



Urban environment and physical activity and capacity in patients with chronic obstructive pulmonary disease

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ABSTRACT

Background: Physical activity and exercise capacity are key prognostic factors in chronic obstructive pulmonary disease (COPD) but their environmental determinants are unknown.

Objectives: To test the association between urban environment and objective physical activity, physical activity experience and exercise capacity in COPD.

Methods: We studied 404 patients with mild-to-very severe COPD from a multi-city study in Catalonia, Spain. We measured objective physical activity (step count and sedentary time) by the Dynaport MoveMonitor, physical activity experience (difficulty with physical activity) by the Clinical visit-PROactive (C-PPAC) instrument, and exercise capacity by the 6-min walk distance (6MWD). We estimated individually (geocoded to the residential address) population density, pedestrian street length, slope of terrain, and long-term (i.e., annual) exposure to road traffic noise, nitrogen dioxide (NO₂) and particulate matter (PM_{2.5}). We built single- and multi-exposure mixed-effects linear regressions with a random intercept for city, adjusting for confounders.

Results: Patients were 85% male, had mean (SD) age 69 (9) years and walked 7524 (4045) steps/day. In multi-exposure models, higher population density was associated with fewer steps, more sedentary time and worse exercise capacity (−507 [95% CI: 1135, 121] steps, +0.2 [0.0, 0.4] h/day and −13 [−25, 0] m per IQR). Pedestrian street length related with more steps and less sedentary time (156 [9, 304] steps and −0.1 [−0.1, 0.0] h/day per IQR). Steeper slope was associated with better exercise capacity (15 [3, 27] m per IQR). Higher NO₂ levels related with more sedentary time and more difficulty in physical activity. PM_{2.5} and noise were not associated with physical activity or exercise capacity.

Discussion: Population density, pedestrian street length, slope and NO₂ exposure relate to physical activity and capacity of COPD patients living in highly populated areas. These findings support the consideration of neighbourhood environmental factors during COPD management and the attention to patients with chronic diseases when developing urban and transport planning policies.

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Abbreviations

BMI	body mass index
CAT	COPD assessment test
CCQ	clinical COPD questionnaire
COPD	chronic obstructive pulmonary disease
C-PPAC	Clinical visit—PROactive Physical Activity in COPD
dB	decibels
FEV ₁	forced expiratory volume in 1 s
FFMI	fat free mass index
FVC	forced vital capacity
GIS	Geographic Information Systems
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HADS-A:	hospital anxiety and depression scale – anxiety
HADS-D:	hospital anxiety and depression scale – depression
INE	Instituto Nacional de Estadística

ICGC	Institut Cartogràfic i Geològic de Catalunya
IQR	interquartile range
L _{den}	day evening night sound level
LUR	land-use regression
mMRC	modified Medical Research Council
6MWD	6-min walk distance
6MWT	6-min walk test
NO ₂	nitrogen dioxide
PM	particulate matter
P25	25 th percentile
P75	75 th percentile
SD	standard deviation
VIF	variance inflation factor
VO ₂	oxygen uptake

1. Introduction

Chronic obstructive pulmonary disease (COPD) is an important cause of morbidity and mortality worldwide (Soriano et al., 2017). The global burden of disease study estimated that COPD affected more than 174 million patients and caused 3.2 million deaths in 2015 (Soriano et al., 2017). COPD is characterised by a progressive airflow limitation leading to breathlessness that often limits the ability to carry out daily activities, including physical activities. Patients are typically less active than healthy controls from the early stages of the disease onwards (Pitta et al., 2005; Shrikrishna et al., 2012; Van Remoortel et al., 2013) and this inactivity affects COPD prognosis. Indeed, COPD patients who maintain regular levels of physical activity have lower risk of exacerbations of the disease, attenuated lung function decline and lower mortality (Demeyer et al., 2019; Gimeno-Santos et al., 2014). Thus, COPD guidelines such as those provided by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommend physical activity for all COPD patients (Vestbo et al., 2013). To provide adequate support to physical activity interventions, knowing and understanding which factors other than the disease itself may influence the physical activity behaviour is key.

The ecological model of the determinants of physical activity (Bau-man et al., 2012) suggests a major role for factors in the ‘environmental’ domain. In line with this notion, a range of studies have reported that environmental factors such as residential density or land-use mix (Cerin et al., 2020; Ding et al., 2013; Frank et al., 2005; McCormack, 2017; Witten et al., 2012), noise or noise annoyance (Dzhambov et al., 2017; Foraster et al., 2016; Roswall et al., 2017) and air pollution (An et al., 2018) are associated with physical activity in the general population. Thus, it is likely that such environmental factors can influence the physical activity of COPD patients also. Nonetheless, the evidence for this assumption remains currently uncertain. One study found that high levels of ozone (O₃) and particulate matter (PM₁₀) were associated with a reduced step count in patients with COPD (Alahmari et al., 2015). However, another study based on the same cohort as the current manuscript observed that urban greenness was not related to physical activity in COPD patients, which lead to the hypothesis that the ability of environment to stimulate physical activity could be lower in these patients than in the general population due to their underlying chronic condition (Arbillaga-Etxarri et al., 2017). Unfortunately, the role of other environmental factors in the physical activity of COPD patients has not been tested so far.

