Specific aims

I. To determine the weekly amount of PA in which Spanish youth and adults with COPD, asthma and ACO are engaged, considering the differences by sex, age, education level, marital status, living together, smoking habits, alcohol consumption and BMI. (Papers I, III and V)

II. To analyze PA levels (low, moderate, high) among Spanish youth and adults with COPD, asthma and ACO according to sex, age, education level, marital status, living together, smoking habits, alcohol consumption and BMI. (Papers I, III and V)

III. To determine the prevalence of 31 different comorbidities among Spanish youth and adults with COPD, asthma and ACO. (Papers II, IV and VI).

IV. To evaluate the influence of PA levels on the presence of comorbidities among Spanish youth and adults with COPD, asthma and ACO (Papers II, IV and VI).

# MÉTODOS

La presente tesis doctoral se basa en los datos obtenidos de seis artículos de tipo descriptivo y observacional con un diseño transversal, que se han llevado a cabo siguiendo la lista de verificación STROBE (Strenghtening the Reporting of Observational Studies in Epidemiology). En todos ellos, se analizaron los datos del cuestionario de adultos de la Encuesta Nacional de Salud 2017, en la que participaron un total de 23.089 personas residentes en España, de las cuales 17.777 respondieron al cuestionario de AF. Aquellos adultos mayores de 69 años fueron excluidos, pues no completaron el Cuestionario Internacional de Actividad Física versión corta (IPAQ-SF), dado que éste ha sido desarrollado y testado en personas de entre 15 y 69 años. El IPAQ ha sido validado en poblaciones adultas de diferentes países mostrando una validez ($\rho$ = 0.30, 95% CI: 0.23–0.36) y fiabilidad aceptables ($\rho$ = 0.81, 95% CI: 0.79–0.82) (Craig et al., 2003). En función del estudio, se incluyeron como participantes aquellos que respondieron positivamente a la pregunta: "¿Alguna vez ha sido diagnosticado por un médico con EPOC y/o asma?

Los métodos seguidos aparecen detallados en cada uno de los artículos. No obstante, a continuación, se recoge en formato tabla la información metodológica de manera resumida para cada uno de los estudios (Tabla 1):

I. Patrones de actividad física en personas con EPOC residentes en España: Un análisis transversal.
II. Relación entre actividad física y comorbilidades en personas con EPOC residentes en España: un análisis transversal.
III. Nivel de actividad física en asmáticos españoles: Un estudio transversal.
IV. Análisis de actividad física y comorbilidades en asmáticos españoles.
V. Patrones de actividad física en personas con solapamiento asma-EPOC residentes en España: un análisis transversal.
VI. Relación entre actividad física y comorbilidades en españoles con solapamiento asma-EPOC.

**Tabla 1.** Resumen de la metodología de los diferentes artículos.

| Diseño | Artículos | Participantes | Variables | Análisis Estadístico |
|---|---|---|---|---|
| Transversal Descriptivo Observacional Relacional | I. Patrones de AF en personas con EPOC residentes en España. | 615: ♀327 ♂288 Edad: 15-69 | AF Sexo, edad, educación, estado civil, convivencia, tabaco, alcohol, IMC | Descriptivos U Mann-Whitney H Kruskal-Wallis Chi-cuadrado |
| | III. Nivel de AF en asmáticos españoles. | 1014: ♀587 ♂427 Edad: 15-69 | | |
| | V. Patrones de AF en personas con ACO residentes en España. | 198: ♀120 ♂78 Edad: 15-69 | | |
| | II. Relación entre AF y comorbilidades en personas con EPOC residentes en España. | 601: ♀314 ♂287 Edad: 15-69 | AF (Exposición) Comorbidities (Resultado) Sexo, edad, educación, estado civil, tabaco, alcohol, IMC, medicación, presencia de comorbilidades | Descriptivos Chi-cuadrado T-student Regresión logística multivariable |
| | IV. Análisis de AF y comorbilidades en asmáticos españoles. | 1014: ♀587 ♂427 Edad: 15-69 | | |
| | VI. Relación entre AF y comorbilidades en españoles con ACO. | 198: ♀120 ♂78 Edad: 15-69 | | |

*AF: Actividad Física; EPOC: Enfermedad Pulmonar Obstructiva Crónica; ACO: Solapamiento asma-EPOC; IMC:Índice de Masa Corporal*

# [METHODS]

This doctoral thesis is based on data obtained from six descriptive and observational papers with a cross-sectional design. All papers have been carried out following the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist. Data from the Spanish National Health Survey 2017 were analysed. A total of 23 089 people residing in Spain and aged 15 years and over participated in the survey, of which 17 777 answered the PA questionnaire. Those aged over 69 years were excluded, since they did not complete the International Physical Activity Questionnaire short form (IPAQ-SF). IPAQ has been validated in adult populations from different countries showing an acceptable validity ($\rho = 0.30$, 95% CI: 0.23–0.36) and reliability ($\rho = 0.81$, 95% CI: 0.79–0.82) (Craig et al., 2003). Depending on the paper, those who answered positively to the following question: Have you ever been diagnosed with COPD/asthma/both by a physician? were included in the analyses.

Methods are detailed in each paper. However, the methodological information of each paper is summarized on the following table (Table 1):

I. Physical Activity Behaviour in People with COPD Residing in Spain: A Cross-Sectional Analysis.
II. Associations between Physical Activity and Comorbidities in People with COPD Residing in Spain: A Cross-Sectional Analysis.
III. Levels of Physical Activity in Spanish Asthmatics: A Cross-Sectional Study.
IV. Analysis of Physical Activity and Comorbidities in Spanish Asthmatics.
V. Physical activity behavior in people with asthma and COPD overlap residing in Spain: a cross-sectional analysis
VI. Association between Physical Activity and Comorbidities in Spanish People with Asthma-COPD Overlap.

**Table 1.** Summary of the methods of the different articles.

| Design | Papers | Participants | Variables | Statistical Analysis |
|---|---|---|---|---|
| Cross-sectional Descriptive Observational Relational | I. PA Behaviour in People with COPD Residing in Spain | 615: ♀327 ♂288 Age: 15-69 | PA Sex, age, education, marital status, cohabiting, smoking, alcohol, BMI | Descriptives Mann-Whitney U Kruskal-Wallis H Chi-squared |
| | III. Levels of PA in Spanish Asthmatics. | 1014: ♀587 ♂427 Age: 15-69 | | |
| | V. Physical activity behavior in people with ACO residing in Spain. | 198: ♀120 ♂78 Age: 15-69 | | |
| | II. Associations between PA and Comorbidities in People with COPD Residing in Spain. | 601: ♀314 ♂287 Age: 15-69 | PA (Exposure) Comorbidities (Outcomes) Sex, age, education, marital status, smoking, alcohol, BMI, medication, presence of comorbidities | Descriptives Chi-squared Student-T Multivariable logistic regression |
| | IV. Analysis of PA and Comorbidities in Spanish Asthmatics. | 1014: ♀587 ♂427 Age: 15-69 | | |
| | VI.Association between PA and Comorbidities in Spanish People with ACO. | 198: ♀120 ♂78 Age: 15-69 | | |

*PA: Physical Activity; COPD: Chronic Obstructive Pulmonary Disease; ACO: Asthma-COPD Overlap; BMI: Body Mass Index*

# ARTÍCULOS PUBLICADOS

# [PUBLISHED PAPERS]

# ENFERMEDAD PULMONAR OBSTRUCTIVA CRÓNICA

# [COPD]

## Artículos I y II

## [Papers I and II]

# ARTÍCULO I [PAPER I]

## Physical Activity Behaviour in People with COPD Residing in Spain: A Cross-Sectional Analysis

Sánchez-Castillo, S., Smith, L., Díaz-Suárez, A., López-Sánchez, G.F.

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**Abstract:**

***Purpose*** Chronic obstructive pulmonary disease (COPD) represents a major public health problem due to its high prevalence, morbidity and health cost. It has been demonstrated that physical activity (PA) is one of the most beneficial measures to prevent chronic diseases. The aim of this study was to examine PA levels of adults with COPD residing in Spain, and to analyse the differences by sex, age, education, marital status, cohabiting, tobacco consumption, alcohol consumption and body mass index.

***Methods*** A total of 615 adults aged 15 to 69 years participated in this study. Data from the Spanish National Health Survey 2017 were used. This survey included the short version of IPAQ to measure PA levels. PA was expressed in total volume (MET·min/week), classified as low, moderate and high, and analysed according to sample characteristics. Statistical significance was set at $p < 0.05$ (CI = 95%).

***Results*** Level of PA was higher in men than in women (1808.8 vs. 1575.6 MET·min/week; $p = 0.016$), in those aged under 30 years than in those older than 60 years (2129.4 vs. 1381.4 MET·min/week; $p = 0.047$) and in those who drank alcohol than in those who did not drink (1912.8 vs. 1248.2 MET·min/week; $p = 0.004$). Also, underweight and obese participants participated in lower levels of PA than normal weight participants ($p= 0.001$). When classifying PA level, a total of 37.9% had a low level, 47.5% had a moderate level and only 14.6% had a high level of PA ($p < 0.001$).

***Conclusion*** It is recommendable to implement programs to raise awareness of the importance and benefits of PA in the control of COPD, and these programs should focus on those with lower levels of PA.

**Keywords:** Physical exercise · Lung disease · Public health · Adults

## Introduction

Chronic Obstructive Pulmonary Disease (COPD) represents an important challenge for public health because of its increasing prevalence, high morbidity and socioeconomic burden [1]. Moreover, a large body of literature shows that COPD is associated with a decline in patient's quality of life [2]. Indeed, currently COPD is the forth cause of global death [3, 4], and in 2012, more than 3 million people died because of COPD, representing 6% of all global mortality.

Spanish national data collected in the EPI-SCAN study found a COPD prevalence of 10.2% in people aged 40 to 80 years, with an unequal distribution between the sexes: 15.1% in men versus 5.7% in women [5]. This study defined COPD by the GOLD criteria where the ratio between forced expiratory volume in the first second ($FEV_1$) and the forced vital capacity (FVC) is < 0.70 post-bronchodilator use. Following these findings, it was extrapolated that a 2,185,764 people in Spain suffer from COPD [6]. Importantly, a total of 10% of primary care consultations, 40% of neumology consultations and 7% of annual hospitalizations in Spain are owing to COPD. In those with COPD comorbidities, cardiovascular, metabolic, musculoskeletal and psychological comorbidities are high [7]. These comorbidities are likely driving the high rate of hospitalization. Therefore, in order to minimize the economic burden of COPD, such comorbidities need to be prevented.

It is important to underline that COPD prevalence rises with age and it is more frequent in men. This may be owing to the accumulative effect of other risk factors to which individuals have been exposed to throughout life, including behavioural factors [e.g. tobacco smoking, low levels of physical activity (PA)], environmental factors (e.g. air pollution, biomass fuel), physiological factors (e.g. genetic abnormalities) and social factors (e.g. socioeconomic status) [1]. One important observed risk factor for COPD is a lower level of cardiorespiratory fitness across the lifespan [8]. Indeed, maintaining adequate levels of PA allows one to improve cardiorespiratory fitness. When possible, all populations should participate in PA, and if done in natural environments exposure to other COPD risk factors such as air pollution may be reduced [9–11].

Regular and sustained participation in PA aids the prevention of several chronic diseases, and importantly for those with COPD, in both primary and secondary prevention [12, 13]. PA is limited by COPD [14] even in early stages [15, 16]. This limitation in levels of PA is related to a high risk of hospitalization and readmission [17] and even death [18, 19]. The lack of PA in COPD's patients is not only conditioned by respiratory

functional impairment. There are other determinants that affect patients' PA like dyspnoea, hyperinflation, age and peripheral muscle weakness [20]. Nonetheless, regular participation in PA is related to a better quality of life [21–23] and fewer morbidities in people with COPD [17, 24]. In a prospective cohort study carried out in Barcelona (Spain), participants with COPD who walked for at least 1 h a day had less risk of admission by COPD exacerbation [22]. In a recent prospective observational study, where the clinic efficacy of a walking program in COPD patients was evaluated, there were improvements in both quality of life and exacerbation's number [21]. Despite these, a small body of evidence on patients with COPD shows a tendency towards a sedentary lifestyle [25, 26]. However, these studies have been carried out in small samples and therefore not representative of the wider population. Moreover, little research to date has been carried out on this topic in Spain; as barriers and facilitators to PA differ between countries, owing to social and political context, it is important to establish levels of PA in those with COPD in each country in order to inform policy and practice. To the best of our knowledge, just one study has analysed differences in PA between sex and age in adults with COPD. This determined PA volume is lower in women, but is less than the value obtained in healthy adults in both sexes. According to age, it has been shown that PA volume is lower in older adults [27].

It is believed that people with COPD do not practise enough PA. Moreover, it has been suggested that PA is lower in women than in men, in older adults, in tobacco and alcohol consumers, in those from a lower socioeconomic status and in those with a higher body mass index (BMI), among adults with COPD.

Therefore, the aim of this study was to examine the level of PA in people with COPD residing in Spain, and to analyse the differences according to sex, age, level of studies, marital status, cohabiting, tobacco consumption, alcohol consumption and BMI.

## Methods

### *Sample*

Data from the Spanish National Health Survey 2017 were analysed. This survey was undertaken in Spain between October 2016 and October 2017. Details of the survey method have been published elsewhere [28]. In brief, for the data collection, a stratified three-stage sampling was used in which the census sections were first considered, then

the family dwellings and then an adult (15 years or more) was selected within each dwelling. The dwellings were selected by systematic sampling and to select the person who had to complete the Adult Questionnaire the random Kish method was used. For this study, inclusion criteria were as follows: (1) affirmative answer to the question "Have you ever been diagnosed with COPD?" and (2) age between 15 and 69 years because this is the age range in which PA level of the survey respondents was evaluated. The age group of adults ≥ 70 years was not considered in this study as they did not complete the IPAQ short form.

This research was conducted in accordance with the Declaration of Helsinki, 1961 (revised in Tokyo in 1989 and in Edinburgh in 2000) and ethical approval was granted by Investigation Ethics Commission of the University of Murcia (Spain).

### *Instruments*

IPAQ short form was used to measure PA. Please see https://sites.google.com/site/theipaq/ [29] for the full survey. This is an instrument designed primarily for population surveillance of PA among adults, and it has been developed and tested for use in adults (age range of 15–69 years), and until further development and testing is undertaken the use of IPAQ with older and younger age groups is not recommended [30]. IPAQ has been validated in adult populations from different countries showing acceptable validity ($\rho$ = 0.30, 95% CI 0.23–0.36) and reliability (Spearman's $\rho$ = 0.81, 95% CI 0.79–0.82) [31].

### *Procedure*

Participants completed a questionnaire that included sociodemographic questions (age, sex, level of studies and marital status), physical characteristics (weight and height), PA levels, smoking habits and alcohol consumption. The selection of the control variables was based on the past literature [32, 33]. PA levels were assessed with the short version of the IPAQ. PA level was calculated following the formula for computation of MET·min/week, established in the guidelines for data processing and analysis of the IPAQ [30]. Subsequently, PA level was classified as follows: low (less than 600 MET·min/week), moderate (at least 600 MET·min/week) and high (at least 3000 MET·min/week), according to the same guidelines. All of them signed an informed consent form before responding to the survey questions.

Age was divided in three groups: < 30 years, between 30 and 60 years, and 60 years or older. Level of education was classified as university and no university (no studies, primary studies, secondary studies, A level, middle grade and major grade). Marital status was categorised as married and not married (single/widow/divorced/separated). Cohabiting was categorised as yes or no. Alcohol consumption was treated as a dichotomous variable: yes or no, considering as no consumption for those who had not drunk alcohol in the last 12 months and for those who had never drunk alcohol. Smoking was classified in three groups: those who smoked currently, those who did not smoke currently but had smoked before and those who had never smoked [34]. BMI was classified as underweight (< 18.5 kg/m2), normal weight (18.5–24.9 kg/m2), overweight (25–30 kg/m2) and obesity (> 30 kg/m2), according to the methods established by the Spanish National Health Survey [28].

***Data Analysis***

Descriptive statistics (frequency and percentage) was used to describe demographic characteristics. To describe the PA level (MET·min/week) of the participants according to sex, age, level of education, marital status, smoking habits, alcohol consumption and BMI, descriptive statistics were used. To prove the normality of data, Chi-square test was used for categorical variables and Kolomogorov-Smirnov test for continuous variables. Statistical significance was calculated with Mann–Whitney U test for dichotomous variables (sex, education level, marital status and alcohol consumption) and Kruskal–Wallis H test for polytomous variables (age, smoking habits and BMI).

Significant differences in PA level classification between groups in each variable were investigated using crosstabs, including Chi-square test and adjusted residual values. In those variables in which Chi-square tests were significant, the *p*-value of each box was calculated based on the adjusted residual value in order to know between which groups the differences existed.

Moreover, the effect size was calculated using Cohen's d. Finally, Pearson Correlation was applied to measure the correlation between physical activity and age.

Statistical significance was set at $p < 0.05$ (CI = 95%). Analyses were carried out with the Statistical Package for Social Sciences (SPSS), version 23.

## Results

The sample consisted of 615 adults residing in Spain (327 women and 288 men). Participants' average age was 52.7 years (SD 14.1; range 15–69; Mo: 66). Sample characteristics are shown in Table 1.

**Table 1** Sample characteristics

| Total sample ($n = 615$) | *N* | % |
|---|---|---|
| Sex | | |
| Women | 327 | 53.2 |
| Men | 288 | 46.8 |
| Age | | |
| < 30 | 50 | 8.1 |
| 30–60 | 323 | 52.5 |
| ≥ 60 | 242 | 39.3 |
| Education level | | |
| No University | 535 | 87.0 |
| University | 80 | 13.0 |
| Marital status | | |
| Married | 322 | 52.4 |
| Not married | 293 | 47.6 |
| Living in couple | | |
| Yes | 327 | 53.5 |
| No | 284 | 46.5 |
| BMI | | |
| Underweight | 22 | 3.6 |
| Normal weight | 195 | 31.7 |
| Overweight | 229 | 37.2 |
| Obesity | 169 | 27.5 |
| Smoking | | |
| Currently | 205 | 33.3 |
| Not currently | 207 | 33.7 |
| No, never | 203 | 33.0 |
| Alcohol last 12 month | | |
| Yes | 404 | 65.7 |
| No | 211 | 34.3 |

The total amount of participants' PA is shown in Table 2. There were significant differences between sexes, with men more physically active. Participants under 30 years were significantly more active than those over 60. In addition, when Pearson correlation was applied, a low negative correlation between age and physical activity was observed ($r = -0.129$; $p = 0.001$). Those who drank alcohol did more PA than those who did not drink. There were also significant differences in BMI between underweight and normal weight participants, and between normal weight and obesity participants, in favour of those with normal weight.

**Table 2.** Total amount of physical activity in MET·min/week, according to sample characteristics

| | ***n*** | **Av** | **SD** | **Med** | **IQR** | **p** | **d** |
|---|---|---|---|---|---|---|---|
| Sex | | | | | | | |
| Women | 327 | 1575.6 | 2517.4 | 816.0 | 1668.0 | 0.016* | 0.1952 |
| Men | 288 | 1808.8 | 2191.6 | 1122.0 | 2046.0 | | |
| Age | | | | | | | |
| 1. < 30[3] | 50 | 2129.4 | 2820.0 | 1386.0 | 1670.6 | 0.047* | 0.3555 |
| 2. 30–60 | 323 | 1843.3 | 2571.0 | 990.0 | 1828.8 | | 0.2039 |
| 3. ≥ 60[1] (Ref.) | 242 | 1381.4 | 1926.4 | 706.5 | 1845.0 | | – |
| Education level | | | | | | | |
| No university | 535 | 1628.3 | 2330.5 | 942.0 | 1831.5 | 0.140 | 0.1771 |
| University | 80 | 2062.5 | 2612.8 | 1386.0 | 2427.0 | | |
| Marital status | | | | | | | |
| Married | 322 | 1577.8 | 2179.3 | 990.0 | 1782 | 0.944 | 0.0057 |
| Not married | 293 | 1802.3 | 2564.5 | 924.0 | 1994 | | |
| Living in couple | | | | | | | |
| Yes | 327 | 1595.3 | 2224.1 | 990.0 | 1831.5 | 0.784 | 0.0222 |
| No | 284 | 1800.7 | 2541.1 | 933.0 | 1842.0 | | |
| Smoking | | | | | | | |
| Currently (Ref.) | 205 | 1770.9 | 2799.6 | 792.0 | 1551.0 | 0.559 | – |
| Not currently | 207 | 1779.8 | 2303.9 | 990.0 | 2419.5 | | 0.0035 |
| No, never | 203 | 1500.9 | 1927.1 | 990.0 | 1770.0 | | 0.1122 |
| Alcohol (last 12 months) | | | | | | | |
| Yes | 404 | 1912.8 | 2683.4 | 1039.5 | 2049.0 | 0.004* | 0.2825 |
| No | 211 | 1248.2 | 1527.1 | 792.0 | 1858.5 | | |
| BMI | | | | | | | |
| 1. Underweight[2] | 22 | 1420.8 | 2424.3 | 495.0 | 2076.7 | 0.001* | 0.2773 |
| 2. Normal weight [1,4] (Ref.) | 195 | 2146.9 | 2639.1 | 1386.0 | 2343.0 | | – |
| 3. Overweight | 229 | 1660.5 | 2318.4 | 966.0 | 1782.0 | | 0.1968 |
| 4. Obesity[2] | 169 | 1218.9 | 2000.9 | 693.0 | 1406.2 | | 0.3925 |
| Total | 615 | 1684.8 | 2371.4 | | | | |

Superscript numbers indicate significant differences between groups.
*n:* Sample size, *Av*: average, *SD*: standard deviation, *Med*: median, *IQR*: interquartile range, *d:* Cohen's d, *Ref:* Reference category *Statistical significance at $p < 0.05$

In Table 3, PA level is classified as low, moderate and high. No significant differences were found between the categories of each variable for each PA level, except in BMI, as the high level of PA was significantly more frequent in those with normal weight. Considering the entire sample, significant differences were observed ($p < 0.001$), with the moderate level being the most frequent (47.5%) PA level.

**Table 3.** Classification of PA level following IPAQ guidelines, according to sample characteristics

| | n | PA level | | | d |
|---|---|---|---|---|---|
| | | Low | Moderate | High | |
| Sex | | | | | |
| Women | 327 | 132 (40.4) | 158 (48.3) | 37 (11.3) | 0.1985 |
| Men | 288 | 101 (35.1) | 134 (46.5) | 53 (18.4) | |
| Age | | | | | |
| < 30 | 50 | 15 (30.0) | 28 (56.0) | 7 (14.0) | 0.1036 |
| 30–60 | 323 | 116 (35.9) | 152 (47.1) | 55 (17.0) | |
| ≥ 60 | 242 | 102 (42.1) | 112 (46.3) | 28 (11.6) | |
| Education level | | | | | |
| No university | 535 | 205 (38.3) | 256 (47.9) | 74 (13.8) | 0.1142 |
| University | 80 | 28 (35.0) | 36 (45.0) | 16 (20.0) | |
| Marital status | | | | | |
| Married | 322 | 116 (36.0) | 167 (51.9) | 39 (12.1) | 0.1985 |
| Not married | 293 | 117 (39.9) | 125 (42.7) | 51 (17.4) | |
| Living in couple | | | | | |
| Yes | 327 | 122 (37.3) | 163 (49.8) | 42 (12.8) | 0.1142 |
| No | 284 | 109 (38.4) | 127 (44.7) | 48 (16.9) | |
| Smoking | | | | | |
| Currently | 205 | 77 (37.6) | 95 (46.8) | 33 (15.6) | 0.1811 |
| Not currently | 207 | 77 (37.2) | 93 (44.9) | 37 (17.9) | |
| No, never | 203 | 79 (38.9) | 103 (50.7) | 21 (11.3) | |
| Alcohol (last12 months) | | | | | |
| Yes | 404 | 142 (35.1) | 191 (47.3) | 71 (17.6) | 0.2437 |
| No | 211 | 91 (43.1) | 101 (47.9) | 19 (9.0) | |
| BMI* | | | | | |
| Underweight | 22 | 13 (59.1) | 7 (31.8) | 2 (9.1) | 0.3667 |
| Normal weight | 195 | 62 (31.8) | 90 (46.2) | 43 (22.1) | |
| Overweight | 229 | 83 (36.2) | 115 (50.2) | 31 (13.5) | |
| Obesity | 169 | 75 (44.4) | 80 (47.3) | 14 (8.3) | |
| Total* | 615 | 233 (37.9) | 292 (47.5) | 90 (14.6) | 0.9075 |

Values are expressed in frequency (%); *n:* sample size. *Statistical significance at $p<0.05$

## Discussion

The total volume of PA for people with COPD that participated in this study was 1684.8 MET·min/week. This level of PA is higher than the recommendations of the Centres for Disease Control and Prevention (CDC) [35] and the World Health Organization [36], which recommends a total volume of 600 MET·min/week. Nevertheless, the total volume of PA in the present study is lower than the value observed in the international validation of IPAQ Short version (957 participants from 12 different countries), which established the average value in healthy adults to be 2514 MET·min/ week [31].

