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Restrictive spirometry pattern is associated with low physical activity levels. A population based international study

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A B S T R A C T

Introduction: Restrictive spirometry pattern is an under-recognised disorder with a poor morbidity and mortality prognosis. We compared physical activity levels between adults with a restrictive spirometry pattern and with normal spirometry.

Methods: Restrictive spirometry pattern was defined as a having post-bronchodilator $FEV_1/FVC \geq$ Lower Limit of Normal and a FVC < 80% predicted in two population-based studies (ECRHS-III and SAPALDIA3). Physical activity was measured using the International Physical Activity Questionnaire. The odds of having low physical activity (< 1st study-specific tertile) was evaluated using adjusted logistic regression models.

Results: Subjects with a restrictive spirometry pattern (n = 280/4721 in ECRHS, n = 143/3570 in SAPALDIA) reported lower levels of physical activity than those with normal spirometry (median of 1770 vs 2253 MET·min/week in ECRHS, and 3519 vs 3945 MET·min/week in SAPALDIA). Subjects with a restrictive spirometry pattern were more likely to report low physical activity (meta-analysis odds ratio: 1.41 [95%CI 1.07–1.86]) than those with a normal spirometry. Obesity, respiratory symptoms, co-morbidities and previous physical activity levels did not fully explain this finding.

Conclusion: Adults with a restrictive spirometry pattern were more likely to report low levels of physical activity than those with normal spirometry. These results highlight the need to identify and act on this understudied but prevalent condition.

1. Introduction

Restrictive spirometry pattern is an under-recognised disorder with a poor morbidity and mortality prognosis [1–3]. It is characterised by reduced levels of both forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC), while the FEV_1/FVC ratio remains within normal ranges. This heterogeneous disorder is composed partly of subjects who exhibit reduced total lung capacity (TLC) (*truly* restrictive disease) but also includes subjects with normal TLC [4]. Its causes are diverse and include lung fibrosis, systemic inflammation, obesity and psychological health, among others [1,5]. The prevalence of restrictive spirometry pattern in adults is estimated to be between 5 and 10% [6,7], nearly as high as the prevalence of chronic obstructive pulmonary disease (COPD). In contrast to COPD, which is very well known and studied, restrictive spirometry pattern has only recently received any attention and there is no clear recommendation for its management [8].

Impaired quality of life [9], important functional limitations [10] and a higher risk of suffering cardiovascular events [11–13] have all been associated with restrictive spirometry pattern. Furthermore, an association between restrictive spirometry pattern and mortality has been consistently found across studies in different settings and using different definitions [1–3,14,15]. However, the underlying causes of these observed associations remain unknown.

We here hypothesize that reduced levels of physical activity in subjects with a restrictive spirometry pattern could be one potential pathway linking this condition to higher mortality, in particular from cardiovascular disease [3]. Indeed, low physical activity levels have been consistently associated with high mortality in general population samples from diverse geographical origins [16,17]. In some chronic respiratory diseases, low physical activity levels have been related to a worse prognosis in terms of exacerbations and mortality [18]. Therefore, studying physical activity levels in subjects with a restrictive spirometry pattern is timely as it may identify potentially modifiable factors that could affect the prognosis of this disorder.

The present study aimed to 1) describe current levels of physical activity in adults with a restrictive spirometry pattern, and 2) compare them to the physical activity levels found in adults with normal spirometry, using data from two population-based adult European studies.

2. Material and methods

2.1. Study design

This cross-sectional study used data from two prospective adult cohorts participating in the ALEC project (www.alecstudy.org): the European Community Respiratory Health Survey (ECRHS) [19] and the Swiss study on Air Pollution and Lung Disease in adults (SAPALDIA) [20]. Both studies collected information on lung function and physical activity using similar protocols and highly comparable questionnaires.

Details of both cohorts have been described elsewhere [19,20]. Briefly, ECRHS is a multi-centre cohort involving 46 centres in 25 countries, mostly across Europe (ECRHS I). Participants between 20 and 44 years of age were randomly selected from the population and complemented with a sample of subjects with asthma-related symptoms, the latter of which was excluded in the present analysis. Two follow-ups took place approximately 10 years (ECRHS II) and 20 years (ECRHS III) after the initial recruitment, which was in 1990–92. In SAPALDIA, random samples of the population (between 18 and 60 years of age) were recruited in 1991 in eight communities in Switzerland. Participants were followed-up in 2001 and 2011 (SAPALDIA 1, 2 and 3).

The current analysis uses data collected at the last follow-up of both ECRHS and SAPALDIA, where physical activity was measured using an internationally validated questionnaire. We excluded the symptomatic sample (in ECRHS) and subjects with obstructive spirometry (in both studies). Written informed consent was obtained from all participants and the studies were approved in each participating centre by the appropriate institutional ethics committees.

