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## **Regular physical activity levels and incidence of restrictive spirometry pattern: a longitudinal analysis of two population-based cohorts**

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Running head: Physical activity and restrictive spirometry pattern

## **Abstract**

A restrictive spirometry pattern is associated with high morbidity and mortality. Whether practicing regular physical activity protects against this pattern has never been studied. We estimated the association between regular physical activity and the incidence of restrictive spirometry pattern. Forced expiratory volume in 1 second, forced vital capacity (FVC) and physical activity were assessed between 2000-2002 in the ECRHS (n=2,757, 39-67 years) and SAPALDIA (n=2,610, 36-82 years) population-based European cohorts, and again approximately 10-years later (2010-2013). Subjects with restrictive or obstructive spirometry pattern at baseline were excluded. We assessed the association of being active at baseline (defined as being physically active  $\geq 2$ -3 times/wk for  $\geq 1$  h) with restrictive spirometry pattern at follow-up (defined as a post-bronchodilator forced expiratory volume in 1 second /FVC ratio  $\geq$  Lower Limit of Normal and FVC < 80% predicted) using modified Poisson regression, adjusting for relevant confounders. After 10 years of follow-up, 3.3% of participants had developed restrictive spirometry pattern. Being physically active was associated with a lower risk of developing this phenotype (Relative Risk=0.76, 95% Confidence Interval=0.59-0.98). This association was stronger among those overweight and obese, compared to those with normal weight ( $P_{\text{interaction}}=0.06$ ). In two large European studies, adults practicing regular physical activity were at lower risk of developing restrictive spirometry pattern after 10 years.

**Keywords:** Physical activity, spirometry, restrictive spirometry, BMI, FVC

**Abbreviations:**

FVC: forced vital capacity, FEV<sub>1</sub>: forced expiratory volume in the first second, ECRHS: European Community Respiratory Health Survey, SAPALDIA: Swiss study on Air Pollution and Lung and Heart Diseases in adults, BMI: Body mass index, RR: Relative Risk, CI: confidence interval

Restrictive spirometry pattern is an under-recognised disorder associated with high morbidity and mortality (1-3). It is characterised by low forced vital capacity (FVC), with a preserved forced expiratory volume in the first second (FEV<sub>1</sub>)/FVC ratio. The prevalence of restrictive spirometry pattern varies according to the definition used, ranging between 5 and 10% in the US (3,4) and Europe (5,6). The determinants of restrictive spirometry pattern remain largely unknown.

We hypothesise that regular physical activity could be related to restrictive spirometry pattern incidence as physical activity has been consistently associated with higher lung function levels (7) and individuals with restrictive spirometry pattern were found to have low levels of physical activity in a cross-sectional multicenter analysis (8). The important health benefits of regular physical activity and the modifiability of this behaviour, combined with the largely unknown determinants of restrictive pattern incidence, makes this a highly relevant public health research question.

This study aimed to determine if regular physical activity was associated with the development of restrictive spirometry pattern using two population-based adult cohorts followed for 10 years.

## METHODS

### Study design

Longitudinal data collected from the European Community Respiratory Health Survey (ECRHS), involving 46 centres in 24 countries, and the Swiss study on Air Pollution and Lung Disease in adults (SAPALDIA), involving 8 centres in Switzerland, were used. Both studies followed a very similar protocol, using highly comparable questionnaires and procedures (9,10). The current analysis used data collected during

ECRHS II and SAPALDIA 2 (around 2000-2002) and approximately 10 years later during ECRHS III and SAPALDIA 3, hereon referred to as the baseline and follow-up examinations. Subjects lost to follow-up (25% of the baseline sample) were on average older and more likely to have a greater Body Mass Index (BMI), to report asthma and to be a smoker than subjects who were included, as previously published (11).

All participants with obstructive spirometry pattern at baseline or follow-up and participants with restrictive spirometry pattern at baseline (definitions below) were excluded. Written informed consent was obtained from all participants and the appropriate institutional ethics committees in each participating centre approved the study.