Recently, Carsin et al. [37] compared the data of two prospective cohort studies: European Community Respiratory Health Survey (ECRHS) [38] and Swiss Study on Air Pollution and Lung Disease in Adults (SAPALDIA) [39]. In both, PA was evaluated

using the IPAQ questionnaire, as in the present study. Specifically, it was in the ECRHS ($n$ = 3570) where the short version was used. The ECRHS study showed a total volume of 1770 MET·min/week in those participants with restrictive spirometric pattern ($n$ = 143). This value is slightly higher than the value obtained in the present study (1684.8 MET·min/week). A possible explanation for this difference could be the different age range (20–44 in ECRHS and 15–69 in the present study). In fact, in the present study, PA level was lower in older adults.

It is important to underline that in the vast majority of papers in which PA of people with COPD is studied, the sample is entirely men or with a small percentage of women [40, 41]. Also in Spain the prevalence of COPD is higher in men and older people [1, 5]. However, in the present study, the percentage of women (53.2%) was similar and higher than the percentage of men with COPD (46.8%) and we found that women practised significantly less PA than men. There is no existing literature about why women with COPD practise less PA than men. But regarding people with other diseases, in a study about barriers to practise PA in people with diabetes, it was found that lack of time, lack of knowledge and health limitations were the main reasons, and the last one was identified to be more important in women than in men [42]. This could be owing to women normally practising PA owing to extrinsic motivations such as improving physical aspects or health, but not because they enjoy it [43]. The limited respiratory capacity because of COPD could make it difficult to engage in a PA programs for women owing to a lack of intrinsic motivation.

According to tobacco consumption, significant differences in PA were not found between smokers, ex-smokers and non-smokers with COPD. In the same way, Carsin et al. [37] did not find consistent evidence between restrictive spirometry pattern and low PA. On the other hand, in a prospective cohort study, it was shown that moderate to high levels of regular PA were associated with a lower lung function decline in active smokers, so the risk of developing COPD was reduced [17]. However, a systematic review and meta-analysis of studies performed in 28 countries between 1990 and 2004 [44] and an epidemiological study in Japan [45] concluded that the prevalence of COPD was appreciably higher in smokers and ex-smokers compared with non- smokers. The present study found similar findings in which 67% of participants were smokers or ex-smokers and only 33% were non-smokers.

In reference to alcohol consumption, this study showed that those who drank alcohol did more PA than those who did not drink. The vast majority of the participants

(65.7%) drank alcohol. However, it is important to highlight that in this group all participants who drank alcohol were included, even those who only drank once a month or even less. An explanation for the finding that those with COPD and who drink are more physically active than those who have COPD and don't drink is elusive and further research of a qualitative nature is required to understand this relationship.

The present study showed that normal weight participants practised more PA (2146.9 MET·min/week) than overweight (1660.5 MET·min/week) and underweight (1420.8 MET·min/week) COPD patients. Similarly, Mesquita et al. [33] found that clusters of patients with COPD who were more sedentary had higher BMI (couch potatoes: 30.4 $kg/m^2$; highly sedentary: 25.7 $kg/m^2$; sedentary movers 24.9 $kg/m^2$; sedentary exercisers 23.1 $kg/m^2$; busy bees 22.5 $kg/m^2$).

Several studies have confirmed that PA programs in people with COPD improve their quality of life. In 2010, Breyer et al. [46] were the first to show that Nordic Walking is a feasible, simple and effective physical training modality for patients with COPD. This modality is cheap and easy accessible, and the study demonstrated that Nordic Walking has a long-term effect on patients' daily PA pattern and a reduction in daily symptoms of COPD. Subsequently, Barberán-García et al. [47] suggested that Nordic walking could be an appropriate training modality for patients with moderate to severe COPD because it generated higher intensity at the same rate of perceived exertion (RPE) than standard walking.

Main strengths of this study are the large sample of people with COPD and the use of a validated and internationally recognized questionnaire to evaluate PA level. However, it also has potential limitations including the lack of classification of severity of airflow obstruction and grade of dyspnoea. Presence of comorbidities or other barriers that could affect PA practice were not considered. Moreover, as it was an observational study and not a randomized trial, the association can be demonstrated, but not the causality. In future researches it will be recommendable to use accelerometers in order to measure PA in this kind of population and take into account the severity, comorbidities and barriers to PA practice.

## Conclusion

Almost four out of ten people with COPD residing in Spain had a low level of PA. The level of PA was higher in men, in those aged less than 60 years, in those who drank

alcohol, and in those with normal weight. Therefore, it is recommendable to implement programs to raise awareness of the importance and benefits of PA in the control of COPD among those with COPD residing in Spain, and these programs should focus on women, those older than 60 years, those who do not drink alcohol, and those who do not have a normal weight. These programs should include activities that motivate the participants to do long-term PA. In this way, they could reach PA recommendations and, consequently, they would improve their quality of life.

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***Conflict of interest*** The authors declare that they have no conflict of interest.

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# ARTÍCULO II [PAPER II]

## Associations between Physical Activity and Comorbidities in People with COPD Residing in Spain: A Cross-Sectional Analysis

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**Abstract:**

There is a high prevalence of comorbidities among patients with chronic obstructive pulmonary disease (COPD). Comorbidities are likely common in patients with any COPD degree and are associated with increased mortality. The aim of this study was to determine the prevalence of thirty-one different COPD comorbidities and to evaluate the association between physical activity (PA) levels in people with COPD residing in Spain. Cross-sectional data from the Spanish National Health Survey 2017 were analysed. A total of 601 adults (52.2% females) with COPD aged 15 to 69 participated in this study. PA (exposure) was measured with the International Physical Activity Questionnaire (IPAQ) short form and comorbidities (outcomes) were self-reported in response to the question "Have you ever been diagnosed with …?" Multivariable logistic regression, in three different models, was used to assess this association. Results showed a high prevalence of comorbidities (94%), these being chronic lumbar back pain (38.9%), chronic allergy (34.8%), arthrosis (34.1%), chronic cervical back pain (33.3%), asthma (32.9%) and hypertension (32.8%) the most prevalent. Low PA level was significantly associated with urinary incontinence (2.115[1.213–3.689]), chronic constipation (1.970[1.119–3.459]), cataracts (1.840[1.074–3.153]), chronic anxiety (1.508[1.002–2.269]) and chronic lumbar back pain (1.489[1.044–2.125]). Therefore, people with COPD should increase their PA levels in order to reduce their risk of comorbidities and increase their quality of life.

**Keywords:** lung disease; physical exercise; prevalence; adults

## Introduction

COPD (chronic obstructive pulmonary disease) is an important challenge for public health. Its increasing prevalence, high morbidity and socioeconomic burden are some examples of its importance [1]. Moreover, a large body of literature shows that COPD is associated with a decline in a patient's quality of life [2]. COPD is the fourth largest cause of global death [3,4] and will become the third by 2020. In 2012, greater than three million people died because of COPD (6% of all global mortality).

In Spain, the prevalence of COPD in people aged 40 to 80 was found to be 10.2%, being higher in men (15.1%) than in women (5.7%). [5]. This study used the definition of COPD proposed by the GOLD criteria, where the ratio between forced expiratory volume in the first second ($FEV_1$) and forced vital capacity (FVC) is less than 0.70 post-bronchodilator. Considering these findings, it was extrapolated that 2,185,764 people in Spain suffer from COPD [6]. A total of 10% of primary care consultations, 40% of pneumonology consultations and 7% of Spanish annual hospitalizations are due to COPD. Moreover, in people with COPD comorbidities, the most prevalent comorbidities are cardiovascular, metabolic, musculoskeletal and psychological comorbidities [7]. The presence of comorbidities likely drives the high hospitalization rate [8]. In order to reduce the economic burden of COPD, such comorbidities should be prevented. Comorbidities can occur in patients with any degree of COPD and they are associated with increased mortality [9]. The presence of comorbidities between patients with COPD is high. It was found that 80% of COPD patients had at least one comorbidity [10]. However, generally multiple comorbidities coexist. In 2009, Barr et al. found an average of nine comorbidities in COPD patients [11].

Regular and sustained participation in physical activity (PA) aids in the prevention of several chronic diseases, in relation to both primary and secondary prevention. Indeed, secondary prevention is particularly important for those with COPD [12,13].

PA is limited by COPD [14,15], even in early stages [16,17]. This is related to a high risk of hospitalization and readmission [18] and even death [19,20]. However, this limitation in levels of PA in patients with COPD is not only conditioned by respiratory functional impairment. There are other determinants that affect patients' PA levels like age, dyspnoea, hyperinflation and peripheral muscle weakness [21]. Furthermore, PA

level was found to be impaired by the presence of comorbidities independent of the degree of airflow limitation and of the type of comorbidity [10,22].

Nonetheless, participation in regular PA is associated with a better quality of life [23–25] and fewer morbidities in people with COPD [18,26]. In a prospective Spanish cohort study carried out in Barcelona, people with COPD who walked for at least one hour per day had a lower risk of hospitalization by COPD exacerbation [24]. Recently, another prospective observational study showed improvements in both the number of exacerbations and the quality of life in COPD patients participating in a walking program [23]. Despite this, a scarce body of literature on people with COPD shows a tendency towards a sedentary lifestyle [27,28].

Thus, it could be hypothesized that people with COPD who practise less PA have an increased risk of developing comorbidities than people with COPD who practise more PA. Therefore, the aim of this study was to determine the prevalence of COPD comorbidities and to evaluate the association between PA level and the risk of comorbidities in people with COPD residing in Spain in order to inform the promotion of PA in the treatment and prevention of COPD.

## Materials and Methods

### *Study Design*

The present study is of a cross-sectional design written following the STROBE checklist (https://www.strobe-statement.org) [29].

### *The Survey*

Data from the Spanish National Health Survey 2017 were analysed. This survey was undertaken in Spain between October 2016 and October 2017. Details of the survey method have been published elsewhere [30]. In brief, for the data collection, a stratified three-stage sampling was used in which the census sections were first considered, then the family dwellings and then an adult (15 years or more) was selected within each dwelling. The dwellings were selected by systematic sampling and to select the person who completed the Adult Questionnaire, the random Kish method was used. The method of data collection used was computer-assisted personal interviewing (CAPI), conducted in the homes of the selected participants. The interviewers, previously trained, completed

the questionnaires with the information provided by the participants. All participants signed an informed consent form before responding to survey questions. The present study was conducted in accordance with the Declaration of Helsinki of 1961 (revised in Tokyo in 1989 and in Edinburgh in 2000).

***Participants***

A total of 601 adults with COPD residing in Spain (314 women and 287 men) were included in the present analyses. To be included adults aged between 15 and 69 years needed to provide an affirmative response to the question "Have you ever been diagnosed with COPD?". Those adults older than 69 years were not considered, since they did not complete the International Physical Activity Questionnaire (IPAQ) short form. This instrument was primarily designed for population surveillance of PA among adults and it has been developed and tested for use in adults (age range of 15–69 years) and until further development and testing is undertaken the use of IPAQ with older and younger age groups is not recommended [31].

***Physical Activity (Exposure)***

IPAQ short form was used to measure PA. Total PA MET·min/week were calculated through the following formula: Sum of Walking + Moderate + Vigorous MET·min/week scores. Participants were divided in two categories according to the guidelines for data processing and analysis of the IPAQ [31]: (1) Fewer than 600 MET·min/week and (2) at least 600 MET·min/week, equivalent to meeting current PA recommendations. IPAQ has been validated in adult populations from different countries showing acceptable validity ($\rho = 0.30$, 95% CI: 0.23–0.36) and reliability (Spearman's $\rho = 0.81$, 95% CI: 0.79–0.82) [32]. IPAQ short form has also been validated in the Spanish adult population showing a moderate correlation for total amount of PA ($r = 0.277$; $p < 0.05$) with 75% of sensibility and specificity ($k = 0.33$) [33].

***Comorbidities (Outcomes)***

A total of 31 comorbidities available in the Spanish National Survey 2017 were considered. Those who answered affirmatively to the question "have you ever been diagnosed with ... (each comorbidity studied)?" were considered to have that comorbidity. Moreover, the vast majority of the studied diseases were considered in previous literature as COPD comorbidities [7,10,34,35].

Comorbidities were classified in 13 different groups according to the international classification of the diseases (ICD): Cardiovascular diseases, musculoskeletal disorders, immunological disease, respiratory disease, digestive problems, urogenital diseases, eye problems, dermatological problems, mental health problems, neurological disorder, neoplasias, endocrinal and metabolic diseases and permanent injuries [36].

***Covariates***

The selection of the control variables was based on past literature [37,38]. Sociodemographic variables included age, sex, education and marital status. Education level was based on the highest educational level achieved and was categorized as ≤primary, secondary and ≥tertiary. Marital status was categorised as married or not married (single/widow/divorced/separated). The following variables were also included as covariates: Smoking habits, alcohol consumption and body mass index (BMI). Smoking habit was classified into three groups: Never, former and current smoker. Alcohol consumption was treated as a dichotomous variable: Yes or no. Height and weight were self-reported and used to calculate BMI as weight in kilograms divided by height in meters squared. Obesity was defined as BMI $\geq 30$ kg/m$^2$. The presence of other comorbidities was also treated as a dichotomous variable: Yes (if they had one or more comorbidities) and no (if they had no comorbidities). For medication intake twenty-three different medicaments were considered: Flu/cold medication, pain medication, fever medication, vitamins/minerals/tonics, laxatives, antibiotics, sedatives, allergy medication, diarrhoea medication, rheumatism medication, heart medication, blood pressure medication, digestive problems medication, antidepressants, contraceptive pill, menopausal hormones, slimming medicines, cholesterol medication, diabetes medication, thyroid medication, naturist products and other. This variable was also treated as a dichotomous variable: Yes (if they had taken at least one of this medicines in the last two weeks) and no (if they had not taken any medicine in the last two weeks).

***Statistical Analysis***

Descriptive statistics were used to describe sample characteristics. Frequency and percentage were used for categorical variables (sex, education level, marital status, smoking habits, alcohol consumption, obesity, presence of comorbidities and PA) and mean and standard deviation (SD) were used for continuous variables (age). To describe the prevalence of each comorbidity and group of comorbidities descriptive statistics were

used. Significant differences in sample characteristics between groups were examined using chi squared tests.

Multivariable logistic regression analyses were used to assess the association between PA (exposure) and comorbidities (outcomes). The analyses were carried out in three different models. The first model was not adjusted; the second model was adjusted for age, sex, education, marital status, smoking, alcohol consumption and obesity; and the third model was adjusted for the same variables as model two and also for the variables "presence of other comorbidities" and "medication intake". COPD comorbidities that were significantly associated with PA in model 1 were also analysed in model 2 and COPD comorbidities that were significantly associated with PA in model 2 were also analysed in model 3. All variables were included in the models as categorical variables with the exception of age, which was included as a continuous variable. There were no missing data. Results from the logistic regression analyses are presented as odds ratios (OR) with 95% confidence intervals (CI).

Statistical significance was set at $p < 0.05$. Analyses were carried out with the Statistical Package for Social Sciences (SPSS version 23, IBM, Armonk, New York, USA).

## Results

The sample consisted of 601 adults with COPD residing in Spain. The age range of the sample was 15–69 years, with an average (SD) of 52.8 (14.1) years. A total of 52.2% were women and 47.8% were men. The prevalence of people doing less than 600 MET·min/week was 37.1%. A total of 94% of the people with COPD had comorbidities. An average of six comorbidities at the same time was found. Sample characteristics are shown in Table 1.

**Table 1**.- Sample characteristics

| **Characteristic** | **Category** | ***n*** | ***%*** | ***p*** |
|---|---|---|---|---|
| Sex | Men | 287 | 47.8 | 0.271 |
| | Women | 314 | 52.2 | |
| Education | ≤ Primary | 197 | 32.8 | |
| | Secondary | 170 | 28.3 | 0.006* |
| | ≥Tertiary | 234 | 38.9 | |
| Marital Status | Married | 402 | 66.9 | <0.001* |
| | Not Married | 199 | 33.1 | |
| Smoking | Current | 202 | 33.6 | |
| | Former | 201 | 33.4 | 0.979 |
| | Never | 198 | 32.9 | |
| Alcohol | Yes | 395 | 65.7 | <0.001* |
| | No | 206 | 34.3 | |
| Obesity | No | 433 | 72.0 | <0.001* |
| | Yes (≥30) | 168 | 28.0 | |
| Comorbidities | Yes | 565 | 94.0 | <0.001* |
| | No | 36 | 6.0 | |
| Medication | Yes | 527 | 87.7 | <0.001* |
| | No | 74 | 12.3 | |
| PA | <600 MET·min/week | 223 | 37.1 | <0.001* |
| | ≥600 MET·min/week | 378 | 62.9 | |

*n:* sample size; *%:* percentage; *p*-values were based on chi-squared tests. *$p<0.05$

The differences between groups were significant for education, marital status, alcohol, obesity, presence of comorbidities, medication intake and PA.

Overall, the prevalence of comorbidities among those with COPD are shown in Table 2. Chronic lumbar pain, chronic allergy, arthrosis, chronic cervical pain, asthma and hypertension were the comorbidities with higher incidence, all of them with more than 30%. Considering ICD classification 56.2% of COPD patients suffered from musculoskeletal disorders, followed by cardiovascular diseases (48.8%) and endocrinal and metabolic diseases (40.8%).

**Table 2.-** Prevalence of comorbidities in people with COPD

| | **Comorbidities** | ***n*** | **%** | **%** |
|---|---|---|---|---|
| Cardiovascular diseases | Hypertension | 197 | 32.8 | 48.8 |
| | Myocardial infarction | 18 | 3.0 | |
| | Angina, Coronary HD | 26 | 4.3 | |
| | Other HD | 61 | 10.1 | |
| | Stroke | 18 | 3.0 | |
| | Varicose veins (legs) | 106 | 17.6 | |
| Musculoskeletal disorders | Arthrosis | 205 | 34.1 | 43.8 |
| | CBP cervical | 200 | 33.3 | |
| | CBP lumbar | 234 | 38.9 | |
| | Osteoporosis | 59 | 9.8 | |
| Immunological disease | Chronic allergy | 209 | 34.8 | 34.8 |
| Respiratory disease | Asthma | 198 | 32.9 | 32.9 |
| Digestive problems | Liver dysfunction | 27 | 4.5 | 29.8 |
| | Stomach/duodenal ulcer | 62 | 10.3 | |
| | Chronic constipation | 58 | 9.7 | |
| | Haemorrhoids | 96 | 16.0 | |
| Urogenital diseases | Urinary incontinence | 66 | 11.0 | 25.3 |
| | Kidney problems | 56 | 9.3 | |
| | Prostate problems (men) | 34 | 5.7 | |
| | Menopausal problems (women) | 42 | 13.4 | |
| Eye problems | Cataracts | 78 | 13.0 | 13.0 |
| Dermatological problems | Chronic skin problems | 83 | 13.8 | 13.8 |
| Mental health problems | Depression | 168 | 28.0 | 34.4 |
| | Chronic anxiety | 134 | 22.3 | |
| | Other mental problems | 18 | 3.0 | |
| Neurological disorder | Migraine | 145 | 24.1 | |
| Neoplasias | Malignant tumors | 62 | 10.3 | 10.3 |
| Endocrinal and metabolic diseases | Thyroid problems | 56 | 9.3 | 40.8 |
| | Diabetes | 99 | 16.5 | |
| | High cholesterol | 184 | 30.6 | |
| Permanent injuries (accident) | | 34 | 11.8 | 11.8 |

*n:* sample size; *%:* percentage

Associations between PA and the studied COPD comorbidities (Table 3) show that, when models were adjusted for sex, age, education level, marital status, smoking, alcohol consumption and obesity, less than 600 MET·min/week of PA was associated with significantly higher odds for urinary incontinence (OR = 2.179; 95% CI = 1.251–3.796), chronic constipation (OR: 2.023; 95% CI = 1.150–3.558), cataracts (OR = 1.918; 95%CI = 1.122–3.279) and osteoporosis (OR = 1.713; 95% IC = 0.958–3.064). Chronic lumbar pain, depression and chronic anxiety showed significant odds too. However, when models were adjusted considering also the presence of comorbidities and the medication intake, PA was significantly associated only with urinary incontinence, chronic constipation, cataracts, chronic lumbar pain and chronic anxiety. When models were not

adjusted, myocardial infarction had one of the highest odds, but it was not significant (OR = 2.171; 95% CI = 0.844–5.586).

**Table 3.** Association of physical activity (PA) and chronic obstructive pulmonary disease (COPD) comorbidities (outcome) estimated by multivariable logistic regression..

| Comorbidities | OR [1] | CI 95% [1] | *p* [1] | OR [2] | CI 95% [2] | *p* [2] | OR [3] | CI 95% [3] | *p* [3] |
|---|---|---|---|---|---|---|---|---|---|
| Hypertension | 0.935 | [0.638–1.370] | 0.729 | - | - | - | - | - | - |
| Myocardial infarction | 2.171 | [0.844–5.586] | 0.108 | - | - | - | - | - | - |
| Angina, Coronary HD | 0.893 | [0.391–2.039] | 0.788 | - | - | - | - | - | - |
| Other HD | 1.616 | [0.949–2.752] | 0.077 | - | - | - | - | - | - |
| Stroke | 1.801 | [0.413–2.831] | 0.874 | - | - | - | - | - | - |
| Diabetes | 1.594 | [1.031–2.463] | 0.036 * | 1.347 | [0.844–2.149] | 0.212 | - | - | - |
| High cholesterol | 1.060 | [0.741–1.516] | 0.752 | - | - | - | - | - | - |
| Varicose veins (legs) | 0.936 | [0.605–1.449] | 0.768 | - | - | - | - | - | - |
| Hemorrhoids | 1.323 | [0.849–2.061] | 0.216 | - | - | - | - | - | - |
| Arthrosis | 1.548 | [1.095–2.187] | 0.013 * | 1.230 | [0.832–1.816] | 0.299 | - | - | - |
| CBP cervical | 1.365 | [0.964–1.933] | 0.080 | - | - | - | - | - | - |
| CBP lumbar | 1.718 | [1.225–2.409] | 0.002 * | 1.553 | [1.09–2.204] | 0.014 * | 1.489 | [1.044–2.125] | 0.028 * |
| Osteoporosis | 1.871 | [1.090–3.210] | 0.023 * | 1.713 | [0.958–3.064] | 0.069 | - | - | - |
| Chronic allergy | 0.894 | [0.630–1.268] | 0.529 | - | - | - | - | - | - |
| Asthma | 0.923 | [0.648–1.315] | 0.658 | - | - | - | - | - | - |
| Liver dysfunction | 1.881 | [0.867–4.078] | 0.110 | - | - | - | - | - | - |
| Stomach/duodenal ulcer | 1.6181 | [0.991–2.851] | 0.054 | - | - | - | - | - | - |
| Chronic constipation | 2.268 | [1.313–3.918] | 0.003 * | 2.023 | [1.150–3.558] | 0.015 * | 1.970 | [1.119–3.469] | 0.019 * |
| Urinary incontinence | 2.568 | [1.527–4.317] | 0.000 * | 2.179 | [1.251–3.796] | 0.006 * | 2.115 | [1.213–3.689] | 0.008 * |
| Kidney problems | 1.531 | [0.880–2.663] | 0.132 | - | - | - | - | - | - |
| Cataracts | 1.842 | [1.141–2.974] | 0.012 * | 1.918 | [1.122–3.279] | 0.017* | 1.840 | [1.074–3.153] | 0.026 * |
| Chronic skin problems | 0.897 | [0.552–1.457] | 0.660 | - | - | - | - | - | - |
| Depression | 1.721 | [1.197–2.475] | 0.003 * | 1.494 | [1.017–2.194] | 0.041 * | 1.443 | [0.980–2.126] | 0.063 |
| Chronic anxiety | 1.703 | [1.153–2.513] | 0.007 * | 1.556 | [1.036–2.336] | 0.033 * | 1.508 | [1.002–2.269] | 0.049 * |
| Other mental problems | 1.724 | [0.674–4.410] | 0.256 | - | - | - | - | - | - |
| Migraine | 1.318 | [0.900–1.903] | 0.156 | - | - | - | - | - | - |
| Malignant tumors | 1.563 | [0.921–2.652] | 0.098 | - | - | - | - | - | - |
| Thyroid problems | 0.858 | [0.481–1.533] | 0.606 | - | - | - | - | - | - |
| Prostate problems (men) | 1.617 | [0.782–3.342] | 0.195 | - | - | - | - | - | - |
| Menopausal problems (women) | 0.818 | [0.416–1.609] | 0.561 | - | - | - | - | - | - |
| Permanent injuries (accident) | 0.807 | [0.509–1.278] | 0.360 | - | - | - | - | - | - |

HD: Heart disease; CBP: Chronic back pain; OR: Odd ratio; CI: Confidence interval. * $p<0.05$; [1]models not adjusted; [2] models are adjusted for sex, age, education level, marital status, smoking, alcohol consumption and obesity; [3]modes are adjutes for for sex, age, education level, marital status, smoking, alcohol consumption, obesity, presence of comorbidities and medication intake.

## Discussion

To our knowledge, this is the first Spanish representative study investigating associations between levels of PA and the presence of thirty-one different COPD comorbidities. The results of this study confirm that low levels of PA are associated with higher risk of comorbidities, specifically, urinary incontinence, chronic constipation, cataracts, chronic anxiety and CBP lumbar.

The prevalence of comorbidities in the present study was high, with CBP lumbar (38.9%), chronic allergy (34.8%), arthrosis (34.1%), CBP cervical (33.3%), asthma (32.9%) and hypertension (32.8%) having the highest prevalence. In other countries, hypertension was found to be the most prevalent comorbidity at 48% and 55%, in Swiss and New York COPD patients, respectively [10,11]. Another study carried out in Hungarian COPD patients showed higher prevalence of hypertension (57%), coronary

artery disease (21%) and diabetes (12%) [39]. The higher prevalence of the comorbidity hypertension in Switzerland, Hungary and America compared to Spain is likely owing to the antihypertensive effect of the Mediterranean diet that is consumed in Spain. The high prevalence of comorbidities in Spanish COPD patients observed in the present study is worrisome when considering the profound implications this will have on patients' quality of life, health care management and health care expenditure. Interventions are urgently required to prevent and manage/reduce comorbidities in this population.