2.2. Lung function measurement

Lung function was measured using NDD Easyone spirometers in both studies. In ECRHS, measurements reproducible to 150 mL from at least two of a maximum of five correct manoeuvres were included, following American Thoracic Society recommendations [21]. In SAPALDIA, measurements reproducible within 5% and with less than 100 ml difference were included. We derived the percent value predicted for FVC and the Lower-Limit of Normal (LLN) for the FEV_1/FVC ratio using study-specific equations [9,22]. A restrictive spirometry pattern was defined as having a post-bronchodilator $FEV_1/FVC \geq$ LLN and a FVC < 80% predicted [7].

Subjects with neither a restrictive nor an obstructive (post-bronchodilation FEV_1/FVC < LLN) pattern were defined as having normal spirometry.

2.3. Outcome: physical activity

Physical activity was assessed using two measures. First, we used the International Physical Activity Questionnaire (IPAQ) which has been validated in multiple international settings and population groups

Abbreviations

BMI	Body mass index
ECRHS	European Community Respiratory Health Survey
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
IPAQ-LF	International Physical Activity Questionnaire Long Form
IPAQ-SF	International Physical Activity Questionnaire Short Form
LLN	Lower limit of normal
MET	Metabolic Equivalent of Task
OR	Odds ratio
SAPALDIA	Swiss study on Air Pollution And Lung Disease In Adults

[23] and has two versions: the IPAQ-SF short form (used in ECRHS) and the IPAQ-LF long form (used in SAPALDIA). Both IPAQ versions collect information on the time spent walking and doing physical activity at different intensities in the previous week. From these questions, we obtained continuous measures of Metabolic Equivalents of Task (MET)·min per week, using the official IPAQ scoring protocol (www.ipaq.ki.se). The MET is an intensity unit of physical activity determined as the ratio between the metabolic rate during a given activity over the resting metabolic rate. Physical activity volume (in MET·min/week) in walking, moderate and vigorous physical activity was calculated as the multiplication of the time spent doing each activity during a week and the intensity of this activity. Total physical activity was calculated as the sum of all components. Because the IPAQ-LF includes more detailed questions than the IPAQ-SF, all physical activity estimates from the IPAQ-LF (used in SAPALDIA) are expected to be higher than those from the IPAQ-SF (used in ECRHS) [23]. Thus, we defined study-specific tertiles of walking, moderate, vigorous and total physical activity. Subjects in the lowest tertile were classified as having "low physical activity".

Second, because the physical activity levels derived from the two different IPAQ versions cannot be directly compared, a second definition was used, which is not validated but is homogeneous across the two studies. Using identical questions, both the ECRHS and SAPALDIA collected information on how often (frequency) and for how many hours per week (duration) participants usually exercised so much that they got out of breath or sweaty. Individuals were categorised as active if they exercised with a frequency of 2–3 times a week or more and with a duration of about 1 h a week or more, as previously published [24,25]. Participants were defined as having "low physical activity" otherwise.

2.4. Body weight and composition

Body Mass Index (BMI) was calculated from measured height and weight, and categorised into normal, overweight and obese, according