## Variables

Lung function was assessed by spirometry according to ATS recommendations (12). Details of the spirometers used in each centre are provided elsewhere (7). At baseline, pre-bronchodilator measurements were performed. At follow-up, spirometry was performed both pre- and post-bronchodilation (15 minutes after administering two 100µg puffs of salbutamol using a spacer). We derived the percent value predicted for FVC and the Lower-Limit of Normal for the FEV<sub>1</sub>/FVC ratio using study-specific equations (6, 13). A restrictive spirometry pattern was defined as having a post-bronchodilator FEV<sub>1</sub>/FVC  $\geq$  Lower-Limit of Normal and a FVC < 80% predicted, as done previously with these population-based data (8) to maximise sample size (5). An obstructive spirometry pattern was defined as FEV<sub>1</sub>/FVC < Lower-Limit of Normal. Subjects with neither a restrictive nor an obstructive spirometry pattern were defined as having normal spirometry.



Physical activity was assessed by questionnaire and reported at baseline. Subjects were categorized as being regularly active if they reported usual practice of vigorous physical activity 2-3 times a week or more and with a duration of about 1 hour or more, as done previously (7,8,14). All other participants were defined as non-active.

Information on baseline 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, depression, stroke and hypertension) of the participants was collected using questionnaires. BMI was derived using height and weight measured at baseline and follow-up and classified as normal (<25), overweight (≥25-30) and obese (30+) according to WHO classifications (15)

#### *Statistical analysis.*

As ECRHS and SAPALDIA share a very similar protocol, their recruitment was conducted at similar time-periods, and restrictive spirometry pattern incidence was comparable between studies in both genders, data were pooled to maximise statistical power. Pooling of data was further supported by the lack of differences in the obtained estimates and no evidence of heterogeneity when results were stratified by study and meta-analyzed (not shown).

We assessed the association between physical activity reported at baseline and new onset of restrictive spirometry pattern using modified Poisson regression, adjusting for

age, sex, smoking status, potential confounders that were significantly associated with both physical activity and restrictive spirometry pattern (education, BMI, passive smoke exposure, current and chronic respiratory symptoms, and chronic conditions) and baseline FVC levels. Statistical significance was set at  $P < 0.05$ . Centre was included as a random effect. Stratified analyses by sex, smoking, study and BMI were performed to detect possible effect modification.

The following sensitivity analyses were performed to assess the robustness of the results to assumptions about definitions, confounding and models: (1) GLI equations (16) were used to define restrictive spirometry pattern, (2) an additional adjustment for BMI change between baseline and follow-up was made, (3) asthmatics and (4) those who reported avoiding physical activity because of respiratory symptoms were excluded in separate analyses, and (5) lung function at first examination was removed as an adjustment variable. All analyses were done using Stata 14 (StataCorp, Texas, USA).

## RESULTS

A total of 5,293 participants (2,714 in ECRHS and 2,579 in SAPALDIA) were available after excluding subjects with a restrictive spirometry pattern at baseline (ECRHS  $n=166$ , SAPALDIA  $n=121$ ) and obstructive spirometry at any examination (ECRHS,  $n=422$ , SAPALDIA,  $n=612$ ). At follow-up, 173 (3.3%) subjects had developed a restrictive spirometry pattern.

Table 1 shows the participant characteristics at baseline by spirometry pattern at follow-up. Compared to participants with normal spirometry, those with new-onset restrictive spirometry pattern were more overweight or obese at baseline ( $P < 0.001$ ), had a higher prevalence of respiratory symptoms such as chronic cough, wheezing and waking with a

tight chest, and hypertension, and lower levels of FEV<sub>1</sub> and FVC (but not the FEV<sub>1</sub>/FVC ratio). Baseline characteristics according to physical activity are available in Web Table 1.

Being physically active at baseline was associated with a lower risk of having a restrictive spirometry pattern at follow-up (crude Relative Risk (RR)=0.60, 95% confidence interval (CI) 0.46,0.79, and adjusted RR=0.76, 95% CI 0.59,0.98, Figure 1).

There was no evidence of effect modification by smoking, sex or study (Figure 1).

However, analyses stratified by BMI groups suggested that the association between being active and new onset of restrictive spirometry pattern might be present only in those overweight (RR=0.43, 95% CI 0.24,0.78) and obese (RR=0.46, 95% CI

0.17,1.25). No association was found for normal weight subjects (RR=1.19, 95%CI

0.69,2.04). The  $P_{interaction}$  between overweight/obese vs normal weight and being active

was 0.06. No substantial differences in the estimates were observed for any of the

sensitivity analyses (Figure 2). However, the strength of the association was higher after

removing FVC levels at baseline from the model and lower after additionally adjusting

for change in BMI between the 2 examinations.

