**Supplementary material:**

This file provides:

* further details on data collection and analysis (**supplementary methods**)
* **additional** **Tables** for results:
* Table E1: Participants by centre and wave.
* Table E2: P-values for the pairwise comparisons of the asssociations between different DHEA-S levels and FEV1, FVC and FEV1/FVC ratio.
* Table E3: Cross sectional associations of DHEAS z-score with lung function measures, spirometric restriction and airflow obstruction in ECRHS-2 and ECRHS-3.
* Table E4. Cross-sectional associations of DHEAS z-score with lung function measures, stratified by age and menopausal status.
* Table E5: Baseline characteristics of participating women with valid spirometric measurements at follow-up and were included in the longitudinal analyses vs. women without who were not included in the longitudinal analyses.
* Table E6: Associations of DHEAS z-scores with lung function decline.
* Table E7. Cross-sectional associations of DHEAS z-score with spirometric restriction and airflow obstruction. Results from main model and sensitivity analyses.
* Table E8: Associations of DHEAS z-scores with incidence of spirometric restriction and pre- and post-bronchodilator airway obstruction: sensitivity analyses.
* **funding sources** for the local ECRHS studies

## Appendix: supplementary methods

### Study Population.

This study used data from women who participated in the European Community Respiratory Health Survey (ECRHS), an international, multicenter cohort study on adults from the general population.[1,2] Detailed study design and full protocols of ECRHS are available at [www.ecrhs.org](http://www.ecrhs.org/).

In brief, subjects, were selected from a randomized population sample aged 20 to 44 for a first postal screening in 1990-1992. A random sample of responders (“random sample”) plus an oversampling of subjects who reported respiratory symptoms (“symptomatic sample”) were invited to a clinical examination in 1991-1993, and were then followed up in 1999-2002 (ECRHS-2) and in 2010-2013 (ECRHS-3).

At all clinical examinations, participants completed spirometry and detailed questionnaires on respiratory health and lifestyle factors.[1,2] At ECRHS-2 and ECRHS-3, a questionnaire on women’s health was administered to all women, and serum samples for hormonal measurements were drawn in women from the centers that applied to the “ECRHS hormonal protocol”.[*Table E1*] All the women with complete spirometry and hormonal data in at least one of the surveys were included in the present study.

Ethical approval was obtained by all centers in both studies from the appropriate ethics committees, and written consent was obtained from the participants.

### Respiratory Measurements.

Biomedin or SensorMedics spirometers were mainly used for lung function measurements at the ECRHS-2, whereas NDD EasyOne was used at the ECRHS-3.[*Table*] Pre-bronchodilator maximum FEV1 and FVC were measured at ECRHS-2 and ECRHS-3 according to the American Thoracic Society criteria for repeatability.[3] Post-bronchodilator (post-BD) lung function was measured only at ECRHS 3, after administration of 200 µg salbutamol.

**Table: Spirometers used by center and wave.**

|  |  |  |
| --- | --- | --- |
|  |  | **Spirometer** |
| **Country** | **Centre** | **ECRHS-2** | **ECRHS-3** |
| **Denmark** | Aarhus | - | NDD Easyone |
| **Germany** | Hamburg  | - | NDD Easyone |
|  | Erfurt  | - | NDD Easyone |
| **Spain** | Barcelona  | Biomedin spiro | NDD Easyone |
|  | Galdakao  | Biomedin spiro | NDD Easyone |
|  | Albacete  | - | NDD Easyone |
|  | Oviedo  | Biomedin spiro | NDD Easyone |
|  | Huelva  | Biomedin spiro | NDD Easyone |
| **France** | Bordeaux  | - | NDD Easyone |
|  | Grenoble  | Biomedin spiro | NDD Easyone |
|  | Montpellier  | - | NDD Easyone |
|  | Paris  | Biomedin spiro | NDD Easyone |
| **Iceland** | Reykjavik  | SensorMedics spiro | NDD Easyone |
| **Norway** | Bergen  | SensorMedics spiro | NDD Easyone |
| **Sweden** | Gothenburg  | SensorMedics spiro | NDD Easyone |
|  | Umea  | SensorMedics spiro | NDD Easyone |
|  | Uppsala  | SensorMedics spiro | NDD Easyone |
| **Switzerland** | Basel  | SensorMedics spiro | NDD Easyone |
| **Estonia** | Tartu  | Jaeger pneumo | NDD Easyone |