At difference with previous research (mostly in the general population), where physical activity is assessed as an individual single characteristic, we postulate that understanding the determinants of ‘physical activity behaviour’ in subjects suffering from chronic conditions that limit their mobility in daily life requires a wider approach. Accordingly,

we propose to include as outcomes of the environmental factors not only objective measures of physical activity as obtained by an activity monitor, but also the patient’s experience of difficulty with physical activity (Gimeno-Santos et al., 2015), and the patient’s functional exercise capacity which strongly determines how active a patient can be (Holland et al., 2015; Troosters et al., 2019).

With this background in mind, we aimed to estimate the association between environmental factors (population density, pedestrian street length, slope of terrain, road traffic noise, nitrogen dioxide (NO₂) and PM_{2.5}), and objective physical activity (daily step count, sedentary time), physical activity experience (difficulty with physical activity) and functional exercise capacity (6-min walk distance (6MWD)) in patients with mild-to-very severe COPD. We anticipate that our results will allow for developing strategies to effectively promote physical activity in COPD patients.

2. Methods**2.1. Study design and patient population**

This is a cross-sectional analysis of baseline pre-randomisation data from the multi-centre Urban Training study (NCT01897298) (Arbillaga-Etxarri et al., 2018) that enrolled 407 patients from five Catalan seaside municipalities (Badalona, Barcelona [centre and shore areas], Mataró, Viladecans and Gavà) at 33 primary care centres and 5 tertiary hospitals between October 2013 and February 2015. All patients had a diagnosis of COPD, according to American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (post-bronchodilator forced expiratory volume in 1 s [FEV₁] to forced vital capacity [FVC] ratio <0.70) (Celli et al., 2004). For the present analysis we used the data collected at baseline only and included patients if they had valid data on objective physical activity, physical activity experience, functional exercise capacity, and environmental variables (n = 404, 99% of the total).

The study was approved by all local institutional ethic boards and written informed consent was obtained from all patients.

2.2. Physical activity and capacity outcomes

Objective physical activity was recorded during 24 h of 7 consecutive days using the Dynaport MoveMonitor (McRoberts BV, The Hague, The Netherlands) (Rabinovich et al., 2013; Van Remoortel et al., 2012). Data during waking hours (from 07:00 h to 22:00 h) were retrieved. A valid physical activity measurement was defined as a minimum of three days with at least 8 h of wearing time within waking hours; details have been previously published (Arbillaga-Etxarri et al., 2018). For the present

study, we obtained information on daily step count and sedentary time (sum of lying and sitting time, in hours/day).

Experience with physical activity was assessed by the Clinical visit version of the PROactive physical activity in COPD (C-PPAC) instrument. Briefly, the C-PPAC combines a short patient-reported outcome questionnaire with data from an activity monitor to assess the physical activity experience in three scores: amount of physical activity, difficulty with physical activity, and total physical activity experience, all ranging from 0 (worse physical activity experience, i.e., less amount, more difficulty) to 100 (better physical activity experience, i.e., more amount, less difficulty) (Garcia-Aymerich et al., 2021; Gimeno-Santos et al., 2015). For the present study, we used the difficulty score as an outcome, as the amount score was highly correlated with the objective physical activity variables in our sample (Spearman correlation coefficient [ρ] of amount score with step count $\rho = 0.75$, p -value < 0.001 , and with sedentary time $\rho = -0.62$, p -value < 0.001).

Functional exercise capacity was assessed using the 6-min walk test (6MWT) following published recommendations (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories 2002; Manual de Procedimientos SEPAR, 4; Erratum in ATS statement: Guidelines for the six-minute walk test 2016), determining the 6MWD for each patient. Patients completed two 6MWTs with at least a 30-min rest between, and the longer of the two distances was used for analysis.

2.3. Urban environmental exposures

We estimated the exposure to urban environmental factors individually using Geographic Information Systems (GIS) for each patient at his/her geocoded residential address. We obtained population density (habitants per square kilometre within the census area) from the Spanish National Statistics Institute (Instituto Nacional de Estadística, INE) for the year 2016 (INE, 2016). We obtained pedestrian street length (sum of pedestrian street length [metres] within a 300-m buffer around the residence) from Navteq (licensed data under ArcGIS software, ESRI ArcMap™ 10.0, ArcGIS Desktop 10 Service Pack 4) (ESRI, 2012). We obtained slope of terrain from now on 'slope' (average slope [degrees] within a 300-m buffer around the residence) from the topographic map of the Cartographic Institute of Catalonia (Institut Cartogràfic i Geològic de Catalunya, ICGC) (ICGC, 2012). We obtained road traffic noise from now on 'noise' (annual residential average levels of road traffic noise in the nearest street from the residence [24 h day-evening-night level (L_{den}) EU indicator in decibels (dB)]) from the official strategic noise maps for the year 2012, except for Mataró for which only the 2017 map was available, developed under the EU Directive 2002/49/EC as described previously (Dadvand et al., 2014b; Mapes estratègics del soroll, 2012). Finally, we estimated the annual residential averages of NO_2 and $PM_{2.5}$ ($\mu g/m^3$) temporarily adjusted for each patient (i.e., 12 months prior to data collection). To do that we applied land-use regression (LUR) models from 2009 that were corrected to 2013 levels using daily time series from fixed air quality monitors as described previously (Beelen et al., 2013; Cyrys et al., 2012; Eeftens et al., 2012a, 2012b).