To the best of the authors' knowledge only one other study has investigated associations between levels of PA and the presence of comorbidities among those with COPD [40]. This study aimed to evaluate longitudinal associations between PA and risk of seven categories (cardiovascular, neurological, endocrine, musculoskeletal, malignant, infectious and mental disorders) in 409 COPD patients from the Netherlands and Switzerland. The study suggests that those with high PA levels are less likely to develop depression or anxiety [40]. That concurs with the present study, where it was also found that lower levels of PA are significantly associated with higher risk of depression and chronic anxiety.

Multivariable logistic regression showed that in the present study performing fewer than 600 MET·min/week was associated with 110.6% increased odds of urinary incontinence, 97.2% of chronic constipation, 82.5% of cataracts, 50.8% of chronic anxiety and 48.7% of CBP lumbar. The risk of developing these comorbidities in COPD patients is higher when compared with other studies in healthy populations. A longitudinal study showed that older women performing 6.2 MET·h/week or less was associated with 4% increased risk of urinary incontinence (OR = 1.04 CI 95% = 0.92–1.18) [41]. In a randomized controlled trial follow-up during 12 weeks, it was found that PA improved defecation pattern in middle-aged inactive subjects, reducing Rome criteria for constipation by 37% [42]. In relation to cataracts, a recent study, has shown that performing fewer than 600 MET·min/week of PA was associated with 57.9% increased odds of cataracts in older adults [43]. In a systematic review and meta-analysis, it was found that when cohort studies were considered, people who practiced a medium level of PA had a 10% lower risk of CBP lumbar ($p = 0.0009$). When cross-sectional studies were considered, the association suggested 7% decreased odds, but it was not significant ($p = 0.68$) [44].

The main strengths of this study were the large representative sample of COPD people residing in Spain and the use of a validated, reliable and internationally recognised questionnaire to measure PA. Nevertheless, the results of this study should be considered within its limitations. Spanish adults aged over 70 were not considered, as IPAQ short form is designed for the age range of 15–69 years and this questionnaire only considered PA in the last seven days, so it is not possible to analyse the accumulative effect of PA. Assessments of COPD and comorbidities were self-reported and thus bias was potentially introduced into the analyses. COPD prevalence is higher in men and older people; this may be owing to the accumulative effect of other risk factors to which individuals have been exposed. Tobacco smoking and other types of smoke coming from air pollution or biomass fuel constitute especially important COPD risk factors [1]. Recently, it was shown that outdoor air pollutants, like particulate matter and $NO_2$ were associated with a more rapid lung function decline, increasing COPD prevalence [45,46]. However, external air-borne hazard and also lung function exacerbation history, were not measured in the survey and therefore could not be adjusted for. Moreover, it is a cross-sectional analysis, so the direction of the association is not known. Therefore, future longitudinal studies are needed to clarify the direction and evaluate also the accumulative effect of PA, lung function, exacerbation and airborne hazards, for example from the mineral fibre atlas [47].

## Conclusions

In conclusion, nine of ten COPD patients residing in Spain present comorbidities, with CBP lumbar, chronic allergy, arthrosis, CBP cervical, asthma and hypertension being the most prevalent. A lower level of PA was significantly associated with a higher risk of urinary incontinence, chronic constipation, cataracts, chronic anxiety and CBP lumbar. While the interaction of COPD with PA is not simple straight forward behaviour but an interactive process, it is recommendable for people with COPD to increase their PA levels in an attempt to reduce risk of comorbidities and increase quality of life.

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# ASMA [ASTHMA]

## Artículos III y IV

## [Papers III and IV]

# ARTÍCULO III [PAPER III]

## Levels of Physical Activity in Spanish Asthmatics: A Cross-Sectional Study

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**Abstract**

***Background and objectives:*** 339 million people in the world suffer from asthma. Regular physical activity (PA) could help in its control. Therefore, the aim of this research was to determine the level of PA in Spanish people with asthma considering variation by age, sex, education, marital status, living together, smoking habits, alcohol intake and body mass index (BMI).

***Materials and Methods:*** 1014 Spanish people from 15 to 69 years were included in the study. Data of the Spanish Health Survey (year 2017) were analysed. PA levels were measure with the international physical activity questionnaire short version (IPAQ-SF). PA was categorized as low, moderate and high, and analyzed by sample characteristics. Mann-Whitney U test, Kruskall Wallis H and crosstabs were used to calculate statistical significance ($p < 0.05$).

***Results:*** On average, Spanish asthmatics engaged in a weekly volume of 2228.9 metabolic equivalent of task (MET)·min/week. Males revealed significantly higher PA than females (2516.8 vs 2019.5 MET·min/week; $p = 0.005$), younger participants (<30 years) compared to people aged 30–60 years and older than 60 years (2699.0; 2243.2; 1619.3 MET·min/week; $p < 0.001$) and those with tertiary level of education than those without secondary (2368.3 vs. 2168.3 MET·min/week; $p = 0.001$). Level of PA was lower in those married ($p = 0.001$) and/or living together ($p = 0.010$). Alcohol consumers showed a higher level than the participants who did not drink (2378.3 vs. 1907.9 MET·min/week; $p = 0.001$), but no significant differences were found within current, past and never smokers ($p = 0.890$). Obese asthmatics engaged in less PA than their normal weight and overweight peers ($p < 0.001$). Overall, moderate level was significantly the most frequent (47.7%), but 31.6% showed a low level.

***Conclusions:*** Three out of ten Spanish people with asthma do not achieve PA recommendations, so PA programs should be executed to make people aware of its benefits in asthma control, focusing on those groups with lower PA levels.

**Keywords:** respiratory disease; physical exercise; epidemiology; tobacco; body mass index; alcohol

## Introduction

Asthma is a common and important chronic disease that involves people of all ages [1]. Globally, 339 million people suffer from asthma [2]. In adults, the overall prevalence diagnosed is estimated to be 4.3% [3]. In Spain, an epidemiological study of chronic obstructive pulmonary disease (IBERPOC Project), found a 4.9% prevalence of asthma in Spanish adults aged from 40 to 69 years [4], but according to data of the Spanish Health Survey (year 2017), the prevalence of asthma in Spanish people aged 15 to 69 years was found to be slightly higher, at around 6% [5].

Asthma is a chronic condition that appears with chronic airway inflammation, whose main symptoms are wheeze, chest tightness, shortness of breath, variable expiratory airflow limitation and cough [1]. All these aspects, together with the fear of having exercise-induced bronchoconstriction (EIB), could have a negative effect on levels of physical activity (PA) in people with asthma [6]. Thus, some studies have determined that asthmatics frequently engage in a lower amount of PA than people without asthma [6,7]. Nevertheless, constant practice of PA helps to prevent several chronic diseases [8]. In asthmatics, regular PA aids in the control of asthma [9,10], which consequently reduces the risk of asthma crisis [1]. Different investigations suggest that a usual amount of PA reduces the symptoms of asthma [11,12]: airway responsiveness [13], EIB (demonstrated in children) [10] and the risk of asthma exacerbations [13]. Moreover, it has also been demonstrated that PA improves exercise capacity [14,15] and quality of life [10,13] in people suffering from asthma. Regarding lung function, there is no agreement about the benefits of PA. Carson et al. found that PA had no significant impact on lung function [14], but Eichenberger et al. found improvements in Forced Expiratory Volume in the first second ($FEV_1$) in asthmatics who engaged in exercise training [15].

It is important to underline that a higher number of urgent primary care consultations because of asthmatic exacerbations are related to a higher economic burden [16]. An important part of the cost of asthma is associated to urgent admissions, hospitalization and mortality [17]. Thus, uncontrolled asthma has significantly high costs [18], which could be reduced by improving disease control. In a recent systematic review, the literature analysed suggested that more moderate-vigorous intensity PA was associated with a better control of asthma [4]. Moreover, another systematic review has proposed that people involved in more PA may have less risk of developing asthma [13], which will contribute to reducing health costs.

Nevertheless, the vast majority of studies on PA and asthma have been carried out in populations of children [19,20]. In adults, there is lack of knowledge about levels of PA in asthmatic populations. Some studies have investigated PA in adults with asthma in relation to BMI [21,22] and age [23]. Another investigation found that men, younger and normal weight asthmatics did more PA and had better quality of life than women, older people and overweight or obese adults with asthma [24]. To the authors' knowledge, there is no literature regarding PA levels in asthmatics according to marital status, cohabiting, education level, smoking habits and alcohol consumption, which have all been shown to be potential correlates of PA in the general adult population [25,26].

It is hypothesized that Spanish people with asthma will participate in less PA than their peers without asthma. It is also hypothesized that PA will be lower in women, in older adults, in people with lower education, in tobacco and alcohol consumers and in obese people.

Hence, the aim of the present investigation was to evaluate the PA levels among Spanish people with asthma and to study possible variations by sex, age, education, marital status, cohabiting, tobacco habits, alcohol intake and BMI.

## Materials and Methods

### *Study Design*

The design of this research was cross-sectional, and it is presented according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist (https://www.strobe-statement.org) [27].

### *Setting*

We used data from the last Spanish Health Survey (year 2017). All methods used in this survey have been previously made public [28]. In short, this survey was carried out between October 2016 and October 2017 throughout the Spanish territory. Data was collected by using stratified sampling in three stages. Firstly, census sections were taken into consideration. Then family dwellings were selected by systematic sampling, which allowed self-weighting samples in each stratum. Finally, an adult (aged 15 or over) from each dwelling was chosen to complete the Adult Questionnaire by using the random Kish method. Data were collected by the computer-assisted personal interviewing (CAPI) method, administrated in the participant's homes. The present research was developed

following the Declaration of Helsinki of the World Medical Association. No ethical approval was required because the data used are anonymous and public [28]. Nevertheless, the Ethical Research Committee of the University of Murcia (Spain) approved these secondary analyses (ethical code: 2403/2019; approval date: 30/04/2019).

### *Participants*

The sample was composed of 1014 Spanish people with asthma (587 women). Inclusion criteria were: (1) positive response to the question: "Have you ever been diagnosed with asthma?" and (2) being 15 to 69 years old. Participants of at least 70 years were not included in this study, because they had not answered the questions of the International Physical Activity Questionnaire (IPAQ) short form. This questionnaire was firstly purposed and tested for monitoring PA in adults (15 to 69 years), so until further advancement and testing is carried out in younger and older age groups, its use is not recommendable for those age groups [29].

### *Variables*

The survey included sociodemographic questions (age, sex, last education level completed, marital status, smoking habits and alcohol consumption), physical characteristics (height and weight) and quantity of PA. These sociodemographic variables were chosen considering data available in the survey and previously identified correlates of PA in the general adult population [25,26].

***Physical Activity.*** The instrument used to determine participants' PA level was the IPAQ short form. Total weekly amount of PA was calculated according to the method for computation of metabolic equivalent of task (MET)·minutes/week, previously established in the IPAQ instructions for analysis and data processing of the questionnaire [29]. Then, PA level was classified as: low (<600 MET·min/week), moderate (≥600 MET·min/week) and high (≥3000 MET·min/week), following the same guidelines. This questionnaire has acceptable validity ($\rho$ = 0.30, 95% CI: 0.23–0.36) and reliability (Spearman's $\rho$ = 0.81, 95% CI: 0.79–0.82) [30]. It has also been validated in Spain (r = 0.277; $p < 0.05$; 75% of specificity and sensibility; k = 0.33).

***Sociodemographic Variables.*** Age was divided into three groups: less than 30 years, from 30 to 60 years, and 60 or more years, according to accepted international classifications of adults and older adults [31,32]. Education was grouped based on the highest level completed following the Spanish Classification of Education Levels as

Level A (≤first period secondary), level B (second period secondary and post-secondary (not tertiary), and Level C (tertiary). Marital status was categorized as married and not married (single/widow/divorced/separated). Cohabiting was treated as a dichotomous variable: yes, if they are living together as a couple, or no. Alcohol intake was also categorized as yes/no, considering no consumption if they had never drunk alcohol or if they had never drunk alcohol in the last 12 months. Smoking habits were divided into three groups: those who had never smoked, those who had smoked before but did not smoke currently, and those who smoked currently [33]. In accordance to the methodology determined by the Spanish Health Survey [28], BMI was classified as follows: underweight (<18.5 kg/m$^2$), normal weight (18.5–24.9 kg/m$^2$), overweight (25–30 kg/m$^2$) and obesity (>30 kg/m$^2$).

***Data Analysis***

Sample characteristics were described by frequency and percentage. To check the normality of the data, chi-squared tests were used for qualitative variables and Kolomogorov-Smirnov for quantitative variables. All the studied variables had a nonparametric distribution, except marital status. Descriptive statistics were also used to describe PA level (MET·min/week) of subjects by gender, age, education, marital status, tobacco consumption, alcohol intake and BMI. Statistical significance was tested with the Mann-Whitney U test (gender, education, marital status, alcohol intake) and the Kruskal-Wallis H test for polytomous variables (age, tobacco, BMI) with Bonferroni correction for pairwise comparisons.

To determine significant differences in PA classification between the groups analysed, crosstabs with chi-squared and adjusted residual values were used. In those variables in which chi-squared tests had significant results, the *p*-value of each box was calculated based on the adjusted residual value in order to identify between which groups were the differences significant. Moreover, Pearson Correlation was employed to analyse the association between PA and age. The risk for low PA levels (outcome) was calculated by odds ratio with a confidence interval of 95% (OR; 95%CI); the multivariate regression model was adjusted for age, BMI, sex, education, cohabiting, marital status, tobacco and alcohol consumption. The effect size was calculated using eta squared for the Mann-Whitney U test, epsilon squared for the Krukal Wallis H test and Cramer's V for the chi squared test. Eta squared was calculated by using the following formula: $\eta^2 = Z^2/(k-1)$, epsilon squared was calculated as $\frac{H}{(n^2-1)/(n+1)}$ and Cramer's V by using this formula: V

= $\sqrt{\chi^2/(n \times \min(k-1, c-1))}$ [34]. Effect size of eta squared was classified as small (0.01), medium (0.06) and large (0.14); effect size of epsilon squared was classified as negligible (0.00–0.01), weak (0.01–0.04), moderate (0.04–0.16), relatively strong (0.16–0.36), strong (0.36–0.64) and very strong (0.64–1.00); effect size of Cramer's V was classified as small (0.1), medium (0.3) and large (0.5)

Statistical analyses were performed using the Statistical Package for Social Sciences version 23 (SPSS, International Business Machines Corporation, Armonk, NY, USA). Statistical significance was set at $p < 0.05$ (CI = 95%).

## Results

The sample consisted of 1014 Spanish people with asthma (587 females). The mean age of the participants was 43.2 (SD: 14.7, range: 15–69; Mo: 40). Characteristics of the participants are exhibited in Table 1.

**Table 1.** Sample characteristics

| **Total (*n*=1014)** | | **N** | **%** |
|---|---|---|---|
| Sex | Females | 587 | 57.89 |
| | Males | 427 | 42.11 |
| Age | <30 | 205 | 20.22 |
| | 30-60 | 636 | 62.72 |
| | ≥60 | 173 | 17.06 |
| Education level | Level A | 466 | 45.96 |
| | Level B | 195 | 19.23 |
| | Level C | 353 | 34.81 |
| Marital Status | Married | 509 | 50.20 |
| | Not Married | 505 | 49.8 |
| Living in couple | Yes | 547 | 53.94 |
| | No | 460 | 45.36 |
| | Missing | 7 | |
| BMI | Underweight | 28 | 2.82 |
| | Normal weight | 420 | 42.34 |
| | Overweight | 323 | 32.56 |
| | Obesity | 221 | 22.28 |
| | Missing | 22 | |
| Smoking | Current | 235 | 23.18 |
| | Past | 265 | 26.13 |
| | Never | 514 | 50.69 |
| Alcohol last 12 month | Yes | 692 | 68.24 |
| | No | 322 | 31.76 |

N: sample size; %: percentage; Level A: ≤ first period secondary; Level B: second period secondary and post-secondary (not tertiary); Level C: tertiary; BMI: body mass index.

Total PA of participants (MET·min/week) is presented in Table 2. All variables showed significant differences, except smoking. It was found that men, people with

higher education level, those not married and not living as a couple, and those who drank alcohol, were more physically active. In relation to age, there were significant differences between participants aged 30–60 and over 60 with those under 30, the youngest group being the most active. However, when Pearson Correlation was employed, a low negative association was observed between age and weekly volume of PA ($r = -0.106$; $p = 0.001$). According to BMI, obese participants were significantly less physically active than people with normal weight and those overweight. Standard deviations reveal a high variability based on very low values in many participants.

**Table 2.** Physical Activity in Met·min/week by the characteristics of the sample

| | | n | Av | SD | Med | *p* | ES |
|---|---|---|---|---|---|---|---|
| Sex | Females | 587 | 2019.5 | 3021.8 | 1188.0 | 0.005 | 0.007 |
| | Males | 427 | 2516.8 | 3624.1 | 1386.0 | | |
| Age | 1. <30[2,3] | 205 | 2699.0 | 3109.5 | 1470.0 | | |
| | 2. 30-60[1] | 636 | 2243.2 | 3521.7 | 1350.0 | <0.001 | 0.059 |
| | 3. ≥60[1] | 173 | 1619.3 | 2470.6 | 924.0 | | |
| Education level | Level A[3] | 466 | 2168.3 | 3808.6 | 1039.5 | | |
| | Level B | 195 | 2121.5 | 2552.0 | 1386.0 | 0.001 | 0.014 |
| | Level C[1] | 353 | 2368.3 | 2913.5 | 1386.0 | | |
| Marital Status | Married | 509 | 2089.5 | 3582.4 | 1039.5 | 0.001 | 0.011 |
| | Not Married | 505 | 2369.4 | 2977.5 | 1386.0 | | |
| Living in couple | Yes | 547 | 2177.0 | 3615.5 | 1173.0 | 0.010 | 0.007 |
| | No | 460 | 2301.7 | 2898.5 | 1386.0 | | |
| Smoking | Current | 235 | 2512.5 | 4104.9 | 1188.0 | | |
| | Past | 265 | 2074.5 | 2969.2 | 1386.0 | 0.890 | 0.000 |
| | Never | 514 | 2178.9 | 3030.2 | 1386.0 | | |
| Alcohol (last 12 months) | Yes | 692 | 2378.3 | 3312.9 | 1386.0 | 0.001 | 0.011 |
| | No | 322 | 1907.9 | 3242.5 | 1011.0 | | |
| BMI | 1. Underweight | 28 | 2376.2 | 4050.9 | 1014.7 | | |
| | 2. Normal weight[4] | 420 | 2439.4 | 3071.4 | 1386.0 | <0.001 | 0.035 |
| | 3. Overweight[4] | 323 | 2454.0 | 3726.3 | 1386.0 | | |
| | 4. Obesity[2,3] | 221 | 1599.8 | 2870.2 | 693.0 | | |
| Total | | 1014 | 2228.9 | 3296.4 | 1386.0 | | |

n: Sample size; Av: Average; SD: Standard Deviation; Med: median; Level A: ≤ first period secondary; Level B: second period secondary and post-secondary (not tertiary); Level C: tertiary; Superscripts indicate significant differences between groups; p-values were based on Mann- Whitney U test and Kruskal Wallis H test; ES: Effect size was based on eta squared for Mann-Whitney U test and epsilon squared for Kruskal Wallis H test. Statistical significance: $p < 0.05$

In Table 3, PA was grouped into low, moderate and high level. The variables sex, age, education level, marital status, living together, alcohol intake and BMI showed significant differences. Post hoc analyses indicated significant differences between sex and alcohol consumption and high level of PA, with a higher percentage of men and those who drank alcohol. In relation to age, the significant differences were in high PA level between those under 30 years (29.3%) and those over 60 years (12.7%). There were also significant differences in low level of PA in relation to marital status and living as a

couple, those who were married or were living as a couple having a higher percentage of low level. In relation to education, the significant differences were between those with the first period secondary or less achieved, and those with a tertiary level of education. According to BMI, no significant differences were found within subgroups. However, the percentage of obese participants with a low level of PA (44.9%) was significantly higher than the percentage of those with a high level of PA (12.8%). Considering the whole sample, a moderate level of PA was the most frequent (47.7%), and a high level of PA the least (20.7%).

**Table 3.** Classification of physical activity (PA) level following International Physical Activity Questionnaire (IPAQ) guidelines, by the characteristics of the sample

| | | | PA Level | | | | |
|---|---|---|---|---|---|---|---|
| | | ***n*** | **Low** | **Mod** | **High** | ***p*** | ***V*** |
| Sex | [a]Females | 587 | 198(33.7) | 287(48.9) | 102(17.4)[b] | 0.007 | 0.099 |
| | [b]Males | 427 | 122(28.6) | 197(46.1) | 108(25.3)[a] | | |
| Age | [a]<30 | 205 | 53(25.9) | 92(44.9) | 60(29.3)[c] | 0.001 | 0.094 |
| | [b]30-60 | 636 | 200(31.4) | 308(48.4) | 128(20.1) | | |
| | [c]≥60 | 173 | 67(38.7) | 84(48.6) | 22(12.7)[a] | | |
| Education level | [a]Level A | 466 | 171(36.7)[c] | 208 (44.6) | 87(18.7) | 0.017 | 0.077 |
| | [b]Level B | 195 | 59 (30.3) | 95 (48.7) | 41 (21.0) | | |
| | [c]Level C | 353 | 90 (25.5)[a] | 181 (51.3) | 82 (23.2) | | |
| Marital Status | [a]Married | 509 | 182(35.8)[b] | 237(46.6) | 90(17.7) | 0.005 | 0.102 |
| | [b]Not Married | 505 | 138(27.3)[a] | 247(48.9) | 120(23.8) | | |
| Living in couple | [a]Yes | 547 | 192(35.1)[b] | 254(46.4) | 101(18.5) | 0.019 | 0.089 |
| | [b]No | 460 | 127(27.6)[a] | 224(48.7) | 109(23.7) | | |
| Smoking | Current | 235 | 79(33.6) | 100(42.6) | 56(23.8) | 0.127 | 0.060 |
| | Past | 265 | 73(27.5) | 143(54.0) | 49(18.5) | | |
| | Never | 514 | 168(32.7) | 241(46.9) | 105(20.4) | | |
| Alcohol (last 12 m) | [a]Yes | 692 | 199(28.8)[b] | 333(48.1) | 160(23.1)[b] | 0.003 | 0.107 |
| | [b]No | 322 | 121(37.6)[a] | 151(46.9) | 50(15.5)[a] | | |
| BMI* | [a]Underweight | 37 | 9(32.1) | 14(50.0) | 5(17.9) | <0.001 | 0.112 |
| | [b]Normalweight | 419 | 116(27.6) | 201(47.9) | 103(24.5) | | |
| | [c]Overweight | 320 | 89(27.6) | 163(50.5) | 71(22.0) | | |
| | [d]Obesity | 227 | 102(44.9)[d] | 96(42.3) | 29(12.8)[d] | | |
| Total | | 1014 | 320(31.6) | 484(47.7) | 210(20.7) | <0.001 | |

Values are Frequency (%). *n:* Sample size; Mod: moderate; Level A: ≤ first period secondary; Level B: second period secondary and post-secondary (not tertiary); Level C: tertiary; *V:* Cramer's V. Superscripts indicate significant differences between groups; Statisttical significance: $p < 0.05$

The risk for low level of PA (<600 MET·min/week) was significantly higher in those with level A of education (OR = 1.470; 95%CI 1.055–2.048; p = 0.005) and those with higher BMI (OR = 1.040; 95%CI 1.012–1.069). Living together (OR = 1.141; 95%CI 0.642–2.029), having education level B (OR = 1.236; 95%CI 0.850–1.879), being older (OR = 1.005; 95%CI 0.994–1.016), being alcohol consumer (OR = 0.815; 95%CI 0.599–1.110) and being current smoker (OR = 1.150; 95%CI 0.815–1.624) revealed higher probability of having a low level of PA, but differences were not statistically

significant (p > 0.05). The probability of having a low level of PA was reduced in men (OR = 0.774; 95%CI 0.580–1.031), past smokers (OR = 0.720; 95%CI 0.506–1.023) and/or unmarried participants (OR = 0.764; 95%CI 0.444–1.420). Nevertheless, these differences were not significant ($p > 0.05$).

**Discussion**

The results of this study show an average of 2228.9 MET·min/week in adults with asthma residing in Spain. This amount of PA is higher than the minimum recommended by the Centres for Disease Control and Prevention (CDC) [35] and the World Health Organization [36], which establish a weekly volume of at least 600 MET·min. Nevertheless, 31.6% of participants were found to have a low level of PA, which means a level under the recommendations. Moreover, the mean value of weekly PA in this investigation is lower than the volume observed in the international validation of IPAQ-Short version carried out in 12 different countries with a total of 957 participants, which determine a mean value of 2514 MET·min/week in healthy adults [30].

When differences by sociodemographic characteristics were considered, the present study showed a lower total amount of PA in women, those older than 30, those without tertiary level of education, those married, those living with a couple, those who did no drink alcohol and obese participants. This may be owing to a reduced quality of life in older people and in people with a lower education [37], potentially owing to poorer asthma control, which may be improved by increasing PA levels.