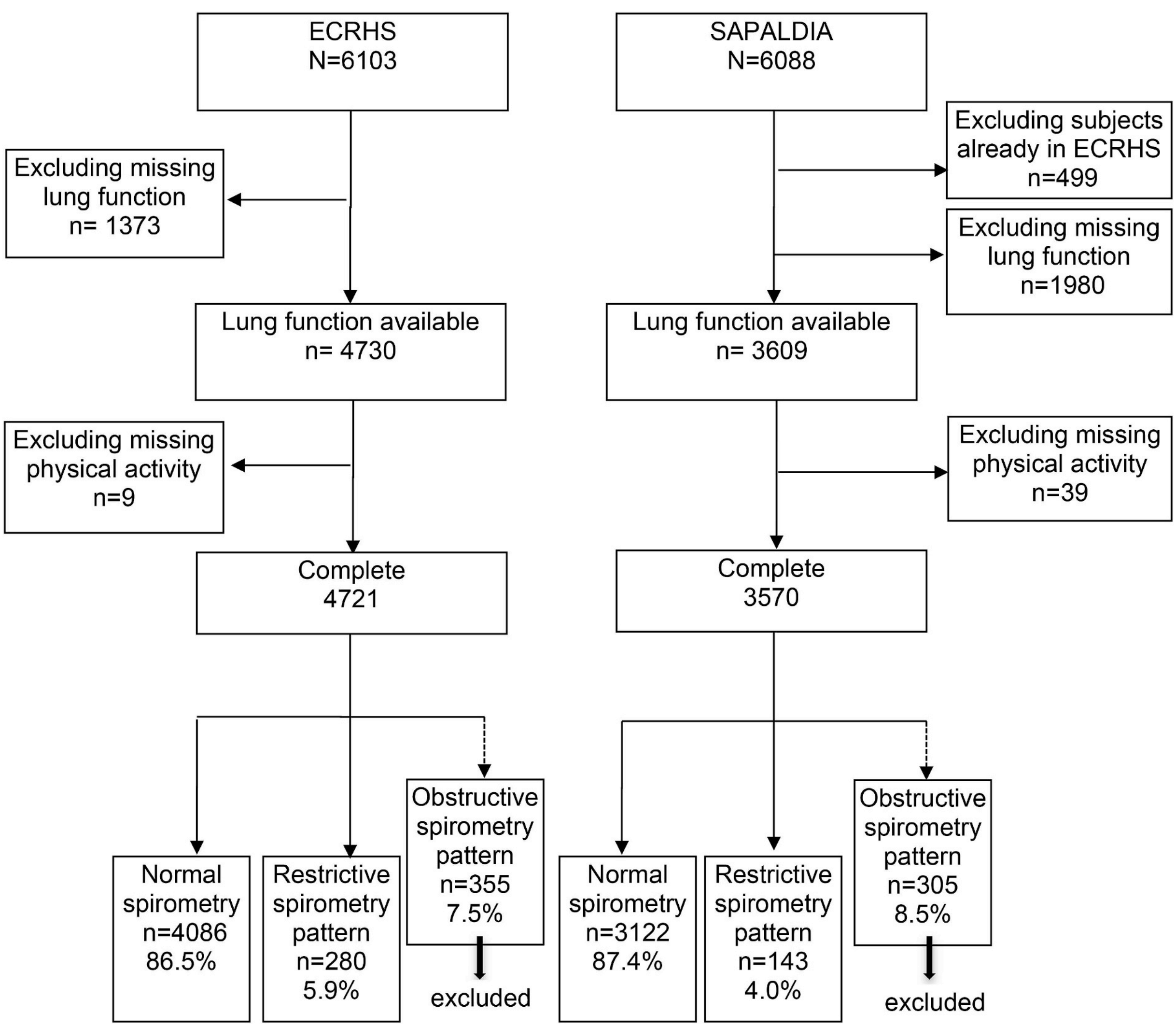

Fig. 1. Study flow-chart.

to the World Health Organization's classification [26]. In ECRHS, fat mass and fat free mass were derived from measurements of resistance and reactance provided by bioimpedance using the equations developed by Sun et al. [27].

2.5. Other relevant covariates

Information on the characteristics (age, sex, education, smoking status and passive smoking), current (within the last 12 months) respiratory symptoms (asthma attack, wheezing, woken with tight chest, woken by attack of shortness of breath, woken by attack of coughing and avoiding exercise because of breathing problems), chronic respiratory symptoms (ever asthma, chronic bronchitis and chronic cough) and diagnosed chronic conditions (diabetes, heart disease, depression, stroke and hypertension) of the participants was collected using questionnaires. Previous levels of physical activity (frequency and duration of vigorous physical activity and active status) were also available from surveys conducted 10 years before.

2.6. Statistical analysis

We used medians and 25^{th}-75^{th} percentiles as well as absolute and relative frequencies to describe the physical activity levels among adults with a restrictive pattern and those with normal spirometry.

To compare the physical activity levels between these groups, we estimated the association between spirometry pattern (restrictive pattern vs normal) and physical activity (low vs not low) using logistic regression. We assessed the odds of having low physical activity

Table 1
Subject characteristics according to study and spirometry patterns.