2.4. Other measurements

We obtained the following data (presented along the lines of the ecological model of the determinants of physical activity (Bauman et al., 2012)) from all patients using standardised procedures: (i) sociodemographic: age, sex, smoking history, education and individual socioeconomic status (based on the employment characteristics and categorised according to the National Statistics Socio-economic Classification); (ii) interpersonal: marital status and working status; (iii) environmental: season of recruitment, land-surface yearly average temperature (average temperature within a 50-m buffer around the residence, derived from three land-surface temperature maps from the Landsat 5 Thematic Mapper data as described previously (Dadvand et al., 2014b)) and urban vulnerability index (a measure of socioeconomic status at the census

tract level) (Atlas of Urban Vulnerability in Spain); (iv) clinical: FEV_1 and FVC by forced spirometry post bronchodilator, the COPD assessment test (CAT) and the clinical COPD questionnaire (CCQ; total score and the three subdomains: symptom, functional and mental state) to measure quality of life, the modified Medical Research Council dyspnoea scale (mMRC), the number of acute COPD exacerbations requiring a hospital admission in the previous 12 months, body mass index (BMI) and fat free mass index (FFMI) by physical examination and bioelectrical impedance; and (v) psychological: the hospital anxiety and depression scale (HADS), providing a score for anxiety (HADS-A) and a score for depression (HADS-D) (Snaith, 2003; Zigmond and Snaith, 1983). Full details on study procedures and quality control have been reported previously (Arbillaga-Etxarri et al., 2017, 2018).

2.5. Statistical analysis

Since the sample size was fixed by the main objective of the Urban Training study (Arbillaga-Etxarri et al., 2018), we calculated the statistical power of the available sample ($n = 404$) to test the association between environmental factors and physical activity in COPD patients. Based on own unpublished data about distribution of population density and air pollution levels in the same geographic areas, and physical activity levels of COPD patients from the same geographic areas and similar care settings (Donaire-Gonzalez et al., 2013), 404 patients allow to detect an association of -493 steps/day or higher per a change of $\approx 20,000$ inhabitants/km² in population density as previously reported (Annegarn et al., 2012; McCormack, 2017), and an association of -5.4 steps/day or higher per increase in $1 \mu g/m^3$ in particulate matter as previously reported (Alahmari et al., 2015) with a statistical power of $> 99\%$. Due to the small proportion of missing data ($< 2\%$ of total data), we used a complete case strategy and reported missing data in the table footnotes.

We estimated the Spearman's rank correlation between the environmental exposures (population density, pedestrian street length, slope, noise, NO_2 and $PM_{2.5}$). To test the association between each of the environmental factors and objective physical activity, physical activity experience and functional exercise capacity variables, we used mixed-effects linear regression models reported per change of an inter-quartile range (IQR) in exposure. We first built unadjusted single-exposure models with a random intercept for city. We then built single-exposure multivariable models, adjusting for age, sex, socioeconomic status, urban vulnerability index, FEV_1 , CCQ mental score, exacerbation with hospital admission in previous 12 months and anxiety (HADS-A score) which we defined a priori as the most compelling confounders based on available literature or those variables which differed across cities and were a source of heterogeneity (see directed acyclic graphs in Appendix, Figures A1 and A2) (Arbillaga-Etxarri et al., 2017). Other relevant factors which had been used as covariates in the literature previously (e.g., depression or dyspnoea) were considered as potential effect modifiers or mediators in our analysis and so not included as covariates in the main models. Finally, we built a multi-exposure model additionally adjusting for all environmental factors simultaneously to control for mutual residual confounding, after checking for possible collinearity (average variance inflation factor (VIF) < 3). We tested goodness of fit of the final models.

Based on observed results and to help interpretation, we conducted two *post-hoc* analyses: (1) we stratified the association between population density and step count, sedentary time and exercise capacity for depression symptoms level (HAD-D score ≤ 11 based on previous research) (Snaith, 2003) to test its role as potential effect modifier of the observed associations; and (2) we included the mMRC dyspnoea score in the single-exposure multivariable model for NO_2 , to indirectly test its role as potential mediator for the effect of NO_2 on sedentary time and C-PPAC difficulty score (see a priori built directed acyclic graph in Appendix, Figure A1).

Finally, as sensitivity analyses, (1) we restricted the final models to

patients not working actively to test for potential miss-classification in the exposures (i.e., assuming that patients who work away from home spend an important part of their time not exposed to residential environmental factors), and (2) we repeated the final models after excluding patients with extreme values (<5th and >95th percentile) in the environmental exposures to omit the influence of extreme observations.

All analyses were performed using Stata/SE 14.2 (StataCorp, College Station, TX, USA).

3. Results

Of 404 patients included in the present analysis 85% were male, age was mean (standard deviation [SD]) 69 ± 9 years, FEV₁ was 57 (18) % predicted and mMRC dyspnoea score was 1.2 (0.9) (Table 1).

Compliance with the activity monitor was excellent with median (P25–P75) 7 (3–7) valid days and m (SD) 14.6 (0.7) wearing hours. The patients walked on average 7524 (4045) steps/day and the 6MWD was 486 (95) metres (Table 2). There were no differences in physical activity, physical activity experience or functional exercise capacity variables according to the season of recruitment. Median population density was 31,284 (14,020–45,344) inhabitants/km² within the census area, pedestrian street length was 245.1 (50.5–517.5) metres within a 300-m buffer around the residence, slope was 2.0 (1.2–3.5) degrees within a 300-m buffer around the residence, noise was 63 (59–67) dB in the nearest street from the residence, annual NO₂ was 43.5 (35.0–48.7) µg/m³ and annual PM_{2.5} was 12.6 (10.7–13.8) µg/m³ (Table 2).