In 2015, Gerovasili et al. carried out a study to analyse levels of PA in 19,978 adults (from 18 to 64 years of age) in 28 different European nations. In Spain, an average of 2166 MET·min/week was found. However, the average in Southern Europe was lower than in the countries in Western Europe (2373 MET·min/week) and Northern Europe (2449.75 MET·min/week) [38]. The present study shows an average in Spanish asthmatics slightly higher than the Spanish average in the study of Gerovasili et al., (2228.9 MET·min/week vs 2166 MET·min/week). This difference may be explained by the presence of disease not being considered in the study of Gerovasili et al.

It should be highlighted that the most of participants used in the investigations of PA in asthmatics are children or adolescents. This could be due to the highest prevalence of asthma in children (14%) [16] in comparison to adults (4.3%) [3]. This is the first Spanish representative study that establishes the levels of PA in adults with asthma

analysing the differences by gender, age, marital status, living together, education level, BMI, smoking habits and alcohol consumption.

Nevertheless, in 2001, Chen et al. analysed energy expenditure (EE) (kcal/kg·day) on leisure activities according to asthma and potential determinants. They found that EE was higher in men, in normal weight participants, in non-smokers and in men who did not drink alcohol (in case of women, EE was higher in those who drank) [23]. This concurs with our study, where PA levels are higher in men and in normal weight asthmatics, but differs in relation to tobacco consumption because there were no significant differences in PA levels between current smokers, past smokers and non-smokers. According to age, Chen et al. found that younger asthmatics were more active than non-asthmatics. However, among older asthmatics, EE were lower than in non-asthmatics [23]. The present study does not compare asthmatics with non-asthmatics, but shows that total amount of PA is significantly higher in younger asthmatics (2699.0 MET·min/week) than in middle age asthmatics (2243.2 MET·min/week) and older adults with asthma (1619.3 MET·min/week) residing in Spain.

Regarding marital status and cohabiting, the present study found a higher percentage of low level of PA among those married and/or living together. In a German longitudinal study with a 19-year follow-up, results showed that cohabiting and being married were associated with reduced weekly PA in comparison with singles [39]. These results are in line with our findings. A possible explanation for the negative impact of relationships on PA level could be that people want to spend more time with their significant other or have wider family commitments and therefore have less time to be physically active. Similarly, a study carried out in adults from Pamplona (Spain) revealed higher risk of sedentarism among married men and women [40].

In relation to alcohol intake, a higher percentage of participants who do not reach PA recommendations was found among those who did not drink in comparison to those who drank (37.6%vs. 28.8%). However, the percentage of alcohol consumers with high level of PA was higher than non-consumers (15.5% vs. 23.1%). Actually, sport per se is associated with high alcohol consumption. Kingsland et al. [41] found that sport clubs alcohol management practices, such as service of alcohol, happy hour promotions and alcohol-only awards, were associated with higher alcohol consumption among club members.

Regarding BMI, Conroy et al. [21] evaluated 125 adults (≥21 years old) with asthma in New York and Denver, and they found that obese (≥30kg/m$^2$) or overweight (25-30kg/m$^2$) individuals engaged in lower moderate-vigorous PA than those with normal weight (35.7, 39.9, 46.2 min/day; $p = 0.09$). This partially concurs with our results, which shows significant differences between BMI groups. A total of 44.9% of the obese asthmatics reported low levels of PA, with only a 12.8% showing a high level. In this way, Russell et al [42] reported that only in participants with normal weight (BMI<25) did PA exhibited a positive correlation with asthma symptoms. Therefore, it is necessary to take BMI into account due to the fact that a high BMI is related to other chronic diseases like cardiovascular diseases, diabetes or cancer, and these could be involved in lower PA levels.

Recently, Sánchez-Castillo et al. carried out a similar study in Spanish people with COPD [43]. The total PA volume in COPD patients was lower (1684.8 MET·min/week) than the total amount of PA found in the asthmatics of the present study (2228.9 MET·min/week). This may be due to the progressive and minimally reversible obstruction that is found in people with COPD, while in asthmatics the obstruction should be variable and reversible [44]. However, when the classification level of PA was analysed, a significant percentage of participants in both the COPD study and the present study demonstrated a moderate level of PA (47.5% in COPD vs. 47.7% in asthma). On the contrary, people with a high level of PA were slightly more frequent in the present study (20.7%) than in the COPD study (14.6%) [43]. When differences by sociodemographic characteristics were considered, both studies found that PA was higher in men, younger adults, in people with normal weight, and in people who drank alcohol. However, the present study also showed higher levels of PA in those married and/or living together and in those with tertiary education. Regarding tobacco consumption, both studies found no significant differences in PA between current, past and non-smokers. A possible explanation of these results could be that PA could act as an ally and mitigate the damage caused by cigarette smoking in respiratory health. Otherwise, the prevalence of smoking (current and past) was higher in people with COPD than in asthmatics (67.0% vs 49.31%).

Regarding the risk for low level of PA, it was found that higher BMI and lower level of education increased the risk of not achieving PA recommendations in asthmatics. Similarly, an American study about correlates of American adults' PA patterns showed

that older ages (≥60 years), female sex, higher BMI and history of chronic disease were significantly associated with lower odds of being more active [45]. Comparisons should be considered carefully, as the present analysis only included Spanish asthmatics. Another cross-sectional study in the Portuguese population revealed that moderate PA was a predictor of controlled asthma in men (OR = 1.84; 95%CI: 1.02–3.30) and vigorous PA doubled the risk of uncontrolled asthma in women (OR = 1.94; 95%CI: 1.13–3.35) [46].

Considering all data, it is important to carry out therapeutic interventions in order to increase PA levels in people with asthma. The main physical therapies for asthmatics are inspiratory muscle training [47], breathing exercises [48] and physical training [14]. Delgado et al. [47] found higher improvements in respiratory muscle strength and functional capacity in asthmatics who were involved in inspiratory muscle training. In relation to breathing exercises, Santino et al. [48] carried out an intervention review of breathing exercises: yoga, breathing retraining and Buteyko. The results revealed a higher change in quality of life (mean difference (MD) up to 3 months = 0.42; MD over 6 months = 1.34), better control of asthma symptoms (MD 0.15 up to 3 months), better control of hyperventilation symptoms (MD 3.22 up to 3 months) and better lung function up to three months ($FEV_1$% predicted; MD: 6.88). Carson et al. [14] studied physical training for asthma and found significant improvement in maximum oxygen intake, positive effect on quality of life and identified no adverse effects, which means physical training was well tolerated by asthmatics. Therefore, physical therapies could be an important non-pharmacological treatment for people with asthma.

Principal strengths of this paper include the use of a representative sample of asthmatics (15–69 years) residing in Spain and the use of a verified and internationally accepted questionnaire to evaluate levels of PA. Nevertheless, these results should be considered in the light of its restrictions. Although the IPAQ is a reference tool to establish a population's level of PA, it is important to underline that it is self-reported, so people could over- or underestimate their PA level. In the same way, diagnosis of asthma was self-reported, too. Another potential limitation is the lack of classification of severity of asthma because data was not available in the survey. Data about possible therapeutic interventions followed by participants were not available, but should be considered in future studies. In addition, as this was a cross-sectional analysis and not a randomized controlled trial, causality cannot be proven, but only correlation. In future studies it will

be advisable to measure PA levels objectively by employing accelerometers and to consider the severity of the asthma.

## Conclusions

Approximately three out of ten Spanish people with asthma exhibited a low level of PA, not achieving PA recommendations. Therefore, PA programs should be executed to make people aware of its benefits in asthma control, and these intervention programs should target women, people with at least 30 years, married people and/or those living in couple, those with a level of education equal or under the first period of secondary, those who do not consume alcohol, and people who do not have a normal weight. Moreover, long term PA programs are needed to increase PA levels and/or reach PA recommendations, so the activities involved in these programs should motivate the participants to sustain PA over time. In this way, asthmatics could make their life better.

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# ARTÍCULO IV [PAPER IV]

## Analysis of Physical Activity and Comorbidities in Spanish Asthmatics

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**Abstract:**

The prevalence of comorbidities in asthmatics is high. Comorbidities may complicate the clinical management of asthma, increasing the risk for exacerbation and even death. The objective of the present research was to establish the prevalence of 31 asthma comorbidities and to assess the association of these comorbidities with physical activity (PA) in Spanish asthmatics. Data of the Spanish National Health Survey 2017 (cross-sectional design) were used in this study. A total of 1014 people (42.1% males) with asthma participated in this study (age range 15–69 years). The IPAQ (International Physical Activity Questionnaire) short form was the instrument administered to evaluate PA (exposure), and the self-reported answer to the question "Have you ever been diagnosed with…?" determined the presence of comorbidities (outcomes). This association was assessed by multivariable logistic regression. Results demonstrated a huge presence of comorbidities (89.3%). The most prevalent were chronic allergy (61.1%), chronic lumbar pain (28.7%), chronic cervical pain (24.2%), high cholesterol (20.9%), Chronic Obstructive Pulmonary Disease (COPD) (19.4%), migraine (19.2%) and hypertension (19.3%). PA level under 600 metabolic equivalent of task (MET)·min/week showed a significant association with urinary incontinence (3.10 [1.62–5.94]), osteoporosis (1.90 [1.00–3.61]) and chronic anxiety (1.69 [1.13–2.53]). Therefore, comorbidities and PA levels should be considered in the prevention and treatment of asthmatics, in order to improve their quality of life.

**Keywords:** respiratory health; exercise; prevalence; adults

## Introduction

Asthma is a frequent and potentially serious chronic condition that affects all age groups [1]. Over 339 million people worldwide are affected by asthma [2]. According to previous research, the worldwide prevalence of asthma diagnosed in the adult population is 4.3% [3]. In Spain, the epidemiological study of chronic obstructive pulmonary disease (IBERPOC) found a prevalence of 4.9% in adults aged 40–69 years [4], and according to the Spanish National Survey 2017, a prevalence of 6 % was found in Spanish people aged 15–69 years [5].

Chronic airway inflammation related to wheezing, chest tightness, shortness of breath, cough and variability in expiratory airflow limitation are some of the symptoms present in asthmatics. An insufficient control of asthma symptoms is a risk factor to develop crisis relating to asthma [1]. The previous aspects, together with the possibility of having EIB (exercise-induced bronchoconstriction), could reduce physical activity (PA) levels in asthmatics [6]. Therefore, asthmatics are usually involved in lower levels of PA in comparison with non-asthmatics [6,7]. In people with asthma, regular PA may be useful in the control of asthma [8–10]. Several studies suggest that regular PA reduces asthma symptoms [11,12], airway responsiveness [13], EIB [9] and the risk of asthma exacerbations [13,14] and increases exercise capacity [15,16] and quality of life [9,11,13] in people with asthma.

However, asthma is a heterogeneous disease that can be associated with a number of comorbidities. The term comorbidity was coined in 1970 by Feinstein and it refers to "any additional co-existing ailment" [17]. Comorbidities could be independent of asthma or be associated with the disease, but they could complicate clinical management of asthma [18,19], increasing the risk for exacerbation [20], unscheduled asthma care [21], poor asthma control and impaired quality of life [1] and mortality [22]. Therefore, it is important to recognize them.

Rhinosinusitis, food allergy, obstructive sleep apnoea syndrome (OSAS), gastroesophageal reflux (GER) and mental health disorders are the most frequent conditions in people with asthma [1,18,19,23]. Asthmatics have significantly more comorbid conditions than non-asthmatics [24,25]. A recent study, which examined the prevalence of 39 comorbidities in more than one million Scottish adults, found that the most prevalent comorbidities in adults with asthma were hypertension (20%), depression

(17%), pain (16%) and COPD (chronic obstructive pulmonary disease) (13%) [26]. Moreover, obese patients show more difficulties in the control of asthma, probably because of a different type of airway inflammation that contributes to other comorbidities like OSAS and GER and due to a poor shape and a decrease in lung volume caused by abdominal fat, which contributes to dyspnoea [1].

It is known that sustained and regular participation in PA helps not only in primary, but also in secondary prevention of a series of chronic conditions [27–29]. However, there is no evidence about how PA can contribute to reduce the risk of suffering from comorbidities in asthmatic adults. It is hypothesized that lower PA levels would increase the risk of comorbidities.

Knowledge about the spectrum of diseases that could affect asthmatics and about how they differ according to PA levels would aid health professionals to identify, prioritize and control asthma comorbidities. Hence, the purpose of this research was to establish the prevalence of 31 different asthma comorbidities and to analyse the associations of levels of PA with the risk of these comorbidities in Spanish people with asthma aged 15–69 years.

## Materials and Methods

### *Study Design*

This research had a cross-sectional design, and it was written following the STROBE guidelines (Strengthening the Reporting of Observational Studies in Epidemiology) [30].

### *The Survey*

We analysed data extracted from the 2017 Spanish National Health Survey. All details about the survey method were previously published [31]. In summary, a stratified three-stage sampling was utilized for data collection. Firstly, the census categories were contemplated, then the family dwellings, and finally, a family member aged 15 or over was elected within each dwelling. The sections were selected within each stratum with probability proportional to their size. A systematic sampling was used to choose the dwellings with equal probability in each section, prior arrangement by size of the dwelling. This procedure led to self-weighting samples in each stratum. To select the

family member who filled out the Adult Questionnaire, the random Kish method was employed, which assigns equal probability to all adults in the dwelling. Data were collected by a CAPI (computer-assisted personal interviewing), carried out in the selected participants' dwellings. The interviewers, who were previously qualified, filled in the questionnaires with the information provided by the participants. This research was executed following the principles of the World Medical Association Declaration of Helsinki. Data from the Spanish National Health Survey are public and anonymous, so no ethical approval was required [31]. The present secondary analyses were approved by the Ethical Research Committee of the University of Murcia.

***Participants***

The participants of this study were Spanish people suffering from asthma (n = 1014; 587 females and 427 males) (Table 1). Inclusion criteria were: (1) age range 15–69 years and (2) affirmative answer to the question "Have you ever been diagnosed with asthma?" People older than 69 years were not taken into account since they did not respond to the PA questions of the survey. The International Physical Activity Questionnaire (IPAQ) short form was firstly designed for supervising PA in adults (age range 15–69 years). Then, until further development and testing is carried out, the use of IPAQ is not advisable in younger and older ages [32]. Before responding to the survey questions, all participants voluntarily agreed to participate in the study by signing an informed consent form.

***Physical Activity (Exposure)***

PA was evaluated with the IPAQ short form. Total PA metabolic equivalent of task (MET)·minutes/week was calculated by the following formula: sum of walking + moderate + vigorous MET·minutes/week scores. Then, following the instructions for data processing and analysis of the IPAQ, participants were divided in two groups [32]: (1) under 600 MET·minutes/week and (2) at least 600 MET·minutes/week, which meant achieving PA recommendations. IPAQ has been validated in adult populations worldwide, and it is a valid ($\rho = 0.30$, 95% CI: 0.23–0.36) and reliable (Spearman's $\rho$ = 0.81, 95% CI: 0.79–0.82) instrument [33]. The IPAQ short form has been validated in Spanish adults as well ($r = 0.277$; $p < 0.05$) with a 75% of sensitivity and specificity (k = 0.33) [34].

***Comorbidities (Outcomes)***

The 31 comorbidities analysed were based on the data available in the 2017 Spanish National Health Survey. Participants who answered affirmatively to the question "Have you ever been diagnosed with… (each comorbidity studied)"? were determined to suffer from that specific condition. The comorbidities studied are described in Table 2. Chronic allergy includes rhinitis, conjunctivitis, dermatitis, food allergy or another kind of allergy (excluding allergic asthma). Some of these diseases were analysed in previous studies, and rhinosinusitis, food allergy, gastroesophageal reflux (GER), psychological diseases and obstructive sleep apnoea syndrome (OSAS) were found to be common in asthma patients [1,23].

Comorbidities were classified following the ICD (International Classification of Diseases) in 13 different groups: (1) cardiovascular diseases; (2) musculoskeletal disorders; (3) immunological diseases; (4) respiratory diseases; (5) digestive problems; (6) urogenital diseases; (7) eye problems; (8) dermatological problems; (9) mental health problems; (10) neurological disorders; (11) neoplasias; (12) endocrinal and metabolic diseases; (13) permanent injuries [35].

***Covariates***

Covariates were selected according to previous research [36,37]. Sex, age, education level and marital status were included as sociodemographic variables. Education level was based on the highest level completed and was categorized according to the Spanish Classification of Education Levels as Level A (≤ 1st period secondary), Level B (2nd period secondary and post-secondary (not tertiary)), and Level C (tertiary) [38]. Marital status was classified as married versus not married, which included those who were single, divorced, separated or widowed. Smoking, alcohol consumption and BMI (body mass index) were also selected as covariates. Smoking was categorised into 3 categories: never, past and current smoking. Consumption of alcohol was categorised as yes/no. BMI was calculated as weight (kg) divided by height (m) squared. Both weight and height were self-reported. The definition of obesity was BMI ≥ 30 $kg/m^2$. In relation to the presence of other comorbidities, participants were divided in two groups: those who had one or more comorbidities and those who had no comorbidities. Medication intake was considered as a dichotomous variable as well. Participants were included in the "yes" group if they had taken at least one of the following twenty-two medications in the last

two weeks: (1) flu/cold medication; (2) pain medication; (3) fever medication; (4) sedatives; (5) allergy medication; (6) antibiotics; (7) diarrhoea medication; (8) heart medication; (9) rheumatism medication; (10) blood pressure medication; (11) digestive problems medication; (12) diabetes medication; (13) antidepressants; (14) laxatives; (15) vitamins/minerals/tonics; (16) slimming medicines; (17) cholesterol medication; (18) thyroid medication; (19) menopausal hormones; (20) contraceptive pill; (21) natural products (plant-based products [31]); (22) others.

***Data Analyses***

The characteristics of the sample were described through descriptive statistics. The mean and SD (standard deviation) were used for continuous variables (age, BMI), while frequencies and percentages were utilized for categorical variables (sex, age, marital status, education level, smoking, alcohol consumption, obesity, medication intake, presence of comorbidities and PA). Descriptive statistics were used to determine the prevalence of every comorbidity and group of comorbidities as well. Statistical significance in sample characteristics according to PA was analysed by chi-squared tests (categorical variables) and T test (continuous variables)

Multivariable logistic regression analyses were employed to study the associations between each comorbidity and quantity of PA. Three different models were used to carry out the analyses. Model 1 was not adjusted; Model 2 was adjusted for sex, age, BMI education level, marital status, smoking habits and alcohol consumption; and Model 3 was adjusted considering the variables "presence of other comorbidities" and "medication intake" as well, in addition to the same variables used in Model 2. All variables were included in the regression analyses as categorical variables except age and BMI, which were treated as continuous variables. There were missing data only on the variable BMI (2.2%). Results from the multivariable logistic regression analyses were presented as odds ratios (OR) with 95% of confidence intervals (CI). Bonferroni correction was applied to control the family-wise error rate, so statistical significance was set at $p < 0.0016$.

Statistical Package for Social Sciences version 23 (SPSS, International Business Machines Corporation, Armonk, NY, USA) was used to carry out these analyses.

## Results

The sample was composed of 1014 Spanish asthmatic people. Participants' mean age (SD) was 43.17 (14.7) years, with a range between 15–69 years. A total of 57.9% were females, and 42.1% were males. The prevalence of participants who do not reach PA recommendations was 31.6%. Nine out of ten people with asthma presented comorbidities. An average of 3.6 concurrent comorbidities (max:20, min:3, mo:1) was found. In Table 1, sample characteristics are described according to PA level.

The differences in sample characteristics according to PA were significant for education level, marital status, alcohol consumption, obesity, BMI and age.

**Table 1**. Sample characteristics according to PA level

| | | | PA <600MET·min/week | | PA ≥600MET·min/week | | |
|---|---|---|---|---|---|---|---|
| **Characteristic** | **Category** | **N** | **N** | **%** | **N** | **%** | ***p*** |
| Sex | Male | 427 | 122 | 28.6 | 305 | 71.4 | 0.081 |
| | Female | 587 | 198 | 33.7 | 389 | 66.3 | |
| Education | Level A | 466 | 171 | 36.7 | 295 | 63.3 | |
| | Level B | 195 | 59 | 30.3 | 136 | 69.7 | 0.003* |
| | Level C | 353 | 90 | 25.5 | 263 | 74.5 | |
| Marital Status | Married | 509 | 182 | 35.8 | 327 | 64.2 | 0.004* |
| | Not Married | 505 | 138 | 27.3 | 367 | 72.7 | |
| Smoking | Current | 235 | 79 | 33.6 | 156 | 66.4 | |
| | Former | 265 | 73 | 27.5 | 192 | 72.5 | 0.254 |
| | Never | 514 | 168 | 32.7 | 346 | 67.3 | |
| Alcohol | Yes | 692 | 199 | 28.8 | 493 | 71.2 | 0.005* |
| | No | 322 | 121 | 37.6 | 201 | 62.4 | |
| Obesity | Yes (≥30) | 220 | 96 | 43.6 | 124 | 56.4 | <0.001* |
| | No | 772 | 214 | 27.7 | 558 | 72.3 | |
| | Missing | 22 | 10 | | 12 | | |
| Comorbidities | Yes | 905 | 292 | 32.3 | 613 | 67.7 | 0.163 |
| | No | 109 | 28 | 25.7 | 81 | 74.3 | |
| Medication | Yes | 822 | 259 | 31.5 | 563 | 68.5 | 0.944 |
| | No | 192 | 61 | 31.8 | 131 | 68.2 | |
| | | | **Av.** | **SD** | **Av.** | **SD** | |
| BMI | | | 27.3 | 5.9 | 25.9 | 5.0 | <0.001* |
| Age | | | 45.2 | 14.4 | 42.2 | 14.8 | 0.003* |

N: sample size; %: percentage. Level A: ≤ 1st period secondary; Level B: 2nd period secondary and post-secondary (not tertiary); Level C: tertiary; Av.: average; SD: Standard deviation. p-values are based on chi-squared tests (categorical) and T test (continuous). * $p<0.05$

Overall, the prevalence of comorbidities in asthmatics is shown in Table 2. Chronic allergy showed the highest prevalence, with 61.1%. Chronic lumbar and cervical pain, high cholesterol, COPD, migraine and hypertension were diseases with a high prevalence as well, all of them with around a 30–20% prevalence. According to the ICD classification, sixty-one-point-one percent of asthma participants had immunological

disease, followed by musculoskeletal disorders (39.1%), cardiovascular diseases (32.2%) and endocrinal and metabolic diseases (27.3%).

**Table 2.** Prevalence of comorbidities in people with asthma

| | **Comorbidities** | **N** | **%** | **Global %** |
|---|---|---|---|---|
| Cardiovascular diseases | Hypertension | 196 | 19.3 | 32.2 |
| | Myocardial infarction | 14 | 1.4 | |
| | Angina, Coronary HD | 20 | 2.0 | |
| | Other HD | 50 | 4.9 | |
| | Stroke | 16 | 1.6 | |
| | Varicose veins (legs) | 143 | 14.1 | |
| Musculoskeletal disorders | Arthrosis | 187 | 18.4 | 39.3 |
| | CBP cervical | 245 | 24.2 | |
| | CBP lumbar | 291 | 28.7 | |
| | Osteoporosis | 49 | 4.8 | |
| Immunological disease | Chronic allergy | 625 | 61.6 | 61.1 |
| Respiratory disease | COPD | 197 | 19.4 | 19.4 |
| Digestive problems | Liver dysfunction | 19 | 1.9 | 18.1 |
| | Stomach/duodenal ulcer | 55 | 5.4 | |
| | Chronic constipation | 64 | 6.3 | |
| | Haemorrhoids | 118 | 11.6 | |
| Urogenital diseases | Urinary incontinence | 51 | 5.0 | 15.5 |
| | Kidney problems | 56 | 5.5 | |
| | Prostate problems (men) | 27 | 6.3 | |
| | Menopausal problems (women) | 57 | 9.7 | |
| Eye problems | Cataracts | 58 | 5.7 | 5.7 |
| Dermatological problems | Chronic skin problems | 118 | 11.6 | 11.6 |
| Mental health problems | Depression | 152 | 15.0 | 20.6 |
| | Chronic anxiety | 143 | 14.1 | |
| | Other mental problems | 28 | 2.8 | |
| Neurological disorder | Migraine | 195 | 19.2 | 19.2 |
| Neoplasias | Malignant tumors | 51 | 5.0 | 5.0 |
| Endocrinal & metabolic diseases | Thyroid problems | 83 | 8.2 | 27.3 |
| | Diabetes | 73 | 7.2 | |
| | High cholesterol | 212 | 20.9 | |
| Permanent injuries (accident) | | 92 | 9.1 | 9.1 |

N: sample size; %: percentage, HD: heart disease, CBP: chronic back pain, COPD: chronic obstructive pulmonary disease

Associations between asthma comorbidities and PA are shown in Table 3. When models were not adjusted, hypertension, arthrosis, chronic cervical and lumbar pain, osteoporosis, chronic constipation, haemorrhoids, urinary incontinence, kidney problems, cataracts, depression, chronic anxiety and migraine were significantly associated with PA ($p < 0.05$). When models were adjusted for age, BMI, sex, education level, marital status, smoking and alcohol consumption, engaging in less than 600 MET·min/week of PA was significantly associated with a greater probability of existing osteoporosis, urinary incontinence and chronic anxiety ($p < 0.05$).