	ECRHS			SAPALDIA		
	Normal spirometry	Restrictive spirometry pattern	p-value	Normal spirometry	Restrictive spirometry pattern	p-value
	n (%)/m (sd)	n (%)/m (sd)		n (%)/m (sd)	n (%)/m (sd)	
Sex Female	2152 (53%)	150 (54%)	0.769	1522 (49%)	81 (57%)	0.065
Age (years)	53.8 (7.0)	53.9 (7.1)	0.876	58.4 (10.9)	60.8 (11.2)	0.011
BMI			< 0.001			< 0.001
Underweight (< 18.5 kg/m^2)	27 (0.7%)	2 (0.7%)		34 (1.1%)	3 (2.1%)	
Normal (18.5–24.9 kg/m^2)	1548 (38.0%)	79 (28.6%)		1311 (42.0%)	41 (28.7%)	
Overweight (25.0–29.9 kg/m^2)	1668 (41.0%)	81 (29.3%)		1230 (39.4%)	54 (37.8%)	
Obese (≥30 kg/m^2)	826 (20.3%)	114 (41.3%)		547 (17.5%)	45 (31.5%)	
Education			0.066			0.001
Low	302 (7.6%)	26 (9.6%)		156 (5.0%)	6 (4.2%)	
Medium	1308 (33.1%)	104 (38.2%)		1995 (63.9%)	113 (79.0%)	
High	2346 (59.3%)	142 (52.2%)		970 (31.1%)	24 (16.8%)	
Smoking status			0.425			0.805
Never smoker	1733 (42.4%)	115 (41.1%)		1402 (44.9%)	66 (46.2%)	
Exsmoker	1636 (40.0%)	105 (37.5%)		1237 (39.6%)	53 (37.1%)	
Current smoker	696 (17.0%)	58 (20.7%)		482 (15.4%)	24 (16.8%)	
Smoking (Pack-years)	9.6 (16.9)	12.5 (17.9)	0.007	10.7 (17.7)	15.5 (23.6)	0.002
Total energy intake (Kcal/day)	2943 (1029)	2986 (1223)	0.577	2160 (937)	2079 (891)	0.444
Exposed to passive smoking (last 12 mo)	677 (16.7%)	72 (25.9%)	< 0.001	360 (11.5%)	24 (16.8%)	0.057
Ever exposed to vapour, gas, dust or fumes[a]	616 (22.7%)	29 (16.5%)	0.055	524 (17.2%)	25 (17.9%)	0.837
Low physical activity 10-years before	1962 (61.4%)	145 (68.1%)	0.052	1907 (67.2%)	97 (77.0%)	0.021
Respiratory symptoms						
Any asthma attacks (last 12 mo)	139 (3.4%)	23 (8.3%)	< 0.001	75 (2.4%)	5 (3.5%)	0.408
Wheezing/whistling (last 12 mo)	681 (16.7%)	104 (37.1%)	< 0.001	309 (10.0%)	29 (20.4%)	< 0.001
Woken with tight chest (last 12 mo)	421 (10.4%)	43 (15.4%)	0.009	316 (10.2%)	17 (11.9%)	0.525
Woken by attack of SOB (last 12 mo)	209 (5.2%)	33 (12.0%)	< 0.001	106 (3.4%)	10 (7.0%)	0.023
Woken by attack of coughing (last 12 mo)	1138 (27.9%)	102 (36.7%)	0.002	591 (19.2%)	31 (21.7%)	0.460
Avoid vigorous exercise[b] (last 12 mo)	115 (3.1%)	32 (12.1%)	< 0.001	44 (1.4%)	5 (3.6%)	0.043
Chronic cough[c]	258 (6.8%)	25 (9.7%)	0.069	137 (4.4%)	12 (8.4%)	0.025
Dyspnea[d]	119 (2.9%)	25 (8.9%)	< 0.001	NA	NA	
Lung function						
Post-bronchodilator FEV_1 (L)	4.2 (0.9)	3.0 (0.7)	< 0.001	3.1 (0.8)	2.2 (0.6)	< 0.001
Post-bronchodilator FVC (L)	3.3 (0.7)	2.4 (0.6)	< 0.001	4.2 (1.0)	3.0 (0.8)	< 0.001
FEV_1/FVC	0.78 (0.05)	0.80 (0.05)	< 0.001	0.74 (0.05)	0.74 (0.07)	0.614
Ever had been diagnosed with the following conditions:						
Asthma	435 (10.7%)	48 (17.1%)	0.001	330 (10.6%)	24 (16.8%)	0.019
Chronic bronchitis[e]	192 (5.1%)	20 (7.5%)	0.090	74 (2.4%)	14 (9.9%)	< 0.001
Other lung disease[f]	290 (7.8%)	25 (9.4%)	0.328	NA	NA	
Heart disease	93 (2.5%)	19 (7.1%)	< 0.001	NA	NA	
Stroke	33 (0.8%)	6 (2.2%)	0.022	43 (1.4%)	2 (1.4%)	0.973
Hypertension	858 (21.1%)	107 (38.2%)	< 0.001	841 (27%)	62 (43.7%)	< 0.001
Diabetes	163 (4.4%)	38 (14.3%)	< 0.001	176 (5.6%)	20 (14.1%)	< 0.001
Cancer	201 (5.0%)	20 (7.1%)	0.108	235 (7.9%)	9 (6.6%)	0.575
Rheumatoid arthritis	130 (3.2%)	14 (5.0%)	0.109	140 (4.5%)	6 (4.3%)	0.887
Depression	600 (14.8%)	61 (21.9%)	0.002	NA	NA	

m: mean sd: standard deviation. SOB: shortness of breath. mo: month. NA: Not Available in this study. P-values from chi^2 test (categorical) and anova (continous).