## DISCUSSION

This study reveals for the first time that regular physical activity was associated with a decreased risk of developing restrictive spirometry pattern after 10-years in two longitudinal European multi-centre cohorts. This association remained after adjusting for baseline lung function and relevant confounders such as active and passive smoking and the presence of respiratory symptoms.

Two previous cross-sectional studies have reported similar associations (8,17). Although the temporality of the observed associations could not be explored, these previous manuscripts suggested that restrictive spirometry pattern could reduce physical activity practice. Since our interest was on the association between physical activity and further restrictive spirometry pattern, we excluded all restrictive spirometry pattern cases at baseline and adjusted our analysis by baseline FVC to reduce any potential confounding of baseline lung function on physical activity (i.e. reverse causation).

Physical activity has been consistently associated with FEV<sub>1</sub> and FVC levels, and less so with their decline (7,18). We hypothesise that the relationship between physical activity and lung function could take on different clinical expressions (i.e., obstructive or restrictive spirometry pattern) depending on the individual distribution of health determinants, which could result in different associations between physical activity and FEV<sub>1</sub> and FVC. Supporting this hypothesis, physical activity appears to consistently protect against developing obstructive pattern among active smokers only (7,18). Since we did not observe any effect modification by smoking, we suggest that different mechanisms, than those involved in the obstructive pattern, may underlie the protective association between physical activity and the development of restrictive spirometry pattern.

Among the possible causes, restrictive spirometry pattern can be generally attributed to abnormalities, either in the lung itself (e.g., fibrosis) or outside of it (e.g., obesity, chest wall deformities), that impair one's ability to fully inflate the lungs. Thus, physical activity may exert its preventive action in relation to restrictive spirometry pattern development through mechanisms playing a role both inside and outside the lung. One

hypothesis is that physical activity prevents weight-gain in the aging population, whose lung function is in the declining phase. Indeed, weight-gain (BMI increase) has been associated with accelerated FVC decline over 10-years in adults (19), which could result in a higher risk of incident restrictive spirometry pattern. This hypothesis is not fully supported by our study because the association between physical activity and the incidence of restrictive spirometry pattern remained after adjustment by BMI changes during follow-up. However, we acknowledge that BMI may not appropriately reflect fat mass and that fat and lean mass have different impacts on lung function (20).

Another possible mechanism could be that regular physical activity prevents systemic inflammation. Indeed physical activity has anti-inflammatory effects (21) and systemic inflammation is associated with lower lung function (22). Furthermore, subjects with restrictive spirometry pattern have elevated levels of fibrinogen and C-reactive protein (23, 24), two markers of inflammation. In our study, associations were strongest among those overweight and obese (who have higher systemic inflammation (25)), possibly suggesting that the anti-inflammatory effects of physical activity may be most important in this high-risk population. However, we did not observe a similar association among smokers, another group with a high inflammatory burden. Further research is warranted to confirm or refute the systemic inflammation pathway as a viable mechanism to explain our findings.

A limitation of this study is that physical activity was assessed using questionnaires, which are likely subject to non-differential misclassification. Second, some subjects were lost to follow-up and they exhibited generally worse health at baseline, which may have introduced some bias in our estimates. Third, residual confounding is possible but

unlikely because most known relevant confounders were accounted for and unknown confounders are unlikely to account for all the observed estimate. Fourth, a single measurement of physical activity ten years prior incidence may lack precision and most likely bias our estimates towards the null. Fifth, we were unable to test whether BMI may be a mediating factor due to the small number of observed incident restrictive spirometry pattern cases. Finally, the exclusion of subjects with obstructive spirometry pattern, done to facilitate the interpretation of the results, may have lowered the statistical power because some subjects develop a mixed pattern (i.e., combination of obstructive and restrictive spirometry pattern).

Although we adjusted for baseline lung function and respiratory symptoms, we cannot exclude the possibility that reverse causation exists to some extent, for example, due to a potential association between early restrictive disease and exercise limitation leading to physical inactivity.