**Table 3.** Association of PA and asthma comorbidities (outcome) estimated by multivariable logistic regression.

| **Comorbidities** | **OR[1]** | **CI 95 % [1]** | **p [1]** | **OR [2]** | **CI 95 % [2]** | **p [2]** | **OR [3]** | **CI 95 % [3]** | **p [3]** |
|---|---|---|---|---|---|---|---|---|---|
| Hypertension | 1.49 | 1.08-2.06 | 0.016* | 1.11 | 0.76-1.61 | 0.592 | 1.10 | 0.75-1.62 | 0.616 |
| Myocardial infarction | 0.87 | 0.27-2.78 | 0.809 | 0.26 | 0.06-1.14 | 0.074 | 0.52 | 0.06-1.13 | 0.071 |
| Angina, Coronary HD | 1.08 | 0.74-4.38 | 0.197 | 0.83 | 0.29-2.38 | 0.734 | 0.83 | 0.28-2.40 | 0.723 |
| Other HD | 1.23 | 0.62-2.23 | 0.489 | 1.08 | 0.58-2.02 | 0.796 | 1.08 | 0.58-2.02 | 0.805 |
| Stroke | 2.20 | 0.82-5.91 | 0.118 | 1.31 | 0.45-3.84 | 0.625 | 1.26 | 0.43-3.74 | 0.672 |
| Varicose veins (legs) | 1.15 | 0.79-1.68 | 0.452 | 0.85 | 0.56-1.28 | 0.437 | 0.85 | 0.56-1.28 | 0.435 |
| Arthrosis | 1.93 | 1.40-2.68 | <0.001** | 1.39 | 0.93-2.07 | 0.109 | 1.37 | 0.91-2.06 | 0.130 |
| CBP cervical | 1.46 | 1.08-1.97 | 0.014* | 1.20 | 0.86-1.67 | 0.289 | 1.20 | 0.86-1.69 | 0.282 |
| CBP lumbar | 1.52 | 1.14-2.02 | 0.004* | 1.31 | 0.96-1.78 | 0.089 | 1.32 | 0.96-1.80 | 0.087 |
| Osteoporosis | 2.58 | 1.45-4.60 | 0.001** | 1.96 | 1.04-3.70 | 0.036* | 1.90 | 1.00-3.61 | 0.048* |
| Chronic allergy | 0.90 | 0.69-1.19 | 0.467 | 0.91 | 0.68-1.21 | 0.495 | 0.83 | 0.60-1.14 | 0.253 |
| COPD | 1.29 | 0.927-1.78 | 0.132 | 1.02 | 0.72-1.46 | 0.899 | 1.01 | 0.70-1.44 | 0.979 |
| Liver dysfunction | 1.98 | 0.80-4.92 | 0.142 | 1.40 | 0.54-3.64 | 0.486 | 1.36 | 0.52-3.54 | 0.536 |
| Stomach/duodenal ulcer | 1.48 | 0.85-2.58 | 0.168 | 1.00 | 0.54-1.84 | 0.995 | 1.01 | 0.54-1.86 | 0.986 |
| Chronic constipation | 2.01 | 1.21-3.34 | 0.007* | 1.56 | 0.90-2.68 | 0.112 | 1.56 | 0.90-2.69 | 0.115 |
| Haemorrhoids | 1.57 | 1.06-2.33 | 0.024* | 1.31 | 0.86-2.00 | 0.207 | 1.33 | 0.87-2.03 | 0.196 |
| Urinary incontinence | 4.32 | 2.39-7.80 | <0.001** | 3.22 | 1.69-6.15 | <0.001** | 3.10 | 1.62-5.94 | 0.001** |
| Kidney problems | 1.96 | 1.14-3.37 | 0.015* | 1.42 | 0.80-2.54 | 0.236 | 1.39 | 0.78-2.50 | 0.265 |
| Prostate problems (males) | 1.51 | 0.67-3.40 | 0.317 | 0.89 | 0.33-2.41 | 0.821 | 0.88 | 0.31-2.48 | 0.813 |
| Menopausal problems (females) | 0.98 | 0.55-1.75 | 0.947 | 0.82 | 0.43-1.54 | 0.532 | 0.82 | 0.43-1.56 | 0.535 |
| Cataracts | 1.97 | 1.16-3.36 | 0.013* | 1.43 | 0.76-2.68 | 0.270 | 1.41 | 0.75-2.65 | 0.292 |
| Chronic skin problems | 1.18 | 0.77-1.77 | 0.428 | 1.15 | 0.76-1.74 | 0.511 | 1.15 | 0.75-1.75 | 0.517 |
| Depression | 1.84 | 1.29-2.61 | 0.001** | 1.37 | 0.92-2.04 | 0.126 | 1.33 | 0.89-1.99 | 0.168 |
| Chronic anxiety | 2.15 | 1.50-3.09 | <0.001** | 1.72 | 1.16-2.56 | 0.007* | 1.69 | 1.13-2.53 | 0.010* |
| Other mental problems | 1.21 | 0.55-2.66 | 0.632 | 0.93 | 0.40-2.15 | 0.866 | 0.89 | 0.39-2.06 | 0.787 |
| Migraine | 1.39 | 1.00-1.92 | 0.050* | 1.21 | 0.86-1.72 | 0.276 | 1.23 | 0.86-1.76 | 0.260 |
| Malignant tumors | 1.56 | 0.88-2.76 | 0.132 | 1.44 | 0.78-2.64 | 0.240 | 1.41 | 0.77-2.59 | 0.272 |
| Thyroid problems | 1.18 | 0.74-1.89 | 0.489 | 1.03 | 0.62-1.70 | 0.910 | 1.03 | 0.62-1.70 | 0.923 |
| Diabetes | 1.38 | 0.85-2.26 | 0.196 | 0.86 | 0.49-1.51 | 0.602 | 0.82 | 0.47-1.45 | 0.497 |
| High cholesterol | 1.18 | 0.86-1.63 | 0.311 | 0.90 | 0.62-1.30 | 0.572 | 0.88 | 0.61-1.28 | 0.505 |
| Permanent injuries (accident) | 1.00 | 0.63-1.58 | 0.994 | 0.86 | 0.53-1.39 | 0.535 | 0.84 | 0.52-1.37 | 0.489 |

HD: heart disease. CBP: chronic back pain. OR: odd ratio. CI: confidence interval. * $p < 0.05$. ** $p < 0.001$ [1] Models not adjusted.

[2] Models adjusted for sex, age, BMI, education level, marital status, smoking and alcohol consumption.

[3] Models adjusted for sex, age, BMI, education level, marital status, smoking, alcohol consumption, medication intake and presence of comorbidities.

When the analyses were adjusted for medication intake and presence of comorbidities as well, PA was also significantly associated with osteoporosis, urinary incontinence and chronic anxiety ($p < 0.05$). Urinary incontinence showed the highest probability with an odds ratio of 3.10 [1.62–5.94]. Nevertheless, when Bonferroni correction was applied, only chronic anxiety, depression, urinary incontinence, osteoporosis and arthrosis were significant (unadjusted models) and urinary incontinence when models were adjusted ($p < 0.001$).

**Discussion**

To the best of authors' knowledge, the present study was the first study carried out in Spain analysing in a representative sample the associations between PA and the presence of 31 different asthma comorbidities. The results of the present study showed that not achieving PA recommendations was associated with more risk of comorbidities, especially urinary incontinence, osteoporosis and chronic anxiety.

The presence of comorbidities was high among Spanish with asthma aged 15–69 years. A total of 87.3% of the participants presented at least one comorbidity. It was higher than the prevalence of comorbidities found in another cross-sectional research among 84,505 Scottish adults with asthma that showed a 62.6% prevalence of asthmatics with one or more health conditions [26]. The most prevalent comorbidity was chronic allergy (61.1%), likely owing to many asthma patients having a phenotype of allergic asthma, which is associated with past and/or a family history of allergic diseases [1]. This concurred with previous studies that have also found allergic conditions like sinusitis, rhinitis, dermatitis, eczema and food allergy as important asthma comorbidities [39,40]. Allergy could be connected to asthma through genetic and environmental factors, which predispose people to contract this disease [25]. However, it is important to underline that our study did not find significant associations between low PA levels and existing chronic allergy among those with asthma ($p = 0.467$).

Chronic lumbar and cervical pain, high cholesterol, COPD, migraine and hypertension showed a high prevalence as well (20–30%) among the participants of the present study. In another study, which analysed the prevalence of comorbidities in asthmatics adults, hypertension (20%), depression (17%), pain (16%) and COPD (13%), showed the highest prevalences [26]. Some of them concurred with our results, but they were slightly lower than in the current study. In a cohort study with a five year follow-up

that compared the risk of comorbidities between individuals with and without asthma by age, a significantly higher physician claim among individuals with asthma aged 18–64 years for the vast majority of comorbidities was found, with 50% or more for respiratory diseases (without including asthma) and psychiatric conditions [25].

Several studies found that cardiovascular diseases [41,42] and metabolic diseases, like diabetes [43], decrease when patients engage in moderate-vigorous PA, but in this research, a significant correlation of these comorbidities in asthmatics who achieved PA recommendations (600 or more MET·min/week) was not found, with the exception of hypertension (OR = 1.49; CI 95% = 1.08–2.06), when models were not adjusted.

In the current study, multivariable logistic regression showed that exercising less than 600 MET·min/week was significantly associated with 210% higher odds of urinary incontinence, 90% of osteoporosis and 69% of chronic anxiety. When compared with healthy population, the odds for developing the previous comorbidities in asthmatics was high [44–47]. A longitudinal study carried out in older women concluded that performing less than 372 MET·min/week was associated with 4% higher odds for urinary incontinence (OR = 1.04 CI 95%=0.92–1.18). Recently, in a population study carried out in 124,434 healthy adults of South Korea, it was found that participants achieving 600–6000 MET·min/week had significantly lower risk of anxiety symptoms [44]. That barely concurred with the results of the present study, where we found a significant positive association between chronic anxiety and engaging in less than 600 MET·min/week of PA in asthmatics. In this way, a recent meta-analysis concluded that higher levels of PA are correlated with a lower probability of developing anxiety [45]. An explanation of this could be the fact that engaging in PA helps them to avoid things they are anxious about, like thoughts relating to their condition. In relation to osteoporosis, Shetty et al. [46] reported a 40% lower risk of osteoporosis among active males and Shenoy et al. [47] found a 32% reduced osteoporosis risk with each extra 10 METs of PA. This barely concurred with our results, which reported a higher risk of osteoporosis in asthmatics who engaged in lower PA levels, but with higher odds (100.2%).

Regarding cataracts, a newly published research work determined that exercising less than 600 MET·min/week was associated with a 32.3% higher risk of cataracts [28]. The present study showed increased odds of cataracts in asthmatics as well, but it was much higher (97.1%). However, the odds were only significant when models were not adjusted.

Recently, Sánchez-Castillo et al. [48] studied Spanish adults with COPD using data from the Spanish National Health Survey as well. When models were adjusted, this study showed significant increased odds for urinary incontinence (110.6%), chronic constipation (97.2%), cataracts (82.5%), chronic anxiety (50.8%) and chronic lumbar pain (48.7%) in those who performed less than 600 MET·min/week. Increased odds for urinary incontinence (231.3%) and chronic anxiety (70.6%) were also found in asthmatics. On the contrary, associations between PA and osteoporosis were reported, and significant associations with chronic constipation, chronic lumbar pain and cataracts in the adjusted models were not found. Currently, with the available literature, it is difficult to explain why different associations between PA and comorbidities among asthmatics and COPD patients appear. Randomized control trials are needed to clarify this.

When focusing on the long-term benefits of PA in asthmatics, Russell et al. [37] found a protective effect by increasing the frequency of low PA, but no significant associations were found with moderate and vigorous PA. Another recent longitudinal study determined that an exercise training program, together with a weight loss lifestyle in obese adults with asthma was able to reduce depression symptoms, asthma symptoms and the risk of obstructive sleep apnoea [49]. The present study found a significant positive correlation between comorbidities (chronic anxiety, urinary incontinence and osteoporosis) and undertaking a low quantity of PA, but long-term benefits could not be established because its cross-sectional character only allowed speculating about the direction of the association. In the contrary, Cassim et al. [50] found no association with PA on asthma nor asthma on PA. However, these associations were analysed in children and adolescents aged 6–14 years, so this comparison should be considered with caution.

The strengths of the current manuscript were its large representative sample of Spanish asthmatic people aged 15–69 years and the administration of an internationally recognized, validated and reliable questionnaire to assess PA. However, some limitations should be considered. IPAQ is a reference instrument in measuring a population's PA level, but it is self-reported, and people may over- or under-report their level of PA. Assessment of asthma and comorbidities was self-reported as well, thus potentially introducing bias into the analyses. Asthma subtype was not established because it was not specified in the Spanish National Health Survey. The question relating to asthma included all types of asthma (allergic, not allergic, adult-onset, asthma with persistent airflow

limitation, asthma with obesity). Furthermore, due to the cross-sectional design, the direction of the associations found was unknown. Consequently, future longitudinal research is required to make this direction clearer.

## Conclusions

Summarizing, nine out of ten people aged 15–69 years with asthma residing in Spain had comorbidities. Chronic allergy was the most prevalent with 61.1%, followed by chronic lumbar and cervical pain, high cholesterol, COPD, migraine and hypertension. Unadjusted models determined significant positive associations between low PA (< 600MET·min/week) and urinary incontinence, osteoporosis, chronic anxiety, arthrosis, depression, chronic back pain (CBP) lumbar, chronic constipation, cataracts, CBP cervical, kidney problems, hypertension, haemorrhoids and migraine. When adjusted by sex, age, BMI, education, marital status, smoking, alcohol, presence of comorbidities and medication intake, there was a significant association between low PA and existing urinary incontinence, osteoporosis and chronic anxiety among asthmatics. Therefore, comorbidities and PA levels should be considered in the prevention and treatment of asthmatics, in order to improve their quality of life.

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# SOLAPAMIENTO ASMA-EPOC

# [ACO]

## Artículos V y VI

## [Papers V and VI]

# ARTÍCULO V [PAPER V]

## Physical activity behavior in people with asthma and COPD overlap residing in Spain: a cross- sectional analysis

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**Abstract:**

***Objectives:*** To identify levels of physical activity (PA) among the Spanish population with asthma and chronic obstructive pulmonary disease overlap (ACO). A further aim was to analyze differences in PA levels by sex, age, education, marital status, cohabiting, smoking habits, alcohol consumption and body mass index (BMI).

***Methods:*** In this cross sectional study, data from the Spanish National Health Survey 2017 were analyzed. A total of 198 people with ACO aged 15–69 years were included in the analyses. The short version of the international physical activity questionnaire (IPAQ) was used to measure total PA (MET·min/week). PA was further classified as low, moderate and high, and analyzed according to sample characteristics. Data were analyzed using the Mann-Whitney U test, Kruskal-Wallis H test and chi squared test. Statistical significance was set at $p < 0.05$.

***Results:*** People with ACO engaged in a mean volume of 2038.1 MET·min/week. Those aged 30–60 years and those with normal weight were significantly more active than those aged ≥60 and those with obesity. When classifying PA level in low, moderate and high, results showed no significant differences between sample characteristics. Overall, moderate and high levels of PA were the most and least frequent levels (48.0% and 16.2%, respectively).

***Conclusions:*** More than three out of ten Spanish adults with ACO do not achieve PA recommendations. Therefore, it is recommended to implement programs that promote the importance and benefits of PA among the Spanish population with ACO, and such programs should focus on older adults and those who are obese.

**Keywords:** Epidemiology; obesity; physiological disorders; prevention; quality of life

## Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are two of the five major respiratory diseases, established by the Forum of International Respiratory Societies (FIRS) (1). Both of these conditions are important public health problems owing to their increasing prevalence, high morbimortality and socioeconomic burden (2,3). In 2019, the Global Burden of Disease (GBD) study found a worldwide prevalence of asthma and COPD in the general population of 3.50% (3.40% males, 3.60% females) and 2.85% (2.85% males, 2.86% females), respectively (4). A previous analysis of the GBD study in 2015 (5) identified a 44.2% increased prevalence and an 11.6% increased risk or mortality from COPD between 1990 and 2015. In relation to asthma, the prevalence increased by 12.6% but mortality decreased by 26.7% between 1990 and 2015. Moreover, both asthma and COPD showed a decrease in age-standardised death and prevalence during this time-period.

These diseases are characterized by chronic respiratory symptoms and airflow limitation, but there are some differences between them. Symptoms of asthma vary over time in intensity and improve with the use of bronchodilators or even spontaneously, so expiratory airflow limitation is variable (2). COPD is characterized by persistent expiratory airflow limitation and respiratory symptoms with or without bronchodilator reversibility (3). Moreover, the onset of asthma tends to be before the age of 40 years while COPD is normally after 40 years and generally in those who have history of smoking or other toxic exposure. A systematic review and meta-analysis on the global burden of COPD found a prevalence of COPD of 9.7% in people aged 40 or over, while people younger than 40 revealed a prevalence of 2.7% (6). However, some patients have persistent airflow limitation and clinical features of both diseases (2). Previous studies have used the term ACOS (Asthma COPD Overlap Syndrome) to describe these patients (7,8), but the latest updates of the Global Initiative for Asthma (GINA) (2) and the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) (3) used the term Asthma-COPD overlap (ACO) or asthma + COPD. It is important to underline that these terms do not mean a new single disease but a term to describe the combination of both asthma and COPD.

The prevalence of ACO in Italian and North Carolina general populations has been identified to be approximately 2% (9,10), while a prevalence of approximately 21% has been identified for asthma patients and COPD patients (11). However, it should be

noted that it is difficult to distinguish ACO patients from COPD patients, especially in smokers and older adults, and thus in these prevalence statistics some ACO patients may be categorized as having COPD.

Patients with ACO are more likely to have respiratory symptoms (12,13), worse lung function (13), more frequent exacerbations and hospitalizations (12–14) and worse general health status (13), compared with those with only COPD. Therefore, the risk of mortality is higher in those with coexisting asthma and COPD.

Regular and sustained participation in physical activity (PA) is beneficial in both primary and secondary prevention of several chronic diseases (15–17). However, there is a lack of evidence in relation to the potential health impact of PA among ACO patients. Importantly, PA has been shown to be beneficial in asthma control (18,19) and also improving quality of life and reducing exacerbations in people with COPD (20,21).

Literature surrounding PA behavior in people with ACO is scarce. One study among Canadian adults found that ACO patients engaged in lower levels of PA than their healthy peers and were more likely to engage in no PA (22). Another investigation found that Spanish adults (aged 40–80 years) with ACO exhibited lower levels of PA in comparison to adults with COPD only (12); however, only 67 subjects with ACO participated in this study and thus the representation of the findings is limited.

Given this background, the aim of the present study was to determine PA levels in a large representative sample of people with ACO residing in Spain and to analyze the differences according to sex, age, level of education, marital status, cohabiting, smoking habits, alcohol consumption and body mass index (BMI).

It is hypothesized that Spanish ACO patients will participate in low levels of PA and that their total weekly amount of PA will be lower than their peers with only COPD or only asthma. It is also hypothesized that PA will be lower in women, in older adults, in tobacco and alcohol consumers, in those with lower education and in those with a higher BMI.

## Methods

### *Study design*

The present study utilized a cross sectional design and was carried out in accordance with the Strengthening the reporting of observational studies in epidemiology (STROBE) statement (23).

### *Setting*

The Spanish National Health Survey was carried out in Spain between October 2016 and October 2017 (24). Details of the survey methods have previously been published elsewhere (25). In brief, a stratified three-stage sampling method was used to select the participants. Firstly, census sections were considered, secondly the family dwellings were selected by systematic sampling, and finally an adult (15 years or more) was randomly selected from each dwelling by using the random Kish method. The method of data collection was computer-assisted personal interviewing (CAPI), conducted in the participant's dwellings. It consisted of a personal interview in which the interviewer used an electronic device to complete the answers. The present research was performed in compliance with the Declaration of Helsinki of the World Medical Association. Data from the Spanish National Health Survey are public and anonymised and thus ethical approval to analyze the data is not required (25). Nevertheless, the present study was approved by the Ethical Research Committee of the University of Murcia.

### *Participants*

A total of 23 089 people residing in Spain completed the survey, of which 17 777 people answered the PA questionnaire. Those adults older than 69 years were excluded, since they did not complete the International Physical Activity Questionnaire (IPAQ) short form because IPAQ is specific for the age range of 15–69 years. Finally, the 198 people (120 women and 78 men) with ACO residing in Spain that had answered the PA questionnaire were included in the present analyses. The inclusion criteria were: 1) affirmative answer to the question: "Have you ever been diagnosed with asthma by a physician?", 2) affirmative answer to the question: "Have you ever been diagnosed with COPD by a physician?", 3) completion of the PA questionnaire. Self-reported diagnosis of chronic conditions is widely used and accepted in epidemiological studies (26). In particular, self-reported diagnosis of asthma and COPD are valid methods (27,28) and

have been frequently used in previous literature (29–31). Before responding to the questions, all participants were informed about the confidentiality of the survey.

***Variables***

Participants completed a questionnaire that included sociodemographic questions (age, sex, education, marital status, smoking habits and alcohol consumption), physical characteristics (weight and height) and quantity of PA. The selection of the sociodemographic variables was based on the data available in the survey and on previously identified correlates of PA in the general adult population (32,33).

***Physical activity.*** The IPAQ short form was used to measure PA (full survey https://sites.google.com/site/theipaq/) (34). This instrument was primarily designed for population surveillance of PA among adults, and it has been developed and tested for use in adults (15–69 years), until further development and testing is undertaken, the use of IPAQ with older and younger age groups is not recommended (35). IPAQ has been validated in adult populations from different countries showing acceptable validity ($\rho$ = 0.30, 95% CI: 0.23–0.36) and reliability (Spearman's $\rho$ = 0.81, 95% CI: 0.79–0.82) (36). PA level was calculated following the formula for computation of MET·minutes/week, established by the guidelines for data processing and analysis of the IPAQ (35). Subsequently, PA level was classified in: low (less than 600 MET·min/week), moderate (at least 600 MET·min/week) and high (at least 3000 MET·min/ week), according to the same guidelines.

***Sociodemographic variables.*** Age was divided into three groups: less than 30 years, from 30 to 60, and 60 years or older. Education level was based on the highest educational level achieved and was categorized according to the Spanish Classification of Education Levels as level A ($\leq 1^{st}$ period secondary), level B ($2^{nd}$ period secondary and post-secondary -not tertiary-), and level C (tertiary) (37). Marital status was categorized as married and not married (single/widow/divorced/separated). Cohabiting was categorized as living as a couple (yes) or not living as a couple (no). Alcohol consumption was treated as a dichotomous variable: yes or no, considering as no consumption those who had not drunk alcohol in the last 12 months. Smoking habits were categorized into three groups: never, former and current smoker (38). Height and weight were self-reported and used to calculate BMI as weight in kilograms divided by height in meters squared. BMI was classified as underweight (<18.5 kg/$m^2$), normal weight (18.5–24.9

kg/m$^2$), overweight (25–30 kg/m$^2$) and obesity (>30 kg/m$^2$), according to the methods established by the Spanish National Health Survey (25).

### *Data analysis*

Descriptive statistics (frequency and percentage) were used to describe sample characteristics. Normality of data were confirmed using chi-squared tests for categorical variables and Kolmogorov-Smirnov tests for continuous variables. The variables sex, age, level of education, BMI, alcohol, quantity of PA and PA classification had a nonparametric distribution, whereas marital status, living in couple and smoking habits had a parametric distribution. To describe the total amount of PA (MET·min/week) according to sample characteristics, descriptive statistics (mean, standard deviation and median) were used. Statistical significance was calculated with Mann-Whitney U test for dichotomous variables (sex, marital status, cohabiting, alcohol consumption) and Kruskal-Wallis H test for polytomous variables (age, education level, smoking habits, BMI) with Bonferroni correction for pairwise comparisons. Significant differences between the different groups of PA and pairwise comparisons were analyzed by chi-squared test. The effect size was calculated using eta squared for Mann-Whitney U test, epsilon squared for Krukal Wallis H test and Cramer's V for chi squared test. The different measures of effect size used were classified as follows: effect size of eta squared was classified as small (0.01), medium (0.06) and large (0.14); effect size of epsilon squared was classified as negligible (0.00–0.01), weak (0.01–0.04), moderate (0.04–0.16), relatively strong (0.16–0.36), strong (0.36–0.64) and very strong (0.64–1.00); effect size of Cramer's V was classified as small (0.1), medium (0.3) and large (0.5) (39). Pearson Correlation was applied to measure the correlation between PA and age.

Statistical significance was set at $p < 0.05$ (CI = 95%). Analyses were carried out with the Statistical Package for Social Sciences version 23 (SPSS, International Business Machines Corporation, Armonk, NY, USA).

## Results

A total of 198 adults with ACO residing in Spain (120 women and 78 men) participated in this study. Participant's mean age was 50.0 (SD: 14.9, range: 15–69; Mo: 66). Sample characteristics are shown in Table 1.