[a] Occupational exposure to vapour, gas, dust and fumes.

[b] Avoid taking vigorous exercise because of breathing problems.

[c] Cough during the day or at night on most days for at least 3 months each year and at least 2 years.

[d] Dyspnea: Dyspnea grade 2 (MMRC Dyspnea Scale).

[e] Doctor-diagnosed chronic bronchitis.

[f] Excluding asthma, chronic bronchitis, COPD and emphysema.

(defined as (1) being in the lowest study-specific tertile of MET·min/week of total physical activity, and (2) being low physically active according to frequency and duration questions) in subjects with a restrictive spirometry pattern compared to those with normal spirometry (reference group). Centre was included as a random effect in order to account for the correlation among individuals within the same area. Models were adjusted for potential confounders if these were significantly associated with the exposure (i.e. spirometry pattern). Tested confounders were: BMI, education, smoking status, pack-years, passive exposure to smoking, reported physical activity at previous survey and each of the available chronic conditions. The linearity of the association for continuous variables (BMI, age and pack-years) was examined using generalised additive models (GAM). Pooling of data from the two studies was not warranted due to some differences in variable definitions. Therefore, study-specific estimates were meta-analysed to obtain a combined estimate. We stratified analyses by BMI, smoking status and gender to assess possible effect modification.

Several sensitivity analyses were performed: (1) GLI equations [28] were used rather than study-specific equations to define spirometry patterns; (2) a cut-off of < 2000 MET·min/week was used to define low physical activity levels in both studies instead of the study-specific lowest tertiles; (3) asthmatics were excluded; (4) subjects with respiratory symptoms were excluded; (5) models were adjusted for percent fat-mass (only available in the ECRHS) to rule out potential residual confounding by obesity; (6) pre-bronchodilator spirometry data were used to define spirometry patterns, thus increasing the number of participants with a restrictive spirometry pattern; and (7) loss of participants from ECRHS I to ECRHS III was corrected for using inverse probability weighting, with the probability weights estimated from a logistic regression having as the outcome "participation to ECRHS III" and as the exposures: age, sex, asthma, smoking status, education, BMI, attack of shortness of breath in the last 12 months, breathing difficulties and dyspnoea, all assessed at ECRHS 1.

3. Results

3.1. Sample characteristics

A total of 4721 ECRHS participants and 3570 SAPALDIA participants had lung function and physical activity data available (Fig. 1).

In both studies, the participants included in the analysis were younger, leaner, more highly educated and less likely to smoke than the initial sample. There were 280 (5.9%) and 143 (4.0%) participants with a restrictive spirometry pattern and 355 (7.5%) and 305 (8.5%) participants with an obstructive spirometry pattern in ECRHS and SAPALDIA, respectively. In both studies, subjects with a restrictive spirometry pattern were more likely to be obese, have a lower level of education, have current respiratory symptoms (wheezing, attack of cough, tight chest) and report a diagnosis of hypertension or diabetes, compared to subjects with normal spirometry. There were no differences in terms of smoking status (Table 1).

3.2. Overall physical activity levels and by spirometry pattern

The median total physical activity level was 2146 (P_{25}—P_{75} = 1023–4158) MET·min/week in ECRHS (from the IPAQ-SF) and 3908 (P_{25}—P_{75} = 2041–7344) MET·min/week in SAPALDIA (from the IPAQ-LF). The main source of total physical activity was 'walking' in ECRHS and 'moderate activity' in SAPALDIA. The proportion of subjects who exercised less than 2 times a week and with a duration of less than 1 h ranged between 55% in the normal spirometry group from ECRHS to 80% in the restrictive spirometry pattern group from SAPALDIA (Table 2).

In ECRHS, subjects with a restrictive spirometry pattern reported significantly lower levels of physical activity than subjects with normal spirometry. In SAPALDIA, these differences were only apparent for total physical activity. The proportion of subjects classified as having low physical activity was higher among participants with a restrictive spirometry pattern compared to those with normal spirometry, using both methods to define low physical activity.

Table 2
Distribution of the physical activity variables by study and spirometry patterns.