The strengths of the study are its longitudinal design and the combination of two large population-based cohorts with long follow-ups. Although the wide geographical distribution across Europe and the randomly selected participants make our results generalizable to diverse population subgroups, our findings should be replicated in other settings. Furthermore, high quality lung function data were available. In particular restrictive spirometry pattern was defined according to post-bronchodilator lung function measurements, which are subject to less misclassification than pre-bronchodilator measurements (5). The adjustment by baseline FVC to reduce reverse causation is a further strength. However, this strategy could have underestimated the magnitude of the association between physical activity and the development of

restrictive spirometry pattern (where lower FVC levels are associated with faster decline, the so-called horse-racing effect (26)).

From a public health perspective, our study provides an important message: restrictive spirometry pattern may need to be added to the list of disorders associated with low physical activity levels. Because having a restrictive spirometry pattern is associated with poor quality of life (6) and mortality (3), if regular physical activity can truly prevent its occurrence, it may also prevent hospitalisations and deaths.

In conclusion, in a large study across Europe, being physically active was associated with a reduced risk of developing restrictive spirometry pattern after 10-years. This result reinforces the importance of promoting regular practice of physical activity in the general population to improve general health and prevent disorders later in life.

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Table 1. Participant Characteristics at Baseline by Spirometry Pattern at Follow-up, ECRHS and SAPALDIA, Europe 2001-2011

| Baseline characteristics                          | Spirometry at Follow-up |       |              |             |       |               | <i>P</i> <sup>a</sup> |
|---------------------------------------------------|-------------------------|-------|--------------|-------------|-------|---------------|-----------------------|
|                                                   | Normal                  |       |              | Restrictive |       |               |                       |
|                                                   | No.                     | %     | Mean (SD)    | No.         | %     | Mean (SD)     |                       |
| Sex, Female                                       | 2,585                   | 50.5% |              | 100         | 57.8% |               | 0.058                 |
| Age                                               |                         |       | 46.57 (9.70) |             |       | 47.12 (10.38) | 0.494                 |
| BMI                                               |                         |       |              |             |       |               | <0.001                |
| Underweight                                       | 59                      | 1.2%  |              | 3           | 1.7%  |               |                       |
| Normal                                            | 2,555                   | 50.0% |              | 59          | 34.1% |               |                       |
| Overweight                                        | 1,876                   | 36.7% |              | 73          | 42.2% |               |                       |
| Obese                                             | 615                     | 12.0% |              | 38          | 22.0% |               |                       |
| BMI change <sup>b</sup>                           |                         |       | 1.08 (2.13)  |             |       | 2.12 (2.96)   | <0.001                |
| Smoking status                                    |                         |       |              |             |       |               | 0.328                 |
| Never smoker                                      | 2,356                   | 46.2% |              | 76          | 43.9% |               |                       |
| Ex-smoker                                         | 1,615                   | 31.7% |              | 50          | 28.9% |               |                       |
| Smoker                                            | 1,146                   | 22.4% |              | 47          | 27.2% |               |                       |
| Pack-year <sup>c</sup>                            |                         |       | 0.25 (0-13)  |             |       | 0.15 (0-17)   | 0.464                 |
| Exposed to passive smoking (last 12 mo)           | 1,494                   | 29.3% |              | 62          | 35.8% |               | 0.062                 |
| Education                                         |                         |       |              |             |       |               | 0.131                 |
| Low                                               | 221                     | 8.5%  |              | 14          | 13.9% |               |                       |
| Medium                                            | 860                     | 33.0% |              | 28          | 27.7% |               |                       |
| High                                              | 1,526                   | 58.5% |              | 59          | 58.4% |               |                       |
| Respiratory symptoms                              |                         |       |              |             |       |               |                       |
| Had an attack of asthma (last 12 mo)              | 99                      | 1.9%  |              | 9           | 5.2%  |               | 0.003                 |
| Wheezing/whistling (last 12 mo)                   | 696                     | 13.6% |              | 40          | 23.1% |               | <0.001                |
| Woken with tight chest (last 12 mo)               | 541                     | 10.6% |              | 33          | 19.1% |               | <0.001                |
| Woken by attack of SOB (last 12 mo)               | 234                     | 4.6%  |              | 10          | 5.8%  |               | 0.458                 |
| Woken by attack of coughing (last 12 mo)          | 1,287                   | 25.2% |              | 51          | 29.5% |               | 0.198                 |
| Chronic cough <sup>d</sup>                        | 237                     | 4.6%  |              | 14          | 8.1%  |               | 0.036                 |
| Avoid vigorous exercise (last 12 mo) <sup>e</sup> | 78                      | 1.5%  |              | 6           | 3.5%  |               | 0.043                 |
| Ever had the following conditions:                |                         |       |              |             |       |               |                       |
| Doctor diagnosed asthma                           | 384                     | 7.5%  |              | 19          | 11.0% |               | 0.090                 |
| Chronic bronchitis <sup>f</sup>                   | 658                     | 12.9% |              | 26          | 15.0% |               | 0.403                 |
| Hypertension                                      | 578                     | 13.6% |              | 34          | 25.8% |               | <0.001                |
| Heart Disease                                     | 221                     | 5.2%  |              | 10          | 7.5%  |               | 0.243                 |
| Depression                                        | 334                     | 7.8%  |              | 12          | 9.0%  |               | 0.629                 |
| Diabetes                                          | 158                     | 3.7%  |              | 6           | 4.5%  |               | 0.640                 |
| Cancer                                            | 209                     | 4.9%  |              | 6           | 4.5%  |               | 0.825                 |
| Stroke                                            | 113                     | 2.6%  |              | 3           | 2.2%  |               | 0.771                 |
| Physically active                                 | 1,860                   | 36.3% |              | 45          | 26.0% |               | 0.005                 |