**Table 1.** Sample characteristics

| Total sample (n=198) | | N | % |
|---|---|---|---|
| Sex | Women | 120 | 60.61 |
| | Men | 78 | 39.39 |
| Age | <30 | 23 | 11.62 |
| | 30-60 | 109 | 55.05 |
| | ≥60 | 66 | 33.33 |
| Education level | Level A | 121 | 61.11 |
| | Level B | 32 | 16.16 |
| | Level C | 45 | 22.73 |
| Marital Status | Married | 100 | 50.51 |
| | Not Married | 98 | 49.49 |
| Living in couple | Yes | 102 | 52.04 |
| | No | 94 | 47.96 |
| | Missing | 2 | |
| BMI | Underweight | 4 | 2.08 |
| | Normal weight | 68 | 35.42 |
| | Overweight | 63 | 32.81 |
| | Obesity | 57 | 29.69 |
| | Missing | 6 | |
| Smoking | Current | 60 | 30.30 |
| | Former | 59 | 29.80 |
| | Never | 79 | 39.90 |
| Alcohol last 12 month | Yes | 116 | 58.89 |
| | No | 82 | 41.41 |

N: sample size; %: percentage; Level A: 1st period secondary; Level B: 2nd period secondary and post-secondary (not tertiary); Level C: tertiary; BMI: body mass index

The total amount of participants' PA (MET·min/ week) is shown in Table 2. Only the variables age and BMI showed significant differences between groups. In relation to age, significant differences were found between participants aged 30–60 and those aged 60 or over, with those aged 30–60 years' the most active. However, when Pearson Correlation was applied, the association between age and total PA was not significant ($r = -0.102$; $p = 0.151$).

According to BMI, people with normal weight were significantly more physically active than those with obesity. Considering the other variables, results showed that men, participants with higher education level, married, living as a couple, current smokers and

alcohol consumers were the most physically active in their groups, but these differences were not significant.

**Table 2.** Total amount of Physical Activity in Met·min/week, according to sample characteristics.

| | | n | Av | SD | Med | *p* | *ES* |
|---|---|---|---|---|---|---|---|
| Sex | Women | 120 | 1813.2 | 3015.2 | 990.0 | 0.645 | 0.001 |
| | Men | 78 | 2384.2 | 4852.2 | 1014.8 | | |
| Age | 1. <30 | 23 | 2309.3 | 3304.3 | 1032.0 | | |
| | 2. 30-60[3] | 109 | 2475.5 | 4724.0 | 1386.0 | 0.040* | 0.033 |
| | 3. ≥60[2] | 66 | 1221.3 | 1724.3 | 693.0 | | |
| Education level | Level A | 121 | 2078.3 | 4581.5 | 924.0 | | |
| | Level B | 32 | 1767.5 | 2330.8 | 1386.0 | 0.118 | 0.022 |
| | Level C | 45 | 2122.4 | 2236.3 | 1386.0 | | |
| Marital Status | Married | 100 | 2448.9 | 4958.5 | 1308.0 | 0.506 | 0.002 |
| | Not Married | 98 | 1318.9 | 2134.5 | 858.0 | | |
| Living in couple | Yes | 102 | 2448.5 | 4971.3 | 1097.3 | 0.847 | 0.000 |
| | No | 94 | 1603.3 | 2016.0 | 954.8 | | |
| Smoking | Current | 60 | 2730.6 | 5560.1 | 717.8 | | |
| | Past | 59 | 1529.5 | 1887.9 | 1230.0 | 0.981 | 0.000 |
| | Never | 79 | 1892.1 | 3269.4 | 990.0 | | |
| Alcohol (last 12 months) | Yes | 116 | 2138.1 | 3765.1 | 1053.0 | 0.460 | 0.003 |
| | No | 82 | 1896.7 | 3970.7 | 990.0 | | |
| BMI | 1. Underweight | 4 | 3374.3 | 5222.8 | 1204.5 | | |
| | 2. Normal weight[4] | 68 | 3014.7 | 4777.0 | 1386.0 | 0.026* | 0.047 |
| | 3. Overweight | 63 | 1890.3 | 4080.9 | 1155.0 | | |
| | 4. Obesity[2] | 57 | 1127.1 | 1504.3 | 693.0 | | |
| Total | | 198 | 2038.1 | 3843.5 | 990.0 | | |

n: Sample size; Av: Average; SD: Standard Deviation; Med: median; Level A: 1st period secondary; Level B: 2nd period secondary and post-secondary (not tertiary); Level C: tertiary; BMI: body mass index; Superscripts indicate significant differences between groups; p-values was based on Mann-Whitney U test and Kruskal Wallis H test. ES: Effect size was based on eta squared for Mann-Whitney U test and epsilon squared for Kruskal Wallis H test. *Statistical significance at $p<0.05$.

Table 3 shows the frequency (percentage) of participants who engage in low, moderate and high PA levels, according to sample characteristics. A low level of PA was most frequent in women, in participants aged 60 and over, in those with level A of education, in those not married, in those who never smoke, in those who drank alcohol and in overweight and obese people. Nevertheless, these differences between subgroups were not significant and the effect size was small for all variables.

Considering the whole sample, differences in PA level categories were significant. Pairwise comparisons established these differences between those who engage in high and moderate levels of PA and between those who participate in high and low levels of PA. Moderate level was the most frequent (48.0%) and high level the least frequent (16.2%).

**Table 3.** Classification of PA level following IPAQ guidelines, according to sample characteristics

| | | | PA Level | | | | |
|---|---|---|---|---|---|---|---|
| | | **n** | **Low[1]** | **Mod[2]** | **High[3]** | ***p*** | ***V*** |
| Sex | Women | 120 | 44 (36.7) | 58(48.3) | 18(15.0) | 0.853 | 0.040 |
| | Men | 78 | 27(34.6) | 37(47.4) | 14(17.9) | | |
| Age | <30 | 23 | 9(39.1) | 10(43.5) | 4(17.4) | | |
| | 30-60 | 109 | 32(29.4) | 55(50.5) | 22(20.2) | 0.163 | 0.128 |
| | ≥60 | 66 | 30(45.5) | 30(45.5) | 6(9.1) | | |
| Education level | Level A | 121 | 47(38.8) | 58(47.9) | 16(13.2) | | |
| | Level B | 32 | 12(37.5) | 15(46.9) | 5(15.6) | 0.411 | 0.100 |
| | Level C | 45 | 12(26.7) | 22(48.9) | 11(24.4) | | |
| Marital Status | Married | 100 | 34(34.0) | 50(50.0) | 16(16.0) | 0.831 | 0.043 |
| | Not Married | 98 | 37(37.8) | 45(45.9) | 16(16.3) | | |
| Living in couple | Yes | 102 | 37(36.3) | 48(47.1) | 17(16.7) | 0.989 | 0.011 |
| | No | 94 | 34(36.2) | 45(47.9) | 15(16.0) | | |
| Smoking | Current | 60 | 21(35.0) | 25(41.7) | 14(23.3) | | |
| | Ex | 59 | 21(35.6) | 32(54.2) | 6(10.2) | 0.370 | 0.104 |
| | Never | 79 | 29(36.7) | 38(48.1) | 12(15.2) | | |
| Alcohol (last 12 m) | Yes | 116 | 40(34.5) | 53(45.7) | 23(19.8) | 0.249 | 0.119 |
| | No | 82 | 31(37.8) | 42(51.2) | 9(11.0) | | |
| BMI | Underweight | 4 | 2(50.0) | 1(25.0) | 1(25.0) | | |
| | Normalweight | 68 | 20(29.4) | 30(44.1) | 18(26.5) | 0.125 | 0.161 |
| | Overweight | 63 | 24(38.1) | 30(47.6) | 9(14.3) | | |
| | Obesity | 57 | 21(36.8) | 32(56.1) | 4(7.0) | | |
| Total | | 198 | 71(35.9)[3] | 95(48.0)[3] | 32(16.2) | <0.001* | - |

Values are expressed in Frequency (%). n: Sample size; Level A: 1st period secondary; Level B: 2nd period secondary and post-secondary (not tertiary); Level C: tertiary; V: Cramer's V *Statistical significance at $p<0.05$. Superscripts numbers indicate the differences between groups of PA level.

## Discussion

The present cross-sectional study found in a large sample of Spanish people with ACO that they engaged in an average of 2038.1 MET·min/week of PA, predominantly at

a moderate level. Therefore, these participants achieved the PA recommendations of the Centers for Disease Control and Prevention (40) and the World Health Organization (41), 600 MET.min/ week. Nevertheless, the quantity of PA in Spanish with ACO is lower than the total amount observed in the reliability and validity study of the IPAQ, where an average of 2514 MET·min/week were found in people aged 18-65 years from 12 different countries (36). Similarly, in a large prospective cohort study among UK adults aged 40-69 years, those with chronic respiratory diseases engaged in significantly less moderate PA than those without chronic diseases (637 min/week vs 705 min/week) (42).

Contrary to our hypothesis, when the total amount of PA of Spanish people with ACO of the present study is compared with their peers with only COPD (29), a higher level is found among those with ACO (2038.1 vs 1684.8 MET·min/week). These results concur with Xavier et al. (43), who found significantly higher levels of total daily life PA in 11 patients with ACO than in 11 patients with COPD (5428 vs 3599 steps/day). These outcomes can be explained based on the results found by Park et al. (44), which determined that patients with ACO had better quality of life, due to a reduction of required hospital admission in comparison with their peers with COPD alone. Therefore, they suggested that ACO was characterized by less severe symptoms, which explained rare severe exacerbation and the possibility of lung function recovery. Contrary, Menezes et al. (13) found that ACO was associated with higher risk for exacerbations, hospitalizations and worse perception of general health status compared with those with only COPD. These findings could explain the results found in Miravitlles et al., where Spanish adults with both asthma and COPD (*n*=67) exhibited significantly reduced PA than their peers with COPD alone (*n*=318) (12). Another study carried out in Canadian adults (*n*=68578) also showed that adults with ACO (*n*=1569) had a reduced PA level than those with only COPD (*n*=3118) (22). However, these studies only included participants over 40 years, then, comparisons should be taken carefully.

Nevertheless, in both Spanish with COPD (29) and Spanish with ACO (present analyses), the percentages of participants who engaged in a moderate level of PA were very similar (47.5% vs. 48.0%). However, the percentage of people with ACO who participated in low levels of PA was slightly higher than in those with only COPD (37.9% vs. 35.9%).

In contrast, when comparing PA levels in Spanish people with ACO with those with only asthma, ACO patients of the present study exhibited a lower weekly amount of

PA (30) (2038.1 vs 2228.9 MET·min/week). These results verified our previous hypothesis. Moreover, the percentage of asthma patients engaging in low levels of PA was lower (35.9% in ACO vs 31.6% in asthmatics).

To the authors' knowledge, this is the first study that establishes the levels of PA in adults with ACO analyzing the differences according to sex, age, marital status, cohabiting, education level, BMI, smoking habits and alcohol consumption. The findings of the present study reveal significant differences in the total amount of PA only between age groups and BMI groups. Those aged 60 or over and those obese were physically less active than their younger and normal weight peers, which verified the initial hypothesis. However, contrary to our hypothesis, no significant differences were found according to sex, tobacco and alcohol consumption. Comparing with other studies analyzing only COPD or only asthma, some differences were found. Other studies among Spanish with only COPD (29,45) or only asthma (30), showed that women with COPD or asthma were less active than men. The present study also found a low level of PA in women, but this difference was not significant. There is no existing literature about why women with only COPD or only asthma practise less PA than men, or why these differences were not significant in ACO patients. However, regarding other diseases, for example diabetes, the barriers to practise PA were lack of time, lack of knowledge and health limitations; importantly, health limitations was identified as the most important barrier in women but not in men (46). Another study focusing on barriers to PA in people with diabetes residing in Spain reported that the barrier of having too much work was significantly more important in women than in men (47).

In relation to age, ACO patients aged 30–60 years were physically more active than those older than 60. Indeed, a recent study which analyzed influence of age on level of PA in Brazilian adults ($n$ = 808), concludes that PA level declines with advancing age (48).

Regarding BMI, the present study shows that normal weight participants were significantly more active (3014.7 MET·min/week) than obese participants (1127.1 MET·min/week). This concurs with the results found in other studies among adults with only COPD (29,49) and only asthma (30,50). Therefore, it is necessary to consider BMI when analyzing PA level in ACO patients due to the fact that a higher BMI is normally related with other chronic diseases like cardiovascular diseases, diabetes or cancer, and the presence of these comorbidities could be one of the reasons of lower PA levels.

A recent study that compared the effects of a high-intensity exercise training on subjects with COPD and ACO determined that the benefits were similar in both groups, indicating improvements after the 12-week high-intensity training program on exercise capacity assessed by the 6 min walk test (COPD: 43 m; ACO: 52 m), peripheral muscle strength (quadriceps femoris improvements: 4 kg (COPD), 3 kg (ACO); biceps and triceps brachialis improvements: 3 kg (ACO), 4 kg (COPD)), inspiratory muscle strength (COPD: 7cm$H_2O$; ACO: 9cm$H_2O$), functional status (COPD: −3 points; ACO: −4 points) and quality of life (–4.3 points; ACO: −12 points) (51). However, it is important to specify that those with acute exacerbations in the last month were excluded and diagnosis of ACO was adapted from Sin et al. (52), which is different from the present study.

The main strengths of this study are the use of an international and validated questionnaire to evaluate PA level and the use of a representative sample of Spanish population. The Spanish National Health Survey selected a sample of approximately 37 500 dwellings distributed in 2,500 census sections. Thus, estimates with good reliability at national level were guaranteed. However, findings from this study should be considered in light of its limitations. IPAQ is a reference instrument in measuring a population's PA level, but it is self-reported and people could over or under estimate their PA level. Another potential limitation is the self-reported diagnosis of ACO. We had no access to participant's medical history, we only had the confirmation of the participants of having been diagnosed with asthma and COPD by a physician. Furthermore, as it was a cross-sectional study and not a randomized controlled trial, the association can be demonstrated, but not the causality. In future research, it is recommendable to use accelerometers in order to objectively measure PA and to take into account the unified criteria for the diagnosis of ACO between the Spanish COPD Guidelines and the Spanish Guidelines on the Management of Asthma (53).

## Conclusion

On average, Spanish people with ACO have a moderate PA level but, it is important to note that more than three out of ten Spanish people with ACO do not achieve PA recommendations. Therefore, it is recommended to implement programs that promote the importance and benefits of PA among those with ACO residing in Spain. These programs should focus on older adults and those who are obese.

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# ARTÍCULO VI [PAPER VI]

## Association between Physical Activity and Comorbidities in Spanish People with Asthma-COPD Overlap

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**Abstract:**

Asthma and chronic obstructive pulmonary disease (COPD) are important conditions which often coexist. Higher rates of comorbidities among people with asthma-COPD overlap (ACO) may complicate clinical management. The aim of this study was to determine the prevalence of 30 different comorbidities and to analyze associations between these comorbidities and physical activity (PA) in Spanish people with ACO. Cross-sectional data from the Spanish National Health Survey 2017 were analyzed. A total of 198 Spanish people with ACO aged 15–69 years (60.6% women) were included in this study. PA was measured with the International Physical Activity Questionnaire (IPAQ) short form. Diagnosis of chronic conditions were self-reported. Associations between PA and comorbidities were analyzed using multivariable logistic regression models. The most prevalent comorbidities were chronic allergy (58.1%), chronic lumbar pain (42.4%), chronic cervical pain (38.4%), hypertension (33.3%) and arthrosis (31.8%). A PA level lower than 600 MET·min/week was significantly associated with urinary incontinence (OR = 3.499, 95% CI = 1.369–8.944) and osteoporosis (OR = 3.056, 95% CI = 1.094–8.538) in the final adjusted model. Therefore, the potential influence of PA on reducing the risk of these conditions among people with ACO should be considered, not only because of the health benefits, but also because PA can contribute to a more sustainable world.

**Keywords:** respiratory conditions; exercise; sustainability; multimorbidity

## Introduction

The Forum of International Societies (FIRS) established chronic obstructive pulmonary disease (COPD) and asthma as two of the five major respiratory diseases [1]. Both conditions are important public health problems based on their high prevalence, socioeconomic burden and morbimortality [2,3]. The Global Burden of Disease (GBD) 2019 [4], revealed a global prevalence of asthma of 3.5% (3.6% females; 3.4% males) and 2.8% of COPD (2.8% females; 2.8% males). Moreover, COPD was accountable for 5.8% of global deaths in 2019 and asthma 0.82% [4]. Importantly, both diseases result in a high socioeconomic burden [5,6].

These respiratory conditions are characterized by airflow limitation and respiratory symptoms, but there are differences between them that need to be noted. In asthma patients, expiratory airflow limitation and symptoms such as wheeze, shortness of breath, cough and chest tightness vary over time in intensity and improve with the use of bronchodilators or even spontaneously [2]. However, COPD is characterized by persistent expiratory airflow limitation and persistent respiratory symptoms, with or without bronchodilator reversibility [3]. Onset of COPD tends to occur after 40 years and generally in those who have been exposed to noxious particles or gases, like tobacco. However, some patients have clinical features of both asthma and COPD [2]. These clinical phenotypes have been named as Asthma-COPD overlap (ACO) or asthma + COPD. Previous studies have used the term Asthma-COPD overlap Syndrome (ACOS) to describe these patients [7,8], but the latest updates of GINA [2] and GOLD [3] have named these clinical phenotypes Asthma-COPD overlap (ACO) or asthma + COPD, since it is not a definition of a single entity but a group of phenotypes. Several studies throughout the world have estimated the prevalence of ACO, identifying large variation, which likely reflects differences in study design, definition of ACO and population characteristics between investigations [9]. Nevertheless, a recent meta-analysis, which analyzed 21 different studies since 2011, established a worldwide pooled prevalence of ACO of 2.0% among the general population, 26.5% among people with asthma and 29.6% among those with COPD [10].

Despite the difficulty of diagnosing ACO patients, especially in smokers and older adults, previous literature suggests that patients with ACO experience higher rates of hospitalizations and use of healthcare resources [11–13], are more likely to have respiratory symptoms [11,14], have worse lung function [11], have poor quality of life

[7,15], experience frequent exacerbations [7] and have a higher rate of mortality [16], in comparison with those with asthma or COPD alone. Moreover, the presence of comorbidities is very common among patients with ACO [17–20]. The most frequent comorbid conditions found among ACO patients in previous investigations were diabetes, cardiovascular disease, hypertension, eczema, rhinitis, musculoskeletal diseases, dyspepsia, arrhythmia, gastric ulcers, anxiety and depression [17–19].

Large investigations have demonstrated the beneficial effects of regular and sustained participation in PA in both primary and secondary prevention of several chronic diseases. [21–25]. Literature about the potential health impact of PA among ACO patients is scarce. However, PA has been shown to be beneficial in asthma control [26,27] and in the reduction of exacerbations, as well as in the improvement of quality of life in people with COPD [28,29]. Moreover, previous investigations that have studied the relationship between PA and comorbidities in respiratory diseases like COPD or asthma have found a higher risk of urinary incontinence, chronic constipation, cataracts, chronic anxiety and chronic lumbar pain among Spanish people with COPD who engaged in low levels of PA [30]. In turn, Spanish asthmatics who did not achieve PA recommendations showed significant associations with the presence of urinary incontinence, osteoporosis and chronic anxiety [31].

To authors' knowledge, to date there is no literature in relation to how PA levels can contribute to reduce the risk of comorbidities in adults with ACO. However, based on the background, it could be hypothesized that low levels of PA are associated with a higher risk of developing several comorbidities.

Therefore, the aim of this investigation was to identify the prevalence of 30 different comorbidities among Spanish people with ACO aged 15–69 years and to analyze the associations between PA levels and the presence of these comorbidities.

## Materials and Methods

### *Study Design*

This was a cross-sectional study conducted according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist [32].

### *The Survey*

Data from the Spanish National Health Survey 2017 were analyzed [33]. This survey was carried out in Spain between October 2016 and October 2017. Details of survey methods have previously been published [34]. In brief, participants were selected by a three-stage sampling method. Firstly, census sections were considered, later a systematic sampling designated the family dwellings and finally an adult (aged 15 years or more) was randomly selected from each dwelling by using the random Kish method. Data was collected by using the computer-assisted personal interviewing (CAPI) method, carried out in the participant's dwellings. The present investigation was performed in compliance with the Declaration of Helsinki of the World Medial Association. Ethical approval was not required, since data from Spanish National Health Survey are public and anonymized. Nevertheless, the present analysis was approved by the Ethical Research Committee of the University of Murcia.

### *Participants*

A total of 23 089 people residing in Spain answered the survey, of which 17,777 responded to the PA questions. Finally, 198 people with ACO residing in Spain (120 women) were included in the present analyses. Inclusion criteria for this investigation were: (1) affirmative answer to the question: Have you ever been diagnosed with COPD by a physician?", (2) affirmative answer to the question: Have you ever been diagnosed with asthma by a physician?", (3) completion of the International Physical Activity Questionnaire (IPAQ). Those adults older than 69 years were excluded, since they did not complete the IPAQ. The IPAQ was firstly designed for supervising PA in people aged from 15 to 69 years old [35], so until further testing and development is carried out in younger and older ages, its use is not advisable. Self-reported diagnosis of chronic conditions is widely used and accepted in epidemiological studies [36]. Specifically, self-report of asthma and COPD are valid methods [37,38] and have been frequently used in previous investigations [39–41]. All participants were informed about the confidentiality of the survey before responding to the questions.

### *Physical Activity (Exposure)*

PA was measured by the IPAQ-short form [42]. Participants were asked for the days, hours and minutes a week that they engaged in vigorous and moderate PA and walking in the previous seven days. Total PA per week was measured as metabolic

equivalent of task per minutes per week (MET·min/week) by the following formula: sum of walking + moderate + vigorous MET·min/week scores, established by the IPAQ guidelines [35]. Then, following these guidelines, PA was classified in two groups: (1) under 600 MET·min/week and (2) at least 600 MET·min/week.

This questionnaire has previously been validated in adult populations from different countries showing acceptable validity (ρ = 0.30, 95% CI: 0.23–0.36) and reliability (Spearman's ρ = 0.81, 95% CI: 0.79–0.82) [43]. It has been validated in Spanish adults (r = 0.277; $p < 0.05$) with a 75% sensitivity and specificity (k = 0.33) [44].

***Comorbidities (Outcomes)***

Thirty different comorbidities were analyzed in the present study, based on the data available in the Spanish National Health Survey 2017. Participants who answered affirmatively to the question "Have you ever been diagnosed with 'chronic condition?" were determined to suffer from that specific condition. The comorbidities studied were: hypertension, myocardial infarction, angina or coronary heart disease (HD), other HD, stroke, varicose veins, arthrosis, chronic lumbar pain, chronic cervical pain, osteoporosis, chronic allergy (which includes rhinitis, conjunctivitis, dermatitis, food allergy or another kind of allergy, excluding allergic asthma), liver dysfunction, stomach or duodenal ulcer, chronic constipation, hemorrhoids, urinary incontinence, kidney problems, prostate problems (only men), menopausal problems (only women), cataracts, chronic skin problems, depression, chronic anxiety, other mental problems, migraine, malignant tumors, thyroid problems, diabetes, high cholesterol and permanent injuries caused by an accident. Some of these diseases have been considered by GINA [2] and GOLD guidelines [3] as important comorbidities in asthmatics and COPD patients. Comorbidities were classified following the ICD (International Classification of Diseases) in 12 different groups: (1) cardiovascular diseases; (2) musculoskeletal disorders; (3) immunological diseases; (4) digestive problems; (5) urogenital diseases; (6) eye problems; (7) dermatological problems; (8) mental health problems; (9) neurological disorders; (10) neoplasias; (11) endocrinal and metabolic diseases; (12) permanent injuries [45].

### *Covariates*

Selection of covariates were based on previous identification of variables related with PA in the general population [46–48]. Unfavorable consumptions habits, like tobacco and alcohol, are important barriers to a sustainable development that need to be considered. Alcohol impacts 13 of the 17 Sustainable Development Goals [49] and tobacco use impacts health, education, poverty, global hunger, economic growth, gender equality, the environment, finance and governance [50]. Covariates included in the analysis were: sex, age, marital status, education level, body mass index (BMI), smoking habits, alcohol consumption, medication intake and presence of comorbidities. Age, BMI and numbers of comorbidities were treated as continuous variables, while the remaining variables were analyzed as categorical variables. Education level was classified based on the highest level completed according to the Spanish Classification of Education (CNED) as Level A ($\leq 1^{st}$ period secondary), Level B ($2^{nd}$ period secondary and post-secondary (not tertiary)), and Level C (tertiary) [51]. Marital status was categorized as married versus not married, which included single, separated, divorced and widowed. Smoking was divided into 3 categories: never, past and current smoker. Alcohol consumption was treated as a dichotomous variable: yes or no (abstinence in the last 12 months). Self-reported weight and height were used to calculate BMI as weight in kilograms divided by height in meters squared. Obesity was only used to describe the sample and was defined as BMI $\geq$30 kg/m$^2$. Comorbidities were analyzed as a dichotomous variable: yes (for those who had at least one comorbidity) and no (for those who did not present comorbidities). Medication intake was divided in yes or no as well. Participants were considered to take medication if they had consumed in the last two weeks at least one of the following 22 medications: (1) heart medication; (2) blood pressure medication; (3) fever medication; (4) flu/cold medication (5) sedatives; (6) rheumatism medication; (7) pain medication; (8) allergy medication; (9) antibiotics; (10) diarrhea medication; (11) digestive problems medication; (12) laxatives (13) antidepressants; (14) vitamins/minerals/tonics; (15) slimming medicines; (16) diabetes medication; (17) cholesterol medication; (18) thyroid medication; (19) contraceptive pill; (20) menopausal hormones; (21) natural products (plant-based products [34]); (22) others.

### *Data Analyses*

Sample characteristics were presented through descriptive statistics. Age, BMI and number of comorbidities were described as mean and standard deviation, while the

categorical variables (sex, marital status, education level, smoking, alcohol, obesity, medication intake, presence of comorbidities and PA) were analyzed through frequencies and percentages. Statistical significance between groups according to PA classification was examined by chi-squared tests, for categorical variables, and *T* tests, for continuous variables. Descriptive statistics were used to establish the prevalence of each comorbidity and group of comorbidities too.