### Respiratory Outcomes.

Lung function decline (ΔFEV1, ΔFVC, ΔFEV1/FVC) was calculated in women with spirometry data, expressed as percentage of predicted, at both examinations as difference between the measures obtained at ECRHS-3 (follow-up) and ECRHS-2 (baseline) divided by the time between the two surveys in years.

Asthma was defined as self-reported doctor-diagnosed asthma with asthma attacks in the last 12 months and/or current use of medication for asthma.

Incident cases of airflow limitation (pre- and post-bronchodilator) and of restrictive pattern on spirometry were evaluated at follow-up among women who not prevalent cases at baseline.

### DHEA-S measurements.

Blood samples were drawn and stored following standardized procedures. At ECRHS-2, DHEA-S serum concentrations were determined using an immunocompetitive immunoassay (Elecsys® DHEA-S electrochemiluminescence immunoassay on an Elecsys 2010 analyser, Roche Diagnostics, Germany) at the Biochemistry Laboratory of Paris Bichat – Claude Bernard Faculty Hospital, Paris (France). At ECRHS-3, DHEAS serum concentrations were measured at the Core Facility for Metabolomics at the University of Bergen (Norway) by high-throughput LC-MS/MS, using an Aquity liquid chromatograph coupled with a Xevo TQ-S mass spectrometer (Waters Corp., Milford, MA, USA).

To account for the physiological dependency of DHEA-S on age and for methodological differences in DHEA-S measurements between the 2 examinations, we derived age-adjusted DHEA-S z-scores by fitting, separately for ECRHS-2 and ECRHS-3 and in women who were not using corticosteroids, mixed-effects (ME) linear regression models on log-transformed DHEA-S concentrations with age included as independent variable and study center as a random effect. The resulting z-score represents how far (in units of the population standard deviation) a measured concentration is from the mean of a population with corresponding age (see Figure S1).[4] DHEA-S z score was then considered either as a continuous variable or as a categorical variable. In particular, women with z-score <-1 were considered as having “low” DHEAs levels, and were compared with the rest of the sample (z-score≥-1).

**Statistical analysis.**

A mixed-effects (ME) linear regression model, with ID as a level-2 unit and center as a level-3 random intercept, was fitted to evaluate the associations between DHEA-S z-score and the following variables, which were entered as the values assessed at the two different examinations: age, body mass index (BMI, classified in ≤25, 25-30, >30 kg/m2) smoking history (coded as lifetime non-smoker, ex-smoker with < 15 pack-years, ex-smoker with ≥ 15 pack-years, current smoker with < 15 pack-years, current smoker with ≥ 15 pack-years, lifetime smokers with unknown pack-years), passive smoke exposure in the last 12 months, vigorous physical activity (physical activity ≥2 times and ≥1hour per week) [5] school education as proxy of social-economic status (completed at 16 years or younger, between 17 and 20 years, or after the age of 20), and menstrual status (regular periods, recently irregular periods, always had irregular periods, periods have stopped), use of corticosteroids in the last 12 months (none, inhaled corticosteroids only, oral corticosteroids).

We used multilevel mixed-effects (ME) linear and Poisson (with robust error variance) regression models to investigate the cross-sectional associations of lung function measures (FEV1, FVC and FEV1/FVC, expressed in percentage of predicted according to the reference equations of the ERS global lung initiative [6]) and dichotomous respiratory outcomes (airflow limitation and restrictive pattern on spirometry), respectively, with DHEA-S z-score (included as independent variable, either continuous or categorized to evaluate both linear and non-linear trends). Data obtained from ECRHS-2 and ECRHS-3 were pooled together, and we fitted multilevel models with subject ID as a level-2 unit nested in the center (level-3) to account for repeated measures, adjusting for the following covariates (level-1): age, BMI, smoking history, passive smoking exposure, vigorous physical activity, school education, and menopausal status.