We found weak to moderate (positive and negative) correlations between all environmental factors (population density, pedestrian street length, slope, noise, NO₂ and PM_{2.5}), except for population density with pedestrian street length and slope, and for noise with NO₂ and PM_{2.5} which were not correlated (Fig. 1). Due to the lack of strong correlations and no evidence of strong collinearity according to the VIF levels we subsequently built multi-exposure models including all exposures simultaneously.

Higher population density was associated with a lower step count, more sedentary time and reduced functional exercise capacity, in unadjusted, single- and multi-exposure adjusted models, although in some models the association did not reach statistical significance (Fig. 2, Appendix Table A1). After stratification by depression symptoms level, the results were stronger and statistically significant among COPD patients with depression symptoms, while they were reduced and lost precision in the COPD patients without depression symptoms (see Appendix, Table A2).

Pedestrian street length was associated with more steps and less sedentary time in single- and multi-exposure adjusted models. Steeper slope was consistently associated with an increased functional exercise capacity in unadjusted, single- and multi-exposure adjusted models but not with the rest of physical activity parameters.

Higher levels of NO₂ were associated with more sedentary time and worse physical activity experience (i.e. more experienced difficulty with physical activity). The latter association was attenuated and lost precision when the mMRC dyspnoea score was included as a covariate (see Appendix, Table A3).

PM_{2.5} and noise were not associated with any physical activity or exercise capacity parameter in this cohort of COPD patients.

When restricting the adjusted models to patients not working actively, all associations persisted except for the associations of pedestrian street length with daily step count and sedentary time (see Appendix, Table A4). When we excluded extreme values in exposure variables, the associations were attenuated (see Appendix, Table A5).

4. Discussion

This study observed that some urban environmental factors were associated with objective physical activity, physical activity experience and functional exercise capacity in COPD patients, specifically: (1) a

Table 1

Characteristics of 404 patients with mild-to-very severe COPD.

	All patients n = 404 ^a
Sociodemographic characteristics	
Age (years), m (SD)	68.8 (8.5)
Sex: men, n (%)	343 (85)
Current smoker, n (%)	97 (24)
Cumulative smoking (pack-years), m (SD)	59.3 (41.4)
Education: high school or higher ^b , n (%)	123 (31)
Socioeconomic status: non-manual skilled or higher ^c , n (%)	114 (28)
Interpersonal characteristics	
Living with a partner ^d , n (%)	306 (76)
Active worker ^e , n (%)	48 (12)
Environmental characteristics	
Recruitment season	
Spring, n (%)	101 (25)
Summer, n (%)	44 (11)
Fall, n (%)	143 (35)
Winter, n (%)	116 (29)
Land surface temperature (°C) ^f , median (P25–P75)	24.4 (24.1–24.7)
Urban vulnerability index (from 0-lowest to 1-highest) ^g , m (SD)	0.64 (0.17)
Clinical characteristics	
FEV ₁ (% predicted), m (SD)	56.8 (17.5)
FEV ₁ /FVC ratio, m (SD)	0.54 (0.12)
Airflow limitation severity:	
Mild (FEV ₁ ≥ 80%), n (%)	38 (9)
Moderate (FEV ₁ 50–79%), n (%)	215 (53)
Severe (FEV ₁ 30–49%), n (%)	120 (30)
Very severe (FEV ₁ < 30%), n (%)	31 (8)
CAT score (from 0-better to 40-worse), m (SD)	12.3 (7.2)
CCQ-total score (from 0-better to 6-worse), m (SD)	1.4 (1.0)
CCQ-symptom score (from 0-better to 6-worse), m (SD)	1.6 (1.1)
CCQ-functional score (from 0-better to 6-worse), m (SD)	1.3 (1.2)
CCQ-mental score (from 0-better to 6-worse), m (SD)	1.3 (1.5)
mMRC dyspnoea score (from 0-better to 4-worse), m (SD)	1.2 (0.9)
Any COPD exacerbation with hospital admission in previous 12 months, n (%)	23 (6)
BMI (kg/m ²), m (SD)	28.4 (5.0)
FFMI (kg/m ²), m (SD)	19.5 (3.2)
Psychological characteristics	
Anxiety (HADS-A score, 0–21), m (SD)	5.2 (4.0)
Depression (HADS-D score, 0–21), m (SD)	3.5 (3.4)

BMI: body mass index; CAT: COPD assessment test; CCQ: clinical COPD questionnaire; FEV₁: forced expiratory volume in 1 s; FFMI: fat free mass index; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; HADS-A: hospital anxiety and depression scale – anxiety; HADS-D: hospital anxiety and depression scale – depression; mMRC: modified Medical Research Council; P25: 25th percentile; P75: 75th percentile; SD: standard deviation.

^a Some variables have missing values, as follows: 2 in pack-years, 1 in education, 2 in socioeconomic status, 1 in living with a partner, 2 in CCQ scores, 11 in any COPD exacerbation with hospital admission in previous 12 months, 39 in FFMI, 2 in anxiety, 4 in depression.

^b Education: high school or higher vs maximum compulsory school.