	ECRHS			SAPALDIA		
	Normal spirometry	Restrictive spirometry pattern	p-value	Normal spirometry	Restrictive spirometry pattern	p-value
Physical Activity measured by IPAQ						
Walking (MET·min/week[a]), median (P_{25}—P_{75})	792 (346.5–1584)	693 (256–1386)	0.025	1089 (396–2376)	1188 (198–2310)	0.434
Moderate activity[b] (MET·min/week[a]), median (P_{25}—P_{75})	360 (0–960)	240 (0–720)	0.068	1740 (630–3780)	1440 (480–3563)	0.157
Vigorous activity (MET·min/week[a]), median (P_{25}—P_{75})	240 (0–1440)	0 (0–960)	0.004	0 (0–1440)	160 (0–960)	0.498
Total physical activity (MET·min/week[a]), median (P_{25}—P_{75})	2253 (1116–4158)	1770 (693–3205)	< 0.001	3945 (2070–7494)	3519 (1584–6732)	0.096
Low physical activity (< 1st tertile of total physical activity[c]), n (%)	962 (32.8%)	94 (46.8%)	< 0.001	655 (32.1%)	32 (37.6%)	0.280
Physical activity measured by questions on frequency and duration of leisure-time vigorous physical activity						
Frequency of exercise, n (%)			0.002			0.476
Never/ < 1month	1465 (36.0%)	130 (46.8%)		1376 (44.7%)	72 (50.7%)	
1/week	694 (17.1%)	44 (15.8%)		686 (22.3%)	31 (21.8%)	
2–3 times/week	1243 (30.6%)	75 (26.9%)		756 (24.6%)	28 (19.7%)	
4 + times/week	667 (16.4%)	29 (10.4%)		261 (8.5%)	11 (7.7%)	
Duration of exercise, n (%)			< 0.001			0.137
< 1 h	1512 (37.8%)	131 (47.6%)		1519 (49.6%)	83 (58.0%)	
1–3 h	1652 (41.3%)	111 (40.4%)		1319 (43.0%)	52 (36.4%)	
4 h or more	832 (20.8%)	33 (12.0%)		226 (7.4%)	8 (5.6%)	
Low physical activity (< 2 times or < 1 h/week), n (%)	2210 (55.3%)	179 (65.3%)	< 0.001	2194 (72.0%)	113 (79.6%)	0.047

MET: metabolic equivalent of task. IPAQ: International Physical Activity Questionnaire. P-values from Kruskal-Wallis rank test (continous) and chi^2 (categorical).

[a] As a reference, WHO recommendation of 75 min/week of vigorous activity is equivalent to 1200 MET·min/week, and 150 min/week of moderate activity are equivalent to 600 MET·min/week.

[b] Not including walking.

[c] < 1390 MET·min/week in ECRHS; < 2550 MET·min/week SAPALDIA.

3.3. Associations between restrictive spirometry pattern and low physical activity

Subjects with a restrictive spirometry pattern had higher odds of reporting low physical activity than those with normal spirometry in the study-specific analyses and the meta-analysis, for both definitions of low physical activity (Fig. 2).

When the models were stratified by BMI, this association was strongest among overweight (but not obese) individuals, although the interaction term was not significant (Fig. S1). There was no consistent evidence for effect modification by gender or smoking status (Fig. S1), but due to the small number of subjects in each subgroup of these stratified analyses, the confidence intervals are large.

No differences in the estimates were observed in any of the sensitivity analyses tested (Fig. S2), except in a single case when using the GLI equations in SAPALDIA. However, the confidence intervals for this association were wide as the number of subjects with a restrictive spirometry pattern was much lower when defined using the GLI equations (n = 53) compared to when using the study-specific lung reference equations (n = 143). Nevertheless, the overall combined estimate remained significantly positive.

4. Discussion

Using data from two large European multi-centre population based studies, we found that physical activity levels were significantly lower among subjects with a restrictive spirometry pattern compared to those with normal spirometry. This paper is the first to explore physical activity levels in those with a restrictive spirometry pattern in a population setting, even though five percent of the population has this condition and it is known to be related to morbidity and mortality. The association observed was independent of age, smoking, co-morbidities, total body mass, fat mass and the presence of respiratory symptoms.

4.1. Main findings

Physical activity levels in subjects with a restrictive spirometry pattern were relatively low. The median total physical activity was 1770 MET·min/week in ECRHS, using the IPAQ-SF, and 3519 MET·min/week in SAPALDIA, using the IPAQ-LF. These values are lower than the corresponding medians of 2514 and 3699 MET·min/week observed in the international validation in adults of the IPAQ-SF and IPAQ-LF, respectively [23]. It is worth noting that the participants in our analysis with a restrictive spirometry pattern barely performed any vigorous physical activity, with median values of 0 MET·min/week in ECRHS and 160 MET·min/week in SAPALDIA. As reference values, the World Health Organization recommends 75 min/week of vigorous activity and 150 min/week of moderate activity, which are equivalent to 1200 MET·min/week and 600 MET·min/week, respectively [29]. Worryingly, because both of the IPAQ versions have been reported to overestimate physical activity levels [23,30,31], it is likely that the true physical activity levels in our study population are lower than reported here. Finally, the lower IPAQ-derived physical activity levels observed in ECRHS compared to SAPALDIA are likely due to the different questionnaire versions used. Indeed, when using the questions about frequency and duration of physical activity, which are identical in both cohorts, the SAPALDIA participants (who are slightly older) reported lower physical activity levels.