|                          |                |              |        |
|--------------------------|----------------|--------------|--------|
| FEV <sub>1</sub> , %pred | 101.93 (10.77) | 88.20 (6.07) | <0.001 |
| FVC, %pred               | 103.37 (11.43) | 89.93 (7.98) | <0.001 |
| FEV <sub>1</sub> /FVC    | 0.79 (0.06)    | 0.80 (0.06)  | 0.141  |
| Study                    |                |              | 0.057  |
| ECRHS                    | 2,613 51.0%    | 101 58.4%    |        |
| SAPALDIA                 | 2,507 49.0%    | 72 41.6%     |        |

ECRHS: European Community Respiratory Health Survey, SAPALDIA: Swiss study on Air Pollution and Lung and Heart Diseases in adults. SD: standard deviation. BMI: Body Mass Index. SOB: shortness of breath. mo: month. FVC: forced vital capacity. FEV<sub>1</sub>: forced expiratory volume in the first second. %pred: percent of predicted value.

<sup>a</sup> *P* from chi<sup>2</sup> test (categorical) and anova (continuous).

<sup>b</sup> BMI at follow-up – BMI at baseline.

<sup>c</sup> Values are expressed as median (25th, 75th percentile).

<sup>d</sup> Cough during the day or at night on most days for at least 3 months.

<sup>e</sup> Avoid taking vigorous exercise because of breathing problems.

<sup>f</sup> Cough and phlegm during the day or at night on most days for at least 3 months.

Figure 1. Relative Risk of Restrictive Spirometry Pattern Incidence (Active vs Inactive). Overall, and Stratified by BMI, Study, Sex and Smoking Status. ECRHS and SAPALDIA, Europe 2001-2011

Legend:

Relative risk from modified Poisson regression, adjusted for age, sex, BMI, chronic cough, woken by tight chest, avoiding physical activity because of respiratory symptoms and FVC at baseline. Centre was included as random effect.

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SEP

Figure 2. Relative Risk of Restrictive Spirometry Pattern Incidence (Active vs Inactive). Sensitivity Analyses. ECRHS and SAPALDIA, Europe 2001-2011.

Legend:

RR: Relative risk from modified Poisson regression, adjusted for age, sex, BMI, chronic cough, woken by tight chest, avoiding physical activity because of respiratory symptoms and FVC at baseline. Centre was included as random effect. **S1**: GLI-equations were used instead of study-specific equations to define spirometry patterns. **S2**: additionally adjusted for change in BMI between baseline and follow-up. **S3**: excluding asthmatics. **S4**: Excluding subjects who avoided physical activity because of their respiratory symptoms. **S5**: no adjustment for FVC levels at baseline.