Longitudinal associations of DHEA-S z-score measured at baseline with lung function decline measures (ΔFEV1, ΔFVC, ΔFEV1/FVC), included as dependent variable), were investigated using ME linear regression models with center included as a random effect. Longitudinal models were adjusted for age, BMI at baseline, ΔBMI (BMI differences between the two examinations), smoking habits between the two surveys (coded as lifetime non-smokers at both examinations, ex-smokers at both examinations, quit smoking between baseline and follow-up, smokers at follow-up with less than 6 pack-years (median) smoked between the two examinations, smokers at follow-up with less than 6 pack-years smoked between the two examinations), history of passive smoking (coded as never exposed, exposed at one examination, exposed at both examinations), change in menopausal status (non-menopausal at both examinations, menopausal at follow-up only, menopausal at baseline).

The associations of DHEA-S z-score withincident cases of airflow limitation and restrictive pattern on spirometry were estimated through incidence rate ratios (IRR) using ME Poisson regression models, with time-at-risk included as offset and centre as random effect. Time-at-risk was calculated as the time (in years) passed between the baseline and follow-up for non-cases, while this time was halved for incident cases. Because of the relatively low number of new cases, the incidence rate ratios for the associations of DHEA-S with airflow limitation, pre- and post-bronchodilator, and with restrictive pattern on spirometry were adjusted only for the variables significantly associated with both DHEA-S levels and pulmonary indices: age, BMI at baseline, ΔBMI, and smoking habits between the two surveys.

In all models, women with missing data on a covariate were removed from the models.

To evaluate whether pooling together DHEA-S measurements obtained with two different methods (ECLIA and LC-MS/MS) has impacted our results, we also replicated the cross-sectional analyses using separately the data from ECRHS-2 and from ECRHS-3.

Sensitivity analyses for the associations of DHEA-S with spirometric outcomes were performed after exclusion from the models of:

1. corticosteroids users, as corticosteroids are known to affect the adrenal function and DHEA-S secretion;
2. women with asthma, as DHEA-S has been associated in literature with asthma occurrence;
3. current smokers, to avoid potential residual confounding by smoking which can significantly alter both lung function and DHEA-S secretion;
4. women sampled in the ECHRS symptomatic sample, to ascertain that the results were not driven by unspecified respiratory conditions.

Stratified analyses were performed a) by median age, as the association of low DHEA-S z-score with lung function might be different at older age, when the DHEA-S concentrations are significantly lower; and b) by menopausal status (regular period vs. recently irregular period or post-menopausal), as the effects of DHEA-S might change according to the hormonal context.

The statistical analyses were performed using STATA software v15.0 (StataCorp, College Station, Texas, USA).

**References:**

1. Burney PG, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. Eur Respir J 1994;7(5):954-60.
2. European Community Respiratory Health Survey II Steering Committee. The European Community Respiratory Health Survey II. Eur Respir J 2002;20(5):1071-9.
3. American Thoracic Society, American Lung Association. Training programs in adult pulmonary disease and critical care and training programs in pediatric pulmonary disease. 1994 editions. Am J Respir Crit Care Med 1994;150(4):1175-204Fischli S, Jenni S, Allemann S, et al. Dehydroepiandrosterone Sulfate in the assessment of the Hypothalamic-Pituitary-Adrenal Axis. J Clin Endocrinol Metab 2008;93(2):539-42.
4. Fuertes E, Carsin AE, Anto JM, et al. Leisure time in vigorous physical activity is associated with better lung function: the prospective ECRHS study. Thorax 2018;73(4):376-384
5. Quanjer PH, Hall GL, Stanojevic S, Cole TJ, Stocks J; Global Lungs Initiative. Age- and height-based prediction bias in spirometry reference equations. Eur Respir J 2012;40(1):190-7.