Our finding that physical activity levels are lower among those with a restrictive spirometry pattern agrees with a previous report which was based on a small number (37) of cases. This previous work found a positive association between having a restrictive spirometry pattern and physical inactivity measured by accelerometer [32]. Cross-sectional studies have also identified that other constructs related to

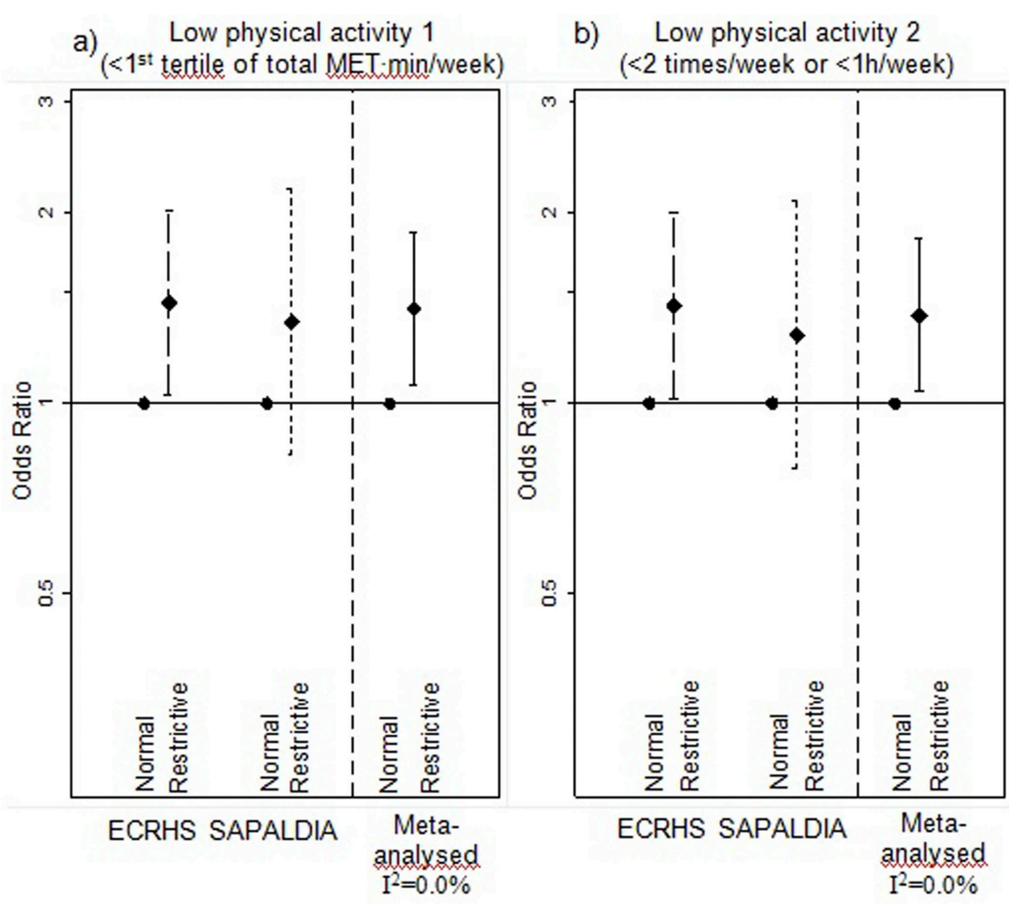

Fig. 2. Odds ratios (OR) and 95% confidence interval for low physical activity in subjects with a restrictive spirometry pattern compared to those with a normal spirometry pattern (reference group), in ECRHS (dashed line), SAPALDIA (dotted line) and the meta-analysis (solid line).
Lowest study-specific tertile in ECRHS: < 1390; in SAPALDIA: < 2550 MET·min/week. OR adjusted for age, sex, ever diagnosed with diabetes, being physically active in previous follow-up and BMI (all models), and, when appropriate, smoking, education, diagnosis of depression, hypertension, stroke or heart disease (see full model in Supplemental Table S1).

physical activity, such as exercise performance and the physical component of quality of life, are reduced in subjects with a restrictive spirometry pattern [9,14], which supports the plausibility of our results.

Our study goes beyond previous work by demonstrating that these differences in physical activity levels are unlikely to be due to confounding by age, smoking, obesity or other health conditions.