^c Socioeconomic status: non-manual skilled or higher vs manual skilled, partly skilled of unskilled occupations (IIIN, II and I vs IIIM, IV and V according to the National Statistics Socio-economic Classification).

^d Marital status: living with a partner vs single, widowed or divorced.

^e Working status: active worker (working full-time or part-time) vs unemployed, housework or retired.

^f Average land-surface temperature within a 50-m buffer around the residence, derived from three land-surface temperature maps.

^g The urban vulnerability index is a measure of socioeconomic status at the census tract level that combines demographic, economic, residential and subjective indicators, and ranges from lowest [0] to highest [1] level of neighbourhood vulnerability.

higher population density was associated with fewer steps, more sedentary time and worse functional exercise capacity, and this association was stronger in COPD patients with symptoms of depression; (2) more pedestrian street length was associated with more steps and less sedentary time; (3) a steeper slope was associated with better functional

Table 2

Objective physical activity, physical activity experience and functional exercise capacity and environmental factors in 404 patients with mild-to-very severe COPD.

	All patients n = 404 ^a
Physical activity and exercise capacity	
Step count (steps/day), m (SD)	7524 (4045)
Sedentary time (h/day), m (SD)	10.4 (1.6)
Physical activity experience (C-PPAC difficulty score, 0–more to 100–less difficulty), m (SD)	81.9 (14.6)
6MWD (metres), m (SD)	486 (95)
Environmental exposures	
Population density (habitants/km ²) ^b , median (P25–P75)	31,284 (14,020–45,344)
Pedestrian street length (metres) ^c , median (P25–P75)	245.1 (50.5–517.5)
Slope (degrees) ^d , median (P25–P75)	2.0 (1.2–3.5)
Noise (L _{den} , dB) ^e , median (P25–P75)	63 (59–67)
NO ₂ (µg/m ³) ^f , median (P25–P75)	43.5 (35.0–48.7)
PM _{2.5} (µg/m ³) ^f , median (P25–P75)	12.6 (10.7–13.8)

C-PPAC: Clinical visit—PROactive Physical Activity in COPD (higher numbers indicate a better physical activity experience); L_{den}: day evening night sound level; 6MWD: 6-min walk distance; NO₂: nitrogen dioxide; PM: particulate matter; P25: 25th percentile; P75: 75th percentile; SD: standard deviation.

^a Some variables have missing values, as follows: 93 in C-PPAC difficulty score, 1 in noise.

^b Habitants per square kilometre within the census area.

^c Sum of pedestrian street length within a 300-m buffer around the residence.

^d Average slope of terrain within a 300-m buffer around the residence.

^e Annual average levels of road traffic noise in the nearest street from the residence.

^f Annual residential averages of NO₂ and PM_{2.5}.

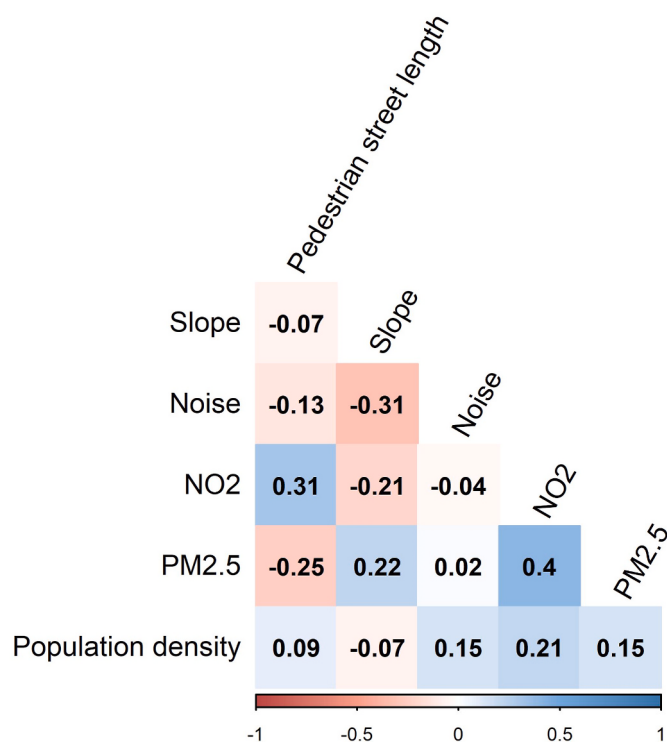


Fig. 1. Correlations between the environmental factors (Spearman correlation coefficients).

NO₂: nitrogen dioxide; PM: particulate matter.

exercise capacity but not with physical activity parameters; (4) higher long-term NO₂ exposure was associated with more sedentary time and more difficulty with physical activity, and this association could be partly mediated by dyspnoea; and (5) PM_{2.5} and noise exposure were not

associated with physical activity or exercise capacity.