Multivariable logistic regression analyses were used to study the associations between weekly amount of PA and the presence of each comorbidity. The analyses were carried out by three different models. Model 1 was not adjusted for any covariates; Model 2 was adjusted for age, BMI, sex, marital status, education level, smoking and alcohol consumption; Model 3 was adjusted for the same variables of model 2 and the variables presence of comorbidities and medication intake. In every model of the regression analysis, covariates were included as categorical variables, except age and BMI, which were added as continuous variables. There were missing data only on the variable BMI (3%).

Results from the multivariable logistic regression analyses were presented as odds ratios (OR) with 95% of confidence intervals (CI).

The present analyses were performed with the Statistical Package for Social Sciences (SPSS) version 23 (International Business Machines Corporation, Armonk, NY, USA).

## Results

A total of 198 Spanish people with ACO (120 women) with a mean age of 50 (14.9) years composed the sample; 57.6% was aged 50 or over. Table 1 shows the sample characteristics according to PA level. None of the characteristics revealed significant differences between Spanish people with ACO who achieved PA recommendations (PA≥ 600 MET·min/week) and those who did not. However, when considering the whole sample, the number of participants who spent at least 600 MET·min/week was significantly higher ($\chi 2 = 15.838$; $p < 0.001$). In relation to comorbidities, a 93.9% of people with ACO suffer from them, with a huge average of 5.3 comorbidities at the same time (maximum: 18; mode: 2; median: 4). Moreover, those who do not present

comorbidities revealed a higher percentage of high PA level in comparison to those who have at least one comorbidity, but these differences were not significant.

**Table 1.** Sample characteristics according to PA level

| | | | PA <600MET·min/week | | PA ≥600MET·min/week | | |
|---|---|---|---|---|---|---|---|
| **Characteristic** | **Category** | **N** | **N** | **%** | **N** | **%** | **p** |
| Sex | Men | 78 | 27 | 34.6 | 51 | 65.4 | 0.769 |
| | Women | 120 | 44 | 36.7 | 76 | 63.3 | |
| Marital Status | Not Married | 98 | 37 | 37.8 | 61 | 62.2 | 0.582 |
| | Married | 100 | 34 | 34.0 | 66 | 66.0 | |
| Education | Level A | 121 | 47 | 38.8 | 74 | 61.2 | |
| | Level B | 32 | 12 | 37.5 | 20 | 62.5 | 0.340 |
| | Level C | 45 | 12 | 26.7 | 33 | 73.3 | |
| Obesity | Yes | 56 | 16 | 28.6 | 40 | 71.4 | |
| | No | 136 | 54 | 39.7 | 82 | 60.3 | 0.145 |
| | Missing | 6 | | | | | |
| Smoking | Current | 60 | 21 | 35.0 | 39 | 65.0 | |
| | Former | 59 | 21 | 35.6 | 38 | 64.4 | 0.977 |
| | Never | 79 | 29 | 36.7 | 50 | 63.3 | |
| Alcohol | Yes | 116 | 40 | 34.5 | 76 | 65.5 | 0.631 |
| | No | 82 | 31 | 37.8 | 51 | 62.2 | |
| Medication | Yes | 179 | 65 | 36.3 | 114 | 63.7 | 0.682 |
| | No | 19 | 6 | 31.6 | 13 | 68.4 | |
| Comorbidities | Yes | 186 | 69 | 37.1 | 117 | 62.9 | 0.153 |
| | No | 12 | 2 | 16.7 | 10 | 83.3 | |
| Total | | 198 | 71 | 35.9 | 127 | 64.1 | <0.001* |
| | | | **Av.** | **SD** | **Av.** | **SD** | |
| Age | | 198 | 51.5 | 15.1 | 49.1 | 14.8 | 0.268 |
| BMI | | 192 | 26.6 | 5.7 | 27.7 | 5.1 | 0.173 |
| Nº comorbidities | | 198 | 6.1 | 4.1 | 4.9 | 4.1 | 0.054 |

N: sample size; %: percentage. Level A: ≤ 1st period secondary; Level B: 2nd period secondary and post-secondary (not tertiary); Level C: tertiary; Obesity: ≥30kg/m2; Av.: average; SD: Standard deviation; BMI: body mass index. p-values are based on chi-squared tests (categorical) and T test (continuous). * $p<0.05$

The prevalence of the studied comorbidities and each category of disease are shown in Table 2. The most prevalent disease among Spanish population with ACO is chronic allergy (58.1%), followed by chronic lumbar pain (42.4%). Considering the ICD classification, more than a half of participants suffer from immunological (58.1%) and

musculoskeletal diseases (56.6%). The least prevalent comorbidities among ACO patients are neoplasias, eye problems, permanent injuries and dermatological problems.

**Table 2.** Prevalence of comorbidities in people with ACO

| Disease category | Comorbidities | N | % | Global % |
|---|---|---|---|---|
| Cardiovascular diseases | Hypertension | 66 | 33.3 | 47.0 |
| | Myocardial infarction | 5 | 2.5 | |
| | Angina, Coronary HD | 11 | 5.6 | |
| | Other HD | 17 | 8.6 | |
| | Stroke | 6 | 3.0 | |
| | Varicose veins (legs) | 37 | 18.7 | |
| Musculoskeletal disorders | Arthrosis | 63 | 31.8 | 56.6 |
| | CBP cervical | 76 | 38.4 | |
| | CBP lumbar | 84 | 42.4 | |
| | Osteoporosis | 21 | 10.6 | |
| Immunological disease | Chronic allergy | 115 | 58.1 | 58.1 |
| Digestive problems | Liver dysfunction | 5 | 2.5 | 25.8 |
| | Stomach/duodenal ulcer | 14 | 7.1 | |
| | Chronic constipation | 28 | 14.1 | |
| | Haemorrhoids | 38 | 19.2 | |
| Urogenital diseases | Urinary incontinence | 29 | 14.6 | 28.8 |
| | Kidney problems | 19 | 9.6 | |
| | Prostate problems (men) | 14 | 7.1 (17.9) | |
| | Menopausal problems (women) | 16 | 8.1 (13.3) | |
| Eye problems | Cataracts | 30 | 15.2 | 15.2 |
| Dermatological problems | Chronic skin problems | 34 | 17.2 | 17.2 |
| Mental health problems | Depression | 52 | 26.3 | 32.8 |
| | Chronic anxiety | 46 | 23.2 | |
| | Other mental problems | 4 | 2.0 | |
| Neurological disorder | Migraine | 62 | 31.3 | 31.3 |
| Neoplasias | Malignant tumors | 19 | 9.6 | 9.6 |
| Endocrinal & metabolic diseases | Thyroid problems | 16 | 8.1 | 41.9 |
| | Diabetes | 30 | 15.2 | |
| | High cholesterol | 62 | 31.3 | |
| Permanent injuries (accident) | | 33 | 16.7 | 16.7 |

ACO: asthma and COPD overlap; N: sample size; %: percentage, HD: heart disease, CBP: chronic back pain, COPD: chronic obstructive pulmonary disease

The associations between ACO comorbidities and PA are shown in Table 3. When models were not adjusted for any covariates, those who engage in less than 600 MET·min/week of PA showed higher probability of suffering from chronic lumbar pain, osteoporosis, urinary incontinence and cataracts. When models were adjusted for age, BMI, education, marital status, smoking and alcohol, results showed a greater probability of existing osteoporosis and urinary incontinence among those who do not practice at least 600 MET·min/week. Considering the third model, adjusted for presence of comorbidities and medication intake, lower levels of PA were associated with higher odds of osteoporosis and urinary incontinence, showing the last one the highest risk with an odds ratio of 3.499 with a 95% CI = 1.369–8.944. When considering those older than 50 years ($n$ = 114), urinary incontinence was significant in all models, showing the highest odds in the fully adjusted model (OR = 3.906; 95% CI = 1.234–12.360; $p$ = 0.02), while osteoporosis was significant in the first and second model (Model 1: OR = 2.866 95% CI = 1.017–8.074, $p$ = 0.046; Model 2: OR = 3.187 95% CI = 1.033–9.826, $p$ = 0.044), but not in the third model ($p$ = 0.051). The other conditions were not significant in those older than 50 years.

**Table 3.** Association between PA (exposure) and ACO comorbidities (outcome) estimated by multivariable logistic regression.

| **Comorbidities** | **OR[1]** | **CI 95 % [1]** | **p [1]** | **OR [2]** | **CI 95 % [2]** | **p [2]** | **OR [3]** | **CI 95 % [3]** | **p [3]** |
|---|---|---|---|---|---|---|---|---|---|
| Hypertension | 1.140 | 0.618-2.104 | 0.675 | 0.978 | 0.478-2.001 | 0.952 | 0.998 | 0.486-1.105 | 0.996 |
| Myocardial infarction | 0.439 | 0.048-4.008 | 0.466 | 0.131 | 0.006-2.824 | 0.194 | 0.128 | 0.005-3.083 | 0.205 |
| Angina, Coronary HD | 0.656 | 0.168-2.557 | 0.544 | 0.473 | 0.096-2.338 | 0.359 | 0.471 | 0.091-2.428 | 0.368 |
| Other HD | 0.973 | 0.344-2.754 | 0.960 | 0.825 | 0.266-2.563 | 0.740 | 0.849 | 0.273-2.643 | 0.778 |
| Stroke | 0.891 | 0.159-4.991 | 0.896 | 0.583 | 0.081-4.176 | 0.591 | 0.606 | 0.085-4.303 | 0.616 |
| Varicose veins (legs) | 0.962 | 0.455-2.032 | 0.919 | 0.687 | 0.296-1.594 | 0.382 | 0.669 | 0.288-1.551 | 0.349 |
| Arthrosis | 1.712 | 0.926-3.165 | 0.087 | 1.350 | 0.643-2.838 | 0.455 | 1.329 | 0.630-2.804 | 0.455 |
| CBP cervical | 1.175 | 0.648-2.130 | 0.595 | 1.025 | 0.534-1.967 | 0.941 | 0.968 | 0.503-1.861 | 0.922 |
| CBP lumbar | 2.028 | 1.124-3.659 | **0.019*** | 1.753 | 0.936-3.283 | 0.080 | 1.702 | 0.902-3.210 | 0.101 |
| Osteoporosis | 3.334 | 1.309-8.492 | **0.012*** | 3.161 | 1.141-8.757 | **0.027*** | 3.056 | 1.094-8.538 | **0.033*** |
| Chronic allergy | 1.071 | 0.594-1.932 | 0.819 | 1.061 | 0.560-2.010 | 0.855 | 0.936 | 0.471-1.859 | 0.850 |
| Liver dysfunction | 1.198 | 0.195-7.345 | 0.845 | 0.583 | 0.074-4.604 | 0.609 | 0.501 | 0.056-4.495 | 0.537 |
| Stomach/duodenal ulcer | 1.373 | 0.457-4.128 | 0.572 | 0.935 | 0.281-3.115 | 0.913 | 0.924 | 0.253-3.370 | 0.924 |
| Chronic constipation | 1.982 | 0.885-4.440 | 0.096 | 1.678 | 0.692-4.069 | 0.252 | 1.619 | 0.665-3.940 | 0.289 |
| Haemorrhoids | 1.054 | 0.506-2.197 | 0.888 | 0.994 | 0.454-2.178 | 0.988 | 0.947 | 0.428-2.092 | 0.892 |
| Urinary incontinence | 4.275 | 1.859-9.828 | **0.001*** | 3.550 | 1.396-9.029 | **0.008*** | 3.499 | 1.369-8.944 | **0.009*** |
| Kidney problems | 1.339 | 0.512-3.501 | 0.551 | 1.034 | 0.361-2.964 | 0.950 | 1.004 | 0.346-2.912 | 0.994 |
| Prostate problems (males) | 2.200 | 0.680-7.113 | 0.188 | 1.165 | 0.267-5.082 | 0.839 | 2.073 | 0.373-11.509 | 0.405 |
| Menopausal problems (females) | 0.758 | 0.245-2.343 | 0.630 | 0.778 | 0.232-2.609 | 0.685 | 0.700 | 0.209-2.345 | 0.563 |
| Cataracts | 2.348 | 1.070-5.155 | **0.033*** | 2.062 | 0.682-6.236 | 0.200 | 2.253 | 0.730-6.954 | 0.158 |
| Chronic skin problems | 1.131 | 0.528-2.424 | 0.751 | 0.969 | 0.428-2.194 | 0.939 | 0.901 | 0.395-2.056 | 0.805 |
| Depression | 1.164 | 0.605-2.239 | 0.649 | 0.772 | 0.357-1.667 | 0.510 | 0.727 | 0.336-1.572 | 0.418 |
| Chronic anxiety | 1.927 | 0.985-3.770 | 0.055 | 1.515 | 0.699-3.283 | 0.293 | 1.431 | 0.659-3.109 | 0.365 |
| Other mental problems | <0.001 | <0.001- <0.001 | - | <0.001 | <0.001- <0.001 | - | <0.001 | <0.001- <0.001 | - |
| Migraine | 1.081 | 0.579-2.018 | 0.806 | 0.952 | 0.468-1.867 | 0.887 | 0.872 | 0.439-1.734 | 0.872 |
| Malignant tumors | 1.339 | 0.512-3.501 | 0.551 | 0.883 | 0.295-2.642 | 0.824 | 0.861 | 0.288-2.572 | 0.789 |
| Thyroid problems | 0.799 | 0.266-2.399 | 0.689 | 1.003 | 0.320-3.143 | 0.996 | 0.981 | 0.314-3.069 | 0.981 |
| Diabetes | 1.042 | 0.465-2.335 | 0.920 | 0.712 | 0.279-1.813 | 0.476 | 0.711 | 0.278-1.814 | 0.475 |
| High cholesterol | 1.081 | 0.579-2.018 | 0.806 | 0.946 | 0.464-1.930 | 0.878 | 0.946 | 0.462-1.936 | 0.879 |
| Permanent injuries (accident) | 1.199 | 0.556-2.584 | 0.643 | 1.026 | 0.455-2.315 | 0.950 | 1.033 | 0.452-2.364 | 0.938 |

HD: heart disease. CBP: chronic back pain. OR: odd ratio. CI: confidence interval. * $p < 0.05$. Reference category: no disease. [1] Models not adjusted.
[2] Models adjusted for sex, age, BMI, education level, marital status, smoking and alcohol consumption.
[3] Models adjusted for sex, age, BMI, education level, marital status, smoking, alcohol consumption, medication intake and presence of comorbidities.

**Discussion**

To the authors' knowledge, this is the first study exploring the association between PA levels and the presence of 30 different comorbidities in Spanish people with ACO. The main results showed that chronic allergy is the most prevalent comorbidity and that those who do not engage in at least 600 MET·min/week of PA have higher risk of urinary incontinence and osteoporosis.

This study revealed that the vast majority of Spanish people with ACO have comorbidities, with a 93.9% suffering from at least one comorbidity. This is higher than the prevalence of comorbidities found in the Spanish population with asthma (87.3%) [31] but similar to the prevalence found in those with COPD (94.0%) [30]. Moreover, participants from this study have a mean of 5.3 comorbidities, which is higher than the average found in Spanish asthmatics (3.6) [31] but lower than those with COPD (6.0) [30].

Previously, a study among British people with diagnosis of both asthma and COPD found that the most common comorbid conditions were diabetes (50.4%), cardiovascular disease (29.9%), hypertension (26.8%), eczema (18.9%) and rhinitis (18.1%) [17]. Moreover, van Boven et al. [20] found that hypertension (49%) was the most prevalent comorbidity among ACO patients from the MAJOrca Real-world Investigation in a COPD and Asthmatic cohort (MAJORICA), followed by anxiety, diabetes, osteoporosis and allergic rhinitis. Hypertension was one of the most prevalent comorbidities in all mentioned studies, while the results in the other comorbidities were different among studies. This slightly differs from the present results where the most prevalent comorbidity was chronic allergy (58.1%), followed by chronic lumbar pain (42.4%), chronic cervical pain (38.4%), hypertension (33.3%) and arthrosis (31.8%). However, it should be taken into account that allergy was not considered as a single comorbidity in previous investigations and these investigations did not include other allergy conditions relating to food, conjunctivitis, or dermatitis. Moreover, chronic back pain was not analyzed in the British and MAJORICA study.

When considering age, a previous study revealed a prevalence of ACO of 1.6% in those aged between 20 to 44 years, 2.1% in those aged between 45 to 64 years, and 4.5% in the 60 to 84 age group [52]. Similarly, the present study revealed a higher number of

ACO participants among those aged 50 and over (57.6%) in comparison to those younger (42.4%).

In relation to PA, a recent study has determined that Spanish people with ACO engaged in an average of 2038.1 MET·min/week, achieving the recommendations of at least 600 MET·min/week established by the Centers for Disease Control and Prevention [53] and the World Health Organization [54]. However, this amount of PA was lower than the 2514 MET·min/week found in the general population aged 18–65 years from 12 different countries [43]. Regarding the association between PA levels and the presence of comorbidities among people with ACO, previous investigations are not available. Nevertheless, to contextualize the impact of PA on ACO comorbidities, it may be useful to compare it with the impact of PA on other health states. Multivariable logistic regression analyses of the present study suggest that engaging in less than 600 MET·min/week was significantly associated with a 249.9% increased odds of urinary incontinence and 205.6% for osteoporosis. No significant associations were found in the remaining 28 comorbidities when models were adjusted, but when models were not adjusted, cataracts and chronic lumbar pain showed increased odds. In comparison with a similar study carried out in Spanish people with COPD aged 15–69 years [30], increased odds for urinary incontinence in those who did not achieve PA recommendations were found (OR = 2.115 CI 95% = 1.213–3.689), but with a lower probability than found in the present study (OR = 3.499 CI 95% = 1.369–8.944). On the contrary, COPD patients showed significant associations with chronic constipation, cataracts, chronic anxiety and chronic lumbar pain. Considering another study among Spanish asthmatics aged 15–69 years [31], significant associations between reduced PA and urinary incontinence, osteoporosis and chronic anxiety were found. The associations between PA and urinary incontinence and osteoporosis concur with our results but with lower odds (osteoporosis: OR = 1.90 CI 95% = 1.00–3.61; urinary incontinence: OR = 3.10 CI 95% = 1.62–5.94). However, chronic anxiety results differ from the present study. In relation to osteoporosis, Oh et al. [55] demonstrated that it was more prevalent in ACO patients than in asthmatics. This may be due to the fact that ACO patients have showed high levels of inflammatory markers such as neutrophil gelatinase-associated lipocalin (NGAL) [56] and interleukin-6 (IL-6) [57], which are related to osteoporosis progression. However, Oh et al. [55] did not consider PA levels in their study and the mean age of the participants was higher (63.3 years) than the present study. Therefore, future investigations are needed to clarify why

the risk of urinary incontinence and osteoporosis are higher in ACO than in COPD or asthma alone when considering PA levels, and why other comorbidities are only significant in COPD (chronic constipation, cataracts, chronic anxiety and lumbar pain) or in asthmatics (chronic anxiety). A possible explanation could be that the number of participants of the present study ($n$ = 198) was lower than the number of participants with COPD ($n$ = 601) or asthma ($n$ = 1014) in previous studies. Nevertheless, with the current available literature, it is difficult to be sure why these differences appear. Thus, randomized control trials are needed to clarify this.

When we compared the risk of comorbidities according to PA with other studies in healthy populations, ACO patients with reduced levels of PA revealed a higher risk of several comorbidities. A longitudinal study in older women showed that performing 6.2 MET·h/week or less was associated with a 4% increased risk of urinary incontinence (OR = 1.04 CI 95% = 0.92–1.18) [58]. In relation to osteoporosis, Shetty et al. [59] reported a 40% lower risk of osteoporosis among active males aged above 50 and Shenoy et al. [60] found a 32% reduced osteoporosis risk with each extra 10 METs of PA in Indian women aged 41–60 years. Similarly, the present study found a higher risk of osteoporosis in those who don't achieve PA recommendations, in the whole sample and in only those aged 50 or over. Regarding cataracts, a recent study, has shown that performing fewer than 600 MET·min/week of PA was associated with 32.4% increased odds of cataracts [61]. This concurs with our results, but the odds were higher in the present study (134.8%). However, cataracts odds of the present study were only significant when models were not adjusted. Similarly, a meta-analysis found that, when cohort studies were considered, people who practiced a medium level of PA had a 10% lower risk of CBP lumbar ($p$ = 0.0009). Our results revealed increased odds too (102.8%), but they were only significant with unadjusted models.

The main strengths of this investigation were the use of data from a large representative survey of Spanish population aged between 15 and 69 years old, and the use of a validated, reliable and internationally recognized questionnaire to assess PA. Nevertheless, some limitations should be considered. Although the IPAQ is a reference instrument to measure PA level in youth and adult populations (15–69 years old), it is self-reported, so participants could under or overestimate their PA level. Diagnosis of asthma, COPD and comorbidities were self-reported, thus potentially introducing bias. Severity of ACO and exacerbation history were not measured in the survey, so models

could not be adjusted for them. Other sociodemographic variables like employment were not included as covariates either. Furthermore, the cross-sectional design did not allow to establish the direction of the associations. Consequently, future longitudinal studies are required to clarify the direction.

## Conclusions

In conclusion, data from the present study suggest that comorbidities are common among Spanish people with ACO, with a prevalence of 93.9%. Considering the thirty different studied comorbidities, chronic allergy was the most prevalent, followed by chronic lumbar pain, chronic cervical pain and hypertension. Analyzing associations between PA and comorbidities when models were fully adjusted, a reduced level of PA (less than 600 MET·min/week) was significantly associated with higher odds of urinary incontinence and osteoporosis, suggesting that higher levels of PA could reduce the risk of both conditions in people with ACO. Moreover, with unadjusted models, cataracts and chronic lumbar pain revealed a significant association. Regarding the other studied comorbidities, no significant associations were found. Therefore, comorbidities, specifically urinary incontinence and osteoporosis, and PA levels, should be considered in the prevention and treatment of people with ACO, not only because of the health benefits, but also because PA can contribute to a more sustainable, equitable and prosperous world [62].

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**Institutional Review Board Statement:** Ethical approval was not required, since data from Spanish National Health Survey are public and anonymized. Nevertheless, the present analysis was approved by the Ethical Research Committee of the University of Murcia (10/04/19).

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** Data supporting the findings of this study are available from the corresponding authors upon reasonable request.

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# CONCLUSIONES

A continuación, se presentan las conclusiones generales de la tesis doctoral, en relación a los objetivos planteados en cada uno de los artículos que la componen:

- En españoles con EPOC y en asmáticos, la cantidad semanal de actividad física varía en función del sexo, la edad, el consumo de alcohol y el IMC. Entre aquellos que presentan EPOC, la cantidad de AF era menor en mujeres, en aquellos mayores de 60 años, en los que no consumen alcohol y en aquellos con obesidad o bajo peso. Entre los asmáticos, la cantidad de AF era significativamente inferior en mujeres, en mayores de 30 años, en aquellos que no consumen alcohol y en aquellos con obesidad. Además, en asmáticos también se encontraron diferencias en el nivel educativo, siendo menor la práctica de AF en aquellos con bajo nivel educativo, y en el estado civil y la convivencia en pareja, siendo la cantidad semanal de AF inferior en casados y/o viviendo en pareja. (Artículos I y III).
- Entre los españoles con ACO, la cantidad semanal de AF es inferior en mayores de 60 y en obesos. (Artículo V).
- En valores medios, los españoles con EPOC, asma o ACO muestran un nivel de AF moderado. No obstante, existe un elevado porcentaje que no alcanza los niveles mínimos recomendados. Aproximadamente tres de cada diez españoles entre 15 y 69 años con estas enfermedades presentan un nivel bajo de AF. El mayor porcentaje de pacientes con nivel bajo de AF es el de personas con EPOC (37.9%), seguido de aquellos con ACO (35.8%) y finalmente se encuentran los asmáticos (31.6%).
- Se recomienda implementar programas para concienciar a la población sobre la importancia y los beneficios de la AF en el control de las enfermedades pulmonares crónicas estudiadas en esta tesis. Además, estos programas deben incluir actividades que motiven a los participantes a mantener la práctica de AF a largo plazo y deben focalizarse en aquellos grupos que muestran niveles de AF más reducidos. Así, se podría mejorar la calidad de vida de estos pacientes (Artículos I, III y V).
- La presencia de comorbilidades en jóvenes y adultos españoles con enfermedades pulmonares crónicas es muy elevada. Aproximadamente nueve de cada diez pacientes con EPOC y/o asma presentan comorbilidades. Entre los que padecen EPOC, las comorbilidades con mayor prevalencia son dolor lumbar crónico, alérgia crónica, artrosis, dolor cervical crónico, asma e hipertensión. En

asmáticos, la comorbilidad con mayor prevalencia es la alergia crónica, seguida del dolor lumbar y cervical, colesterol elevado, EPOC, migrañas e hipertensión. Por su parte, aquellos con solapamiento de ambas muestran una mayor prevalencia también en alergía crónica, seguida de dolor lumbar y cervical e hipertensión (Artículos II, IV y VI).