There are several potential explanations for the associations we observed. First, subjects with a restrictive spirometry pattern have a high prevalence of chronic respiratory symptoms [1], which may lead them to reduce their physical activity levels in order to avoid symptoms. However, our results remained after excluding subjects with respiratory symptoms. Second, confounding by overweight and obesity is possible as both of these conditions are related to restrictive spirometry pattern and low levels of physical activity. However, the results did not change when we adjusted the models by either BMI or percent of fatmass. Third, subjects with a restrictive spirometry pattern might become breathless at lower workloads compared to subjects with normal spirometry, and may therefore reduce their physical activity to avoid breathlessness. Finally, lack of physical activity may lead to higher risk of restrictive spirometry pattern, rather than restrictive spirometry pattern leading to lower physical activity. Doing regular physical activity has been found to be associated with higher lung function levels [25,33], which could lower the risk of having a restrictive spirometry pattern. Although we adjusted the models for physical activity levels ten years prior, the cross-sectional design of our analysis prevents us from establishing the direction of the true causal pathway. Identifying whether low physical activity is a risk factor for the onset of restrictive spirometry pattern is an important question which, needs to be addressed in future longitudinal studies.

We did not observe convincing evidence for effect modification by smoking or sex. However, the stratified analyses had low statistical power which makes it difficult to draw firm conclusions. Future studies with more subjects in each group are needed. We observed a stronger association between having a restrictive spirometry pattern and low physical activity in overweight (but not obese) subjects, compared to those with normal weight. These results need to be interpreted with caution. First, the differences in the effect estimates are not very large and there is no evidence of statistical interaction. Second, despite combining the two study-specific estimates, statistical power to analyse associations within subgroups is still limited. Finally, obesity is known to be a risk factor for restrictive spirometry pattern but it is also known to be a cause and an effect of low physical activity levels. Assessing the inter-relations between these components may require more repeated valid measurements in larger cohorts.

4.2. Implications

Our study has important implications from the public health, clinical and research perspectives. First, our results add 'low physical activity' to the list of detrimental factors that are present in those with a restrictive spirometry pattern. Physical inactivity puts these subjects at risk of many chronic conditions and poor prognosis, and highlights the necessity of detecting this spirometry pattern even in the absence of respiratory symptoms. In the context of the increasing prevalence of overweight and obesity, restrictive spirometry pattern may become a major health concern in the future. Second, interventions encouraging physical activity in individuals with a restrictive spirometry pattern should be designed and tested. Having a restrictive spirometry pattern is associated with poor quality of life and functional limitation [9,10], therefore it is plausible that increasing one's physical activity could improve quality of life and stabilise decreases in lung capacity. Finally, our results suggest that physical inactivity may be behind the previously observed poor prognosis of restrictive spirometry pattern. Further research could elucidate the mechanisms underlying these observations and specifically, the role of overweight and obesity.

4.3. Strengths and limitations

Physical activity data collected using questionnaires is known to be subject to individual misclassification. However any imprecision in the self-assessment of physical activity by questionnaires, and also in the measurement of lung function, is likely to be non-differential, which would attenuate the results. Unfortunately the designs of the two studies were not exactly identical, therefore the odds ratios were estimated from subjects with slightly different age range and using a different set of confounders. The fact that our analysis was based on data from the second follow-up of the original studies could have resulted in a lower number of participants with a restrictive spirometry pattern than in the general population because of healthy-follow-up bias. This fact precludes the interpretation of the observed frequency of subjects with a restrictive spirometry pattern as a prevalence estimate. However, a potential healthy-follow up bias is unlikely to bias our results towards a positive finding. Indeed, repeating the analysis using an inverse-weighting method to correct for loss of follow-up in ECRHS did not change the results. The use of study-specific lung reference equations could be seen as a limitation since a different threshold was used to define restrictive spirometry pattern in each study. However, the methodology to derive the LLN and FVC %predicted was the same in both studies and allows reference equations to approach better the lung function distribution of each population. Further, the combined results in the sensitivity analysis using GLI equations remained unchanged. Finally, the analysis on the effect modification by BMI, sex and smoking were underpowered despite our large sample.

The strengths of our study include the use of post-bronchodilator lung function measurements to define restrictive spirometry pattern, which are less prone to misclassification compared to pre-bronchodilator measurements [7]. Second, we used two distinct methods for assessing physical activity levels. Both methods yielded the same conclusion, thereby increasing the validity of our study.

Thirdly, the large number of participants and the detailed questionnaires and clinical visits allowed us to correct for most potential confounders. Finally, our findings are likely to be generalisable given that we could capitalise on data from two large population-based studies.

5. Conclusion

In two large European studies, adults with a restrictive spirometry pattern had higher odds of low physical activity than those with normal spirometry. These results were independent of BMI or the presence of comorbidities and have important implications for the identification and management of this understudied but prevalent condition.

Declarations of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2018.11.017.

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