A first striking result is that higher population density was associated with worse physical activity and capacity outcomes in COPD patients. This is in contrast with several previous studies that reported a positive association between population density and physical activity of older adults (Corseuil et al., 2016; Hino et al., 2020; Portegijs et al., 2017) and attributed this to a stimulating effect of a more liveable neighbourhood (i.e., more shops and services, better public transport) (Udell et al., 2014). However, we need to consider that those studies refer to cities with a lower population density. Barcelona (where 46% of our patients were recruited) is among one of the most densely populated cities of Europe (Population Stat, 2020; World population review, Barcelona, 2020). Indeed, the median population density for our study population was very high, above 30,000 habitants/km². In agreement with our results, other studies have found higher population density associated with lower physical activity (McCormack, 2017; Cerin et al., 2020) and hypothesised that extreme density may have negative effects on physical activity due to increased traffic hazards, fumes and noise. Indeed, our results support the latter thesis. We additionally speculate that the negative effect of high population density might be stronger in our patients due to their COPD. These patients report the need to take breaks or slow down during walking (Dobbels et al., 2014), which could deter them from walking in crowded environments. Additionally, the underlying chronic lung disease can impact negatively on the mood when practicing physical activity. We observed that the negative effect of high population density was much stronger in COPD patients with symptoms of depression. Although these findings are derived from *post hoc* analyses and are based on small numbers, they are in line with previous qualitative research reporting that the embarrassment caused by symptoms such as breathlessness and immobility in public was a personal barrier for physical activity in COPD patients (Kosteli et al., 2017).

Secondly, and in line with previous literature in the general older population (Cerin et al., 2017), we found pedestrian street length associated with higher physical activity (more steps and less sedentary time). Of note, the magnitude of the association in our study was small (around 150 steps and 3 min sedentary time/day per IQR change, i.e., 467 m within a 300-m buffer) but similar as the one observed for other built environment factors such as shop and service density, or sidewalk length in the general population (McCormack, 2017). There is debate on whether pedestrian street length is directly promoting more walking or whether this association could be explained by the fact that more pedestrian walkways reflect less air pollution. The fact that the association persisted in the multi-exposure models and that pedestrian street length and NO₂ exposure were positively correlated (Fig. 1) does not support this latter hypothesis. Unfortunately, we did not have any information on complementary features of pedestrian streets (e.g., benches, trees, or shadow/sun) which could have provided further insights (Cerin et al., 2017; Steinmetz-Wood et al., 2020). Finally, it has been reported that good pedestrian infrastructure may promote active commuting in the general population (Mäki-Opas et al., 2016) which in turn would increase physical activity levels (Rissel et al., 2012). Our sample was composed of a mostly retired population and our sensitivity analysis excluding active workers resulted in the loss of an association between pedestrian street length and physical activity (Appendix, Table A4), thus supporting that the observed association between pedestrian street length and physical activity could have been indeed driven by patients who were still working, and actively commuted to work.

Another novel finding was the association between steeper slope and better exercise capacity, which had not been tested before despite the clinical relevance of understanding determinants of exercise capacity. Hills are mostly perceived as a barrier to physical activity (Barnett et al., 2017). However, the very fact that walking on a slope is more strenuous than walking at an even level could actually help to protect the patients' functional exercise capacity. Actually, a validation study of urban trails for COPD patients (Arbillaga-Etxarri et al., 2016) showed that urban

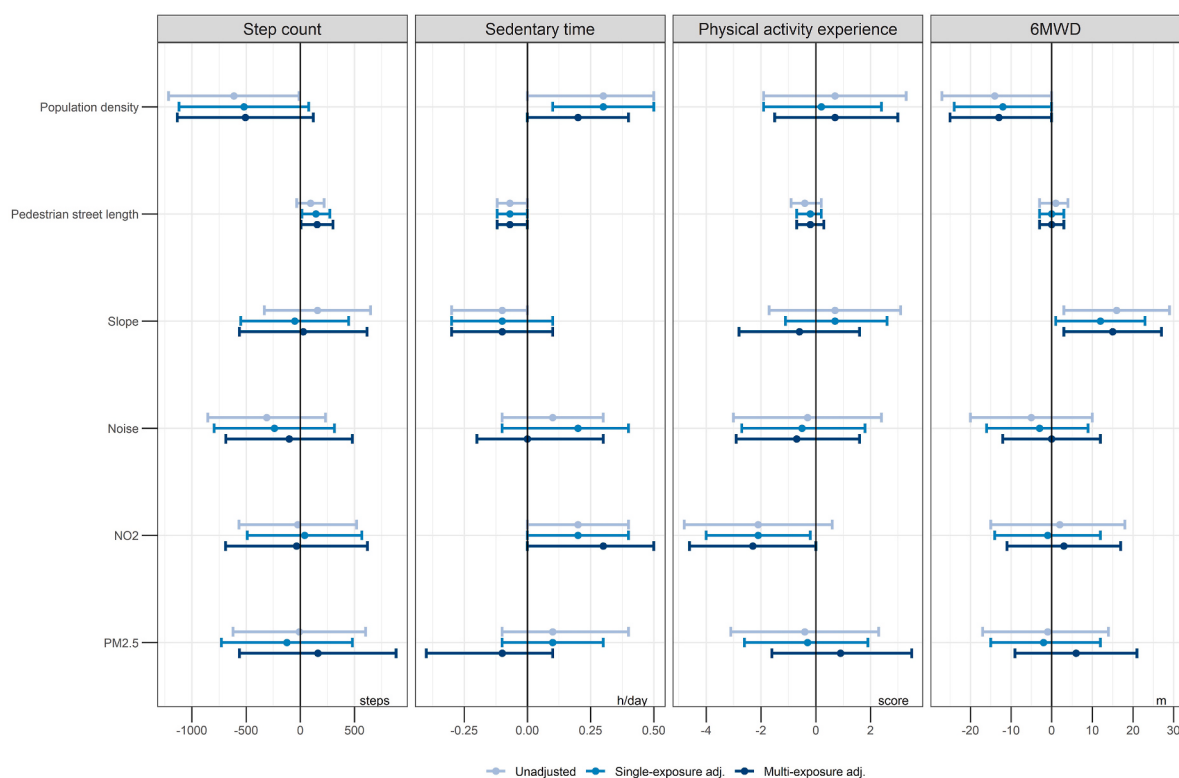


Fig. 2. Associations between the urban environmental factors, and objective physical activity, physical activity experience and functional exercise capacity in 387 patients with mild-to-very severe COPD.