- Un nivel bajo de AF se asocia con un mayor riesgo de incontinencia urinaria, estreñimiento, cataratas, ansiedad crónica y dolor lumbar crónico en pacientes con EPOC; incontinencia urinaria, osteoporosis y ansiedad crónica en asmáticos; e incontinencia urinaria y osteoporosis en aquellos con ACO, con los modelos ajustados según sexo, edad, nivel educativo, estado civil, consumo de tabaco y alcohol, obesidad, presencia de comorbilidades y consumo de medicamentos. Por tanto, se sugiere que la realización de la cantidad de AF recomendada podría reducir el riesgo de comorbilidades en pacientes con EPOC, asma y ACO.
- La presencia de comorbilidades, especialmente de incontinencia urinaria, estreñimiento, dolor lumbar, cataratas, ansiedad crónica y osteoporosis, y los niveles de AF deberían tenerse en cuenta tanto en la prevención como en el tratamiento de pacientes con EPOC, asma y ACO, con la intención de mejorar su calidad de vida.

# [CONCLUSIONS]

The general conclusions of this doctoral thesis are presented in relation to the aims brought up in the six papers that compose it:

- In Spanish people with COPD and in asthmatics, weekly amount of PA varies according to sex, age, acohol consumption and BMI. In those with COPD, PA was significantly lower in women, those older than 60 years, those who didn't drink alcohol and in those with obesity or underweight. In asthmatics, PA was significantly lower in women, those older than 30 years, those who didn't drink alcohol and in those with obesity. Moreover, asthmatics revealed significant differences according to education level, marital status and living in couple. Those with low education level and those married and/or living together presented a lower weekly amount of PA (Papers I and III).
- In Spanish people with ACO, weekly amount of PA was significantly lower in those older than 60 years and in those with obesity. (Paper V).
- On average, Spanish people with COPD, asthma or ACO revealed a moderate level of PA. Even though, there is a high percentage of people that do not acieved PA recommendations. Around three out of ten Spanish people aged from 15 to 69 years showed a low level of PA. The highest percentage of people with a low level of PA was found among those with COPD (37.9%), followed by those with ACO (35.8%) and finally asthmatics (31.6%) (Papers I, III and V).
- It is recommendable to implement programs to raise awareness of the importance and benefits of PA in the control of the chronic pulmonary diseases. These programs should include activities that motivate participants to do long-term PA and should focus on those groups with lower PA. This way, they could improve their quality of life (Paper I, III, and V).
- The presence of comorbidities among Spanish youth and adults with chronic pulmonary diseases is very high. Nine out of ten COPD and/or asthmatis patients present comorbidities. In people with COPD, the most prevalent comorbidities are chronic lumbar pain, chronic allergy, arthrosis, chronic cervical pain, asthma and hypertension. In asthmatics the most prevalent one is chronic allergy, followed by chronic lumbar and cervical pain, high cholesterol, COPD, migraine and hypertension. In those with ACO, the most prevalent comorbidity is also chronic allergy, followed by chronic lumbar and cervical pain and hypertension. (Paper II, IV and VI)

- A low level of PA is associated with a higher risk of urinary incontinence, chronic constipation, cataracts, chronic anxiety and chronic lumbar pain among those with COPD; urinary incontinence, osteoporosis and chronic anxiety among those with asthma; and urinary incontinence and osteoporosis among those with ACO. Models were adjusted for sex, age, education level, marital status, smoking, alcohol consumption, obesity, presence of comorbidities and medication intake. Thus, it is suggested that achieving PA recommendatios could reduce the risk of comorbidities in patients with COPD, asthma and ACO.
- Comorbidities, especially urinary incontinence, chronic constipation, lumbar pain, cataracts, chronic anxiety and osteoporosis, and PA levels should be considered in the prevention and treatment of people with COPD, asthma and ACO, in an attempt to improve their quality of life.

# FUTURAS INVESTIGACIONES

En futuras investigaciones se debería llevar a cabo una revision sistemática y meta-análisis de la literatura existente sobre la práctica de AF y su influencia en personas con enfermedades pulmonares crónicas (EPOC, asma y ACO) de todo el mundo. Con ello se pretende sintetizar la evidencia disponible en esta temática, para incrementar la validez de las conclusiones de los estudios que componen esta tesis e identificar áreas de incertidumbre donde sea necesario seguir investigando. También sería conveniente corroborar los resultados obtenidos con otros estudios en los que se valore la AF de manera directa mediante acelerómetros previamente validados.

Asimismo, se considera necesario realizar en un futuro investigaciones de seguimiento longitudinal en las que se apliquen diferentes programas de AF en personas con las enfermedades pulmonares crónicas abordadas en esta tesis y con niveles bajos de AF que permitan observar su evolución y determinar qué tipo de programas son más efectivos. Por ejemplo, se podría plantear un seguimiento de un programa de AF mediante marcha nórdica y otro basado en el trabajo de fuerza de los músculos respiratorios.

# [FUTURE INVESTIGATIONS]

In future investigations, a systematic review and meta-analysis of the existing literature about PA and its influence on people with chronic pulmonary diseases (COPD, asthma and ACO) all over the world should be developed. This aims to synthesize the available evidence on this topic to increase the validity of the conclusions reached in all the papers that compose this thesis, and to identify areas of uncertainty where it is necessary to continue investigating. It would be also convenient to corroborate the results obtained on this thesis with other studies that assess PA directly by using previously validated accelerometers.

Moreover, it is necessary to carry out longitudinal follow-up researches, applying different PA programs in people with the chronic pulmonary diseases presented in this thesis and low levels of PA. This way, their evolution could be observated and the most effective programs could be established. For example, a follow-up of a PA program using Nordic walking and another one based on resistance training of respiratory muscles could be considered.

# FINANCIACIÓN Y CONFLICTO DE INTERESES

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- Contrato predoctoral de Formación de Personal Investigador: 20773/FPI/18. Fundación Séneca. Región de Murcia (España).
- Ayudas para la realización de estancias externas destinadas a los investigadores predoctorales contratados con cargo al subprograma regional de contratos de formación de personal investigador. Fundación Séneca. Región de Murcia (España).

No hay conflicto de intereses (financieros, políticos, ideológicos, académicos, religiosos, comerciales o de cualquier otro tipo) que declarar en relación a esta tesis.

# [FUNDING AND COMPETING INTERESTS]

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There are no competing interests (financial, political, ideological, academic, religious, commercial ot any other) to declare in relation to this thesis.

# ANEXOS

# [ANNEXES]

ANEXO 1: Informe favorable del Comité de Ética de la Universidad de Murcia



UNIVERSIDAD DE MURCIA | Vicerrectorado de Investigación y Transferencia — CEI Comisión de Ética de Investigación — CAMPUS MARE NOSTRUM

**INFORME DE LA COMISIÓN DE ÉTICA DE INVESTIGACIÓN DE LA UNIVERSIDAD DE MURCIA**

Jaime Peris Riera, Catedrático de Universidad y Secretario de la Comisión de Ética de Investigación de la Universidad de Murcia,

CERTIFICA:

Que D.ª Sheila Sánchez Castillo ha presentado la memoria de trabajo de la Tesis Doctoral titulada *"Influencia de la actividad física en la prevención y el tratamiento de la Enfermedad Pulmonar Obstructiva Crónica (EPOC)"*, dirigida por D. Arturo Díaz Suarez, a la Comisión de Ética de Investigación de la Universidad de Murcia.

Que dicha Comisión analizó toda la documentación presentada, y de conformidad con lo acordado el día diez de abril de dos mil diecinueve[1], por unanimidad, se emite INFORME FAVORABLE, desde el punto de vista ético de la investigación.

Y para que conste y tenga los efectos que correspondan firmo esta certificación con el visto bueno del Presidente de la Comisión.

Vº Bº
EL PRESIDENTE DE LA COMISIÓN
DE ÉTICA DE INVESTIGACIÓN DE LA
UNIVERSIDAD DE MURCIA

Fdo.: Francisco Esquembre Martínez

ID: 2403/2019

[1]A los efectos de lo establecido en el art. 19.5 de la Ley 40/2015 de 1 de octubre de Régimen Jurídico del Sector Público (B.O.E. 02-10), se advierte que el acta de la sesión citada está pendiente de aprobación

ANEXO 2: Factor de Impacto de las revistas en las que se han publicado los artículos.

**Table 2.** Impact Factor and quartile of the journals in which the papers of this thesis have been published, according to Journal Citation Reports (JCR).

| **Journal** | **Year of P.** | **IF*** | **Q*** | **Category** |
|---|---|---|---|---|
| Lung | 2019 | 2.584 | Q4 | Respiratory System |
| International Journal of Environmental Research and Public Health | 2020 | 3.390 | Q1 | Public Environmental & Occupational Health |
| Medicina | 2020 | 2.430 | Q2 | Medicine, general & Internal |
| Sustainability | 2020-2021 | 3.251 | Q2 | Environmental studies |
| Journal of asthma | 2021 | 2.515 | Q3 | Respiratory System |

**Updated 2020. Year of P: Year of Publication; IF: Impact Factor; Q: Quartile.*

Anexo 3: Primera página artículo I

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COPD

# Physical Activity Behaviour in People with COPD Residing in Spain: A Cross-Sectional Analysis

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## Abstract

**Purpose** Chronic obstructive pulmonary disease (COPD) represents a major public health problem due to its high prevalence, morbidity and health cost. It has been demonstrated that physical activity (PA) is one of the most beneficial measures to prevent chronic diseases. The aim of this study was to examine PA levels of adults with COPD residing in Spain, and to analyse the differences by sex, age, education, marital status, cohabiting, tobacco consumption, alcohol consumption and body mass index.

**Methods** A total of 615 adults aged 15 to 69 years participated in this study. Data from the Spanish National Health Survey 2017 were used. This survey included the short version of IPAQ to measure PA levels. PA was expressed in total volume (MET·min/week), classified as low, moderate and high, and analysed according to sample characteristics. Statistical significance was set at $p < 0.05$ (CI = 95%).

**Results** Level of PA was higher in men than in women (1808.8 vs. 1575.6 MET·min/week; $p = 0.016$), in those aged under 30 years than in those older than 60 years (2129.4 vs. 1381.4 MET·min/week; $p = 0.047$) and in those who drank alcohol than in those who did not drink (1912.8 vs. 1248.2 MET·min/week; $p = 0.004$). Also, underweight and obese participants participated in lower levels of PA than normal weight participants ($p = 0.001$). When classifying PA level, a total of 37.9% had a low level, 47.5% had a moderate level and only 14.6% had a high level of PA ($p < 0.001$).

**Conclusion** It is recommendable to implement programs to raise awareness of the importance and benefits of PA in the control of COPD, and these programs should focus on those with lower levels of PA.

**Keywords** Physical exercise · Lung disease · Public health · Adults

## Introduction

Chronic Obstructive Pulmonary Disease (COPD) represents an important challenge for public health because of its increasing prevalence, high morbidity and socioeconomic burden [1]. Moreover, a large body of literature shows that COPD is associated with a decline in patient's quality of life [2]. Indeed, currently COPD is the forth cause of global death [3, 4], and in 2012, more than 3 million people died because of COPD, representing 6% of all global mortality.

Spanish national data collected in the EPI-SCAN study found a COPD prevalence of 10.2% in people aged 40 to 80 years, with an unequal distribution between the sexes: 15.1% in men versus 5.7% in women [5]. This study defined COPD by the GOLD criteria where the ratio between forced expiratory volume in the first second ($FEV_1$) and the forced vital capacity (FVC) is < 0.70 post-bronchodilator use. Following these findings, it was extrapolated that a 2,185,764 people in Spain suffer from COPD [6]. Importantly, a total of 10% of primary care consultations, 40% of neumology consultations and 7% of annual hospitalizations in Spain are owing to COPD. In those with COPD comorbidities, cardiovascular, metabolic, musculoskeletal and psychological comorbidities are high [7]. These comorbidities are likely driving the high rate of hospitalization. Therefore, in order

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ANEXO 4: Primera página artículo II

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*Environmental Research and Public Health*

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# Associations between Physical Activity and Comorbidities in People with COPD Residing in Spain: A Cross-Sectional Analysis

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**Abstract:** There is a high prevalence of comorbidities among patients with chronic obstructive pulmonary disease (COPD). Comorbidities are likely common in patients with any COPD degree and are associated with increased mortality. The aim of this study was to determine the prevalence of thirty-one different COPD comorbidities and to evaluate the association between physical activity (PA) levels in people with COPD residing in Spain. Cross-sectional data from the Spanish National Health Survey 2017 were analysed. A total of 601 adults (52.2% females) with COPD aged 15 to 69 participated in this study. PA (exposure) was measured with the International Physical Activity Questionnaire (IPAQ) short form and comorbidities (outcomes) were self-reported in response to the question "Have you ever been diagnosed with … ?" Multivariable logistic regression, in three different models, was used to assess this association. Results showed a high prevalence of comorbidities (94%), these being chronic lumbar back pain (38.9%), chronic allergy (34.8%), arthrosis (34.1%), chronic cervical back pain (33.3%), asthma (32.9%) and hypertension (32.8%) the most prevalent. Low PA level was significantly associated with urinary incontinence (2.115[1.213–3.689]), chronic constipation (1.970[1.119–3.459]), cataracts (1.840[1.074–3.153]), chronic anxiety (1.508[1.002–2.269]) and chronic lumbar back pain (1.489[1.044–2.125]). Therefore, people with COPD should increase their PA levels in order to reduce their risk of comorbidities and increase their quality of life.

**Keywords:** lung disease; physical exercise; prevalence; adults

## 1. Introduction

COPD (chronic obstructive pulmonary disease) is an important challenge for public health. Its increasing prevalence, high morbidity and socioeconomic burden are some examples of its importance [1]. Moreover, a large body of literature shows that COPD is associated with a decline in a patient's quality of life [2]. COPD is the fourth largest cause of global death [3,4] and will become the third by 2020. In 2012, greater than three million people died because of COPD (6% of all global mortality).

In Spain, the prevalence of COPD in people aged 40 to 80 was found to be 10.2%, being higher in men (15.1%) than in women (5.7%). [5]. This study used the definition of COPD proposed by the GOLD criteria, where the ratio between forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC) is less than 0.70 post-bronchodilator. Considering these findings, it was extrapolated that 2,185,764 people in Spain suffer from COPD [6]. A total of 10% of primary care consultations, 40% of pneumonology consultations and 7% of Spanish annual hospitalizations are due to COPD. Moreover, in people with COPD comorbidities, the most prevalent comorbidities are cardiovascular, metabolic, musculoskeletal and psychological comorbidities [7]. The presence of

ANEXO 5: Primera página artículo III

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# Levels of Physical Activity in Spanish Asthmatics: A Cross-Sectional Study

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**Abstract:** *Background and objectives:* 339 million people in the world suffer from asthma. Regular physical activity (PA) could help in its control. Therefore, the aim of this research was to determine the level of PA in Spanish people with asthma considering variation by, age, sex, education, marital status, living together, smoking habits, alcohol intake and body mass index (BMI). *Materials and Methods:*1014 Spanish people from 15 to 69 years were included in the study. Data of the Spanish Health Survey (year 2017) were analysed. PA levels were measure with the international physical activity questionnaire short version (IPAQ-SF). PA was categorized as low, moderate and high, and analyzed by sample characteristics. Mann-Whitney U test, Kruskall Wallis H and crosstabs were used to calculate statistical significance ($p < 0.05$). *Results:* On average, Spanish asthmatics engaged in a weekly volume of 2228.9 metabolic equivalent of task (MET)·min/week. Males revealed significantly higher PA than females (2516.8 vs2019.5 MET·min/week; $p = 0.005$), younger participants (<30 years) compared to people aged 30–60 years and older than 60 years (2699.0; 2243.2; 1619.3 MET·min/week; $p < 0.001$) and those with tertiary level of education than those without secondary (2368.3 vs. 2168.3 MET·min/week; $p = 0.001$). Level of PA was lower in those married ($p = 0.001$) and/or living together ($p = 0.010$). Alcohol consumers showed a higher level than the participants who did not drink (2378.3 vs. 1907.9 MET·min/week; $p = 0.001$), but no significant differences were found within current, past and never smokers ($p = 0.890$). Obese asthmatics engaged in less PA than their normal weight and overweight peers ($p < 0.001$). Overall, moderate level was significantly the most frequent (47.7%), but 31.6% showed a low level. *Conclusions:* Three out of ten Spanish people with asthma do not achieve PA recommendations, so PA programs should be executed to make people aware of its benefits in asthma control, focusing on those groups with lower PA levels.

**Keywords:** respiratory disease; physical exercise; epidemiology; tobacco; body mass index; alcohol

## 1. Introduction

Asthma is a common and important chronic disease that involves people of all ages [1]. Globally, 339 million people suffer from asthma [2]. In adults, the overall prevalence diagnosed is estimated to be 4.3% [3]. In Spain, an epidemiological study of chronic obstructive pulmonary disease (IBERPOC Project), found a 4.9% prevalence of asthma in Spanish adults aged from 40 to 69 years [4], but according to data of the Spanish Health Survey (year 2017), the prevalence of asthma in Spanish people aged 15 to 69 years was found to be slightly higher, at around 6% [5].

Asthma is a chronic condition that appears with chronic airway inflammation, whose main symptoms are wheeze, chest tightness, shortness of breath, variable expiratory airflow limitation and cough [1]. All these aspects, together with the fear of having exercise-induced bronchoconstriction

ANEXO 6: Primera página artículo IV

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# Analysis of Physical Activity and Comorbidities in Spanish Asthmatics

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**Abstract:** The prevalence of comorbidities in asthmatics is high. Comorbidities may complicate the clinical management of asthma, increasing the risk for exacerbation and even death. The objective of the present research was to establish the prevalence of 31 asthma comorbidities and to assess the association of these comorbidities with physical activity (PA) in Spanish asthmatics. Data of the Spanish National Health Survey 2017 (cross-sectional design) were used in this study. A total of 1014 people (42.1% males) with asthma participated in this study (age range 15–69 years). The IPAQ (International Physical Activity Questionnaire) short form was the instrument administered to evaluate PA (exposure), and the self-reported answer to the question "Have you ever been diagnosed with…?" determined the presence of comorbidities (outcomes). This association was assessed by multivariable logistic regression. Results demonstrated a huge presence of comorbidities (89.3%). The most prevalent were chronic allergy (61.1%), chronic lumbar pain (28.7%), chronic cervical pain (24.2%), high cholesterol (20.9%), Chronic Obstructive Pulmonary Disease (COPD) (19.4%), migraine (19.2%) and hypertension (19.3%). PA level under 600 metabolic equivalent of task (MET)·min/week showed a significant association with urinary incontinence (3.10 [1.62–5.94]), osteoporosis (1.90 [1.00–3.61]) and chronic anxiety (1.69 [1.13–2.53]). Therefore, comorbidities and PA levels should be considered in the prevention and treatment of asthmatics, in order to improve their quality of life.

**Keywords:** respiratory health; exercise; prevalence; adults

## 1. Introduction

Asthma is a frequent and potentially serious chronic condition that affects all age groups [1]. Over 339 million people worldwide are affected by asthma [2]. According to previous research, the worldwide prevalence of asthma diagnosed in the adult population is 4.3% [3]. In Spain, the epidemiological study of chronic obstructive pulmonary disease (IBERPOC) found a prevalence of 4.9% in adults aged 40–69 years [4], and according to the Spanish National Survey 2017, a prevalence of 6 % was found in Spanish people aged 15–69 years [5].

Chronic airway inflammation related to wheezing, chest tightness, shortness of breath, cough and variability in expiratory airflow limitation are some of the symptoms present in asthmatics. An insufficient control of asthma symptoms is a risk factor to develop crisis relating to asthma [1]. The previous aspects, together with the possibility of having EIB (exercise-induced bronchoconstriction), could reduce physical activity (PA) levels in asthmatics [6]. Therefore, asthmatics are usually involved in lower levels of PA in comparison with non-asthmatics [6,7]. In people with asthma, regular PA may be useful in the control of asthma [8–10]. Several studies suggest that regular PA reduces asthma symptoms [11,12], airway

ANEXO 7: Primera página artículo V

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# Physical activity behavior in people with asthma and COPD overlap residing in Spain: a cross-sectional analysis

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**ABSTRACT**

**Objectives:** To identify levels of physical activity (PA) among the Spanish population with asthma and chronic obstructive pulmonary disease overlap (ACO). A further aim was to analyze differences in PA levels by sex, age, education, marital status, cohabiting, smoking habits, alcohol consumption and body mass index (BMI).

**Methods:** In this cross sectional study, data from the Spanish National Health Survey 2017 were analyzed. A total of 198 people with ACO aged 15–69 years were included in the analyses. The short version of the international physical activity questionnaire (IPAQ) was used to measure total PA (MET·min/week). PA was further classified as low, moderate and high, and analyzed according to sample characteristics. Data were analyzed using the Mann-Whitney U test, Kruskal-Wallis H test and chi squared test. Statistical significance was set at $p < 0.05$.

**Results:** People with ACO engaged in a mean volume of 2038.1 MET·min/week. Those aged 30–60 years and those with normal weight were significantly more active than those aged ≥60 and those with obesity. When classifying PA level in low, moderate and high, results showed no significant differences between sample characteristics. Overall, moderate and high levels of PA were the most and least frequent levels (48.0% and 16.2%, respectively).

**Conclusions:** More than three out of ten Spanish adults with ACO do not achieve PA recommendations. Therefore, it is recommended to implement programs that promote the importance and benefits of PA among the Spanish population with ACO, and such programs should focus on older adults and those who are obese.

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Epidemiology; obesity; physiological disorders; prevention; quality of life

## Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are two of the five major respiratory diseases, established by the Forum of International Respiratory Societies (FIRS) (1). Both of these conditions are important public health problems owing to their increasing prevalence, high morbimortality and socio-economic burden (2,3). In 2019, the Global Burden of Disease (GBD) study found a worldwide prevalence of asthma and COPD in the general population of 3.50% (3.40% males, 3.60% females) and 2.85% (2.85% males, 2.86% females), respectively (4). A previous analysis of the GBD study in 2015 (5) identified a 44.2% increased prevalence and an 11.6% increased risk or mortality from COPD between 1990 and 2015. In relation to asthma, the prevalence increased by 12.6% but mortality decreased by 26.7% between 1990 and 2015. Moreover, both asthma and COPD showed a decrease in age-standardised death and prevalence during this time-period.

These diseases are characterized by chronic respiratory symptoms and airflow limitation, but there are some differences between them. Symptoms of asthma vary over time in intensity and improve with the use of bronchodilators or even spontaneously, so expiratory airflow limitation is variable (2). COPD is characterized by persistent expiratory airflow limitation and respiratory symptoms with or without bronchodilator reversibility (3). Moreover, the onset of asthma tends to be before the age of 40 years while COPD is normally after 40 years and generally in those who have history of smoking or other toxic exposure. A systematic review and meta-analysis on the global burden of COPD found a prevalence of COPD of

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ANEXO 8: Primera página artículo VI

*sustainability*

MDPI

*Article*

# Association between Physical Activity and Comorbidities in Spanish People with Asthma-COPD Overlap

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**Abstract:** Asthma and chronic obstructive pulmonary disease (COPD) are important conditions which often coexist. Higher rates of comorbidities among people with asthma-COPD overlap (ACO) may complicate clinical management. The aim of this study was to determine the prevalence of 30 different comorbidities and to analyze associations between these comorbidities and physical activity (PA) in Spanish people with ACO. Cross-sectional data from the Spanish National Health Survey 2017 were analyzed. A total of 198 Spanish people with ACO aged 15–69 years (60.6% women) were included in this study. PA was measured with the International Physical Activity Questionnaire (IPAQ) short form. Diagnosis of chronic conditions were self-reported. Associations between PA and comorbidities were analyzed using multivariable logistic regression models. The most prevalent comorbidities were chronic allergy (58.1%), chronic lumbar pain (42.4%), chronic cervical pain (38.4%), hypertension (33.3%) and arthrosis (31.8%). A PA level lower than 600 MET·min/week was significantly associated with urinary incontinence (OR = 3.499, 95% CI = 1.369–8.944) and osteoporosis (OR = 3.056, 95% CI = 1.094–8.538) in the final adjusted model. Therefore, the potential influence of PA on reducing the risk of these conditions among people with ACO should be considered, not only because of the health benefits, but also because PA can contribute to a more sustainable world.

**Keywords:** respiratory conditions; exercise; sustainability; multimorbidity



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## 1. Introduction

The Forum of International Societies (FIRS) established chronic obstructive pulmonary disease (COPD) and asthma as two of the five major respiratory diseases [1]. Both conditions are important public health problems based on their high prevalence, socioeconomic burden and morbimortality [2,3]. The Global Burden of Disease (GBD) 2019 [4], revealed a global prevalence of asthma of 3.5% (3.6% females; 3.4% males) and 2.8% of COPD (2.8% females; 2.8% males). Moreover, COPD was accountable for 5.8% of global deaths in 2019 and asthma 0.82% [4]. Importantly, both diseases result in a high socioeconomic burden [5,6].

These respiratory conditions are characterized by airflow limitation and respiratory symptoms, but there are differences between them that need to be noted. In asthma patients, expiratory airflow limitation and symptoms such as wheeze, shortness of breath, cough and chest tightness vary over time in intensity and improve with the use of bronchodilators or even spontaneously [2]. However, COPD is characterized by persistent expiratory airflow limitation and persistent respiratory symptoms, with or without bronchodilator reversibility [3]. Onset of COPD tends to occur after 40 years and generally in those who have been exposed to noxious particles or gases, like tobacco. However, some patients have clinical features of both asthma and COPD [2]. These clinical phenotypes have been named as Asthma-COPD overlap (ACO) or asthma + COPD. Previous studies have used the term Asthma-COPD overlap Syndrome (ACOS) to describe these patients [7,8], but the latest updates of GINA [2] and GOLD [3] have named these clinical phenotypes Asthma-COPD