See values in Appendix, Table A1.

Unadjusted models are mixed-effects linear regression models with a random intercept for city. Single-exposure models were adjusted for age, sex, socioeconomic status, urban vulnerability index, %predicted of FEV₁, CCQ mental score, exacerbation with hospital admission in previous 12 months and anxiety. Multi-exposure models were additionally adjusted for all other environmental exposures simultaneously.

6MWD: 6-min walk distance; NO₂: nitrogen dioxide; PM: particulate matter.

elements such as stairs and ramps indeed increased the exercise intensity in COPD patients as reflected by oxygen uptake (i.e., $\dot{V}O_2$), supporting the hypothesis that walking on hills can have a training effect. Evidence from the rehabilitation field shows that downhill walking training can positively affect leg strength in healthy participants (Rodio and Fattorini, 2014) and speed the response to rehabilitation in COPD patients (Camillo et al., 2020), attributable to the increased eccentric activity in the quadriceps femoris muscle (Camillo et al., 2015). Of note, the observed association in our study could be translated into an increase of 12.3 m in the 6MWD per an increase of 2.3° (which corresponds to a very gentle slope (Slope Steepness Index)). This effect appears relevant, given that a change of more than 30 m in the 6MWD is considered as clinically meaningful (Polkey et al., 2013). We therefore argue that COPD patients who live in a hilly neighbourhood may benefit from a “continuous training effect” and that slope has the potential to increase functional exercise capacity in these patients, which would impact in their regular physical activity (Troosters et al., 2019).

Our results showed that higher NO₂ was associated with more sedentary time and the experience of more difficulty with physical activity. These effects were consistent across different complementary and sensitivity analyses, which reinforces their plausibility, and is in line with the established harmful effects of NO₂ as an irritant to the human airways (Federal Register, 2018). However, when we excluded subjects with extreme values, the associations were attenuated suggesting that extremely high NO₂ levels may be especially harmful and drive the observed association. Several mechanisms are conceivable to explain how long-term air pollution in general could influence physical activity and capacity in COPD patients: First, higher levels of air pollution could increase dyspnoea in COPD patients (Schraufnagel et al., 2019). To

avoid the feeling of breathlessness, COPD patients often reduce exertion which leads to deconditioning with a decline in functional exercise capacity and further dyspnoea (Ramon et al., 2018; Reardon et al., 2006); increased pollution could thus trigger the ‘vicious circle of dyspnoea and inactivity’ (Ramon et al., 2018; Reardon et al., 2006). While the sample size and lack of repeated measurements precluded a formal mediation analysis, we found that the effect of NO₂ on sedentary time and C-PPAC difficulty score was attenuated when we added dyspnoea to the analysis, which indirectly supports this hypothesis. Second, patients may be aware of the potential harms associated with air pollution and may therefore avoid to walk in neighbourhoods with more intense traffic (Exercise and air quality: 10 top tips - European Lung Foundation). Finally, exacerbations and hospital admissions due to air pollution could lead to a decrease in physical activity and functional exercise capacity (Alahmari et al., 2014; Demeyer et al., 2018). However, the fact that the association persisted in our models which adjusted for acute COPD exacerbations with hospital admission in the previous twelve months, suggests that the latter mechanism is only of secondary importance.

Of interest, only NO₂ (an indicator of traffic related air pollution) was associated with physical activity in our study while PM_{2.5} (indicator of pollution more generally) was not. Whether this was due to the fact that NO₂ levels deviated more than PM_{2.5} levels from the WHO and EU recommendations, that NO₂ could be a surrogate for pollution with other traffic related constituents such as NO_x, O₃ and ammonium nitrate aerosols thereby reflecting a higher true burden (Johannson et al., 2015; Schraufnagel et al., 2019), or that NO₂ could exert a specific (and more harmful) effect in COPD patients (Dadvand et al., 2014a; Lepeule et al., 2014; Morrow et al., 1992) remains speculative.

We found no association between noise and any of the physical

activity or capacity variables. To our knowledge no study has assessed this association in COPD patients so far. A few studies have previously explored this association in the general population and observed that noise and noise annoyance (Dzhambov et al., 2017; Foraster et al., 2016; Roswall et al., 2017) were negatively associated with physical activity, particularly among patients with a chronic disease. Unfortunately, we do not have any information on noise annoyance for the present study. Whether noise levels alone are not sensitive enough to determine an effect on physical activity in COPD patients or whether noise has less impact on COPD patients due to their underlying disease, will need to be addressed in future studies. The low correlation between noise and air pollutants may seem surprising and could raise doubts on the validity of noise measures. However, it is not unexpected based on the existing literature. Although engine combustion of vehicles is a common source for both noise and air pollution, factors such as road layout and urban planning and a different propagation mode have been shown to impact their exposure levels (Stansfeld, 2015).

Our findings have implications for research, clinical management and urban health policy. First, previous research on the environment was mostly focusing on the general population whilst often ignoring patients with a chronic condition who represent around 35% of the current city population in Europe (Eurostat), something to address in future studies. Second, research on physical activity interventions needs to consider the importance of calibrating the specific role of the environment in the physical activity with the needs of COPD patients and eventually of subjects with other chronic conditions. Specifically, it will be interesting to explore further the likely 'utilitarian' role of pedestrian streets (i.e., higher density of stores, shops and services) (Sugiyama et al., 2012) as well as features of the micro-scale environment (e.g., the availability and condition of benches) (Steinmetz-Wood et al., 2020)) and how these can be integrated into interventions to promote physical activity. Third, the patients' feelings of vulnerability associated with the chronic disease (such as breathlessness or shame to be seen with limited mobility in COPD) may counteract the positive effects of environmental factors (e.g., liveable streets) observed in the general population. The clinical management of COPD patients will need to address such potential barriers to physical activity (especially in those with mental health issues), and advise patients to consider walking in hilly neighbourhoods (to improve functional exercise capacity) and in less polluted areas or hours (to increase the physical activity and mitigate the negative effects of traffic related air pollution) (Carlsten et al., 2020). Finally, urban health policy must aim for an environment which is adequate (e.g., walkable yet not too crowded) for the specific needs of patients with a chronic disease such as COPD and for rigorous control of air pollution. The chronic disease certainly entails a particular lens through which the environment is perceived and which influences patients' behaviour. The understanding of this lens should be at the forefront of future research, COPD management and policy measures.

One of the strengths of our study is the novelty of our research question in COPD patients. We recruited patients with a broad range of COPD severities from several primary care and hospital centres which increases the external validity of our findings. We included a range of objectively measured variables to characterise both the exposures and the outcomes thereby reducing information bias. The use of LUR models for air pollution and geocoding of the home address allowed us to assess individual-level exposure and gain further insight into the distinct roles of NO₂ and PM_{2.5}. The multi-exposure models allowed us to control for residual confounding by the other environmental factors and to assess the specific effect of the factors within the overall neighbourhood context.

A limitation of the present study is that some features of the environment which may also influence physical activity behaviour (neighbourhood safety, design, street connectivity, land use mix, facility or residential density) (Cerin et al., 2018; Frank et al., 2005; Salvo et al., 2018; Udell et al., 2014) were not available in our dataset. [Of note, we did not include greenspace variables in our analyses because these had

been assessed and reported for this patient cohort previously (Arbillaga-Etxarri et al., 2017).] Moreover, we do not report other common pollutants such as PM₁₀ or O₃. Indeed, we decided a priori to focus on NO₂ and PM_{2.5} under the hypothesis that they capture well traffic related air pollution and urban pollution more generally. Secondly, the exposure variables data was not directly measured in our study, but obtained from external sources, and there may be some misclassification due to temporal variations. Specifically, population density, pedestrian street length, slope and annual average noise levels referred to a fixed time point ranging from 1 year before to 1 year after data collection. We consider improbable this has biased our estimates as these variables are stable over time in the absence of major urban changes or migration waves and unlikely to change during such short study period. Therefore, these exposure estimates are probably representative of exposure prior to the study. Thirdly, the use of annual residential averages does not allow us to accurately estimate the real exposure to e.g., air pollutants or noise during physical activity. Particularly, if patients living in more polluted/noisy areas used to practice physical activity in the evenings when pollution and noise are lower, our estimates of exposure would be higher than the real, and this would be underestimating the real association between exposures and physical activity. Fourthly, it could be speculated that some of the environmental factors assessed could act more as a mediator than as an independent risk factor themselves (e.g., higher population density may lead to more air pollution and noise). However, the associations of the individual factors were similar in the single-exposure and multi-exposure models. Finally, our design limits conclusions on directionality of the associations and also makes it difficult to rule out self-selection bias concerning the choice of the residential neighbourhood. However, the relatively low socioeconomic status of our sample makes it unlikely that our patients moved due to their COPD.

5. Conclusion

In conclusion, population density, pedestrian street length, slope and NO₂ exposure relate to physical activity and exercise capacity of COPD patients living in highly populated areas. These neighbourhood environmental factors should be considered in clinical contacts with patients and when developing urban and transport planning policies that aim to promote physical activity in patients with chronic diseases.

Author contributions (credit roles)

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Data statement

Data contain potentially identifying variables. For example, built environment variables together with sociodemographics and clinical conditions could allow identification of patients in some geographic areas. Therefore, data cannot be made publicly available according to the Regulation (EU) 2016/679 of the European Parliament and of the Council of April 27, 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data. The corresponding author and the Coordination and Research Management Office of the Projects Unit (research.management@isglobal.org) could provide, upon request, individual participant data that underlie some of the results reported in this article (except variables that may allow identification of patients), after applying necessary measures to guarantee that no individual is identified or identifiable.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Elena Gimeno-Santos reports a relationship with Chiesi and Boehringer Ingelheim that includes: speaking and lecture fees. Judith Garcia-Aymerich reports a relationship with AstraZeneca that includes: consulting or advisory and speaking and lecture fees. Judith Garcia-Aymerich reports a relationship with Esteve and Chiesi that includes:

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envres.2022.113956>.

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