**Table E1: Participants by centre and wave.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Country | Centre | Women with spirometry and DHEA-S measured at ECRHS-2 | Women with spirometry and DHEA-S measured at ECRHS-3 | Women with spirometry and DHEA-S measured at ECRHS-2 and follow-up spirometry at ECRHS-3 | Women with spirometry and DHEA-S measured at both examinations |
| **Denmark** | Aarhus | - | 83  | - | - |
| **Germany** | Hamburg  | - | 124 | - | - |
|  | Erfurt  | - | 152 | - | - |
| **Spain** | Barcelona  | 95  | - | 47 | - |
|  | Galdakao  | 140  | 157 | 109  | 106 |
|  | Albacete  | - | 107 | - | - |
|  | Oviedo  | 114  | - | 66  | - |
|  | Huelva  | 114  | 77 | 69  | 62 |
| **France** | Bordeaux | - | 32 | - | - |
|  | Grenoble  | 139  | 120 | 97  | 95 |
|  | Montpellier  | - | 64 | - | - |
|  | Paris  | 157  | 127 | 91  | 87 |
| **Iceland** | Reykjavik  | 231  | 208 | 163  | 162 |
| **Norway** | Bergen  | 271  | - | 142  | - |
| **Sweden** | Gothenburg  | 188  | 130 | 91  | 82 |
|  | Umea  | 175  | 117 | 99  | 82 |
|  | Uppsala  | 189  | 148 | 105  | 99 |
| **Switzerland** | Basel  | 144  | - | 102  | - |
| **Estonia** | Tartu  | 74  | 79 | 35 | 26 |
|  | **Total** | **2,045\*** | **1,725\*** | **1,216** | **801** |

\*of these women, 801 had measurements at both ECRHS-2 and ECRHS-3 (last column)

**Table E2A-C: P-values for the pairwise comparisons of the asssociations between different DHEA-S levels and FEV1, FVC and FEV1/FVC ratio (Figure 1 in the main text).**

***Table E2A: p-values for the differences in the associations of different levels of DHEA-S (z-score) with FEV1 (% of predicted).*** *p<.10 is formatted in italics; p<.05 in bold.*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Z<-1 | -1<Z<-0.5 | -0.5<Z<+0,5 | +0.5<Z<+1 | +1<Z |
| Z<-1 | 1 | - | - | - | - |
| -1<Z<-0.5 | *.056* | 1 | - | - | - |
| -0.5<Z<+0,5 | ***.002*** | .497 | 1 | - | - |
| +0.5<Z<+1 | ***.011*** | .639 | .875 | 1 | - |
| +1<Z | *.052* | .971 | .528 | .665 | 1 |

***Table E2B: p-values for the differences in the associations of different levels of DHEA-S (z-score) with FVC (% of predicted).*** *p<.10 is formatte in italics; p<.05 in bold.*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Z<-1 | -1<Z<-0.5 | -0.5<Z<+0,5 | +0.5<Z<+1 | +1<Z |
| Z<-1 | 1 | - | - | - | - |
| -1<Z<-0.5 | ***.044*** | 1 | - | - | - |
| -0.5<Z<+0,5 | ***.007*** | .867 | 1 | - | - |
| +0.5<Z<+1 | ***.011*** | .732 | .797 | 1 | - |
| +1<Z | .260 | .396 | .222 | .203 | 1 |

***Table E2C: p-values for the differences in the associations of different levels of DHEA-S (z-score) with FEV1/FVC (% of predicted).*** *p<.10 is formatted in italics.*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Z<-1 | -1<Z<-0.5 | -0.5<Z<+0,5 | +0.5<Z<+1 | +1<Z |
| Z<-1 | 1 | - | - | - | - |
| -1<Z<-0.5 | .714 | 1 | - | - | - |
| -0.5<Z<+0,5 | .115 | .286 | 1 | - | - |
| +0.5<Z<+1 | .498 | .786 | .394 | 1 | - |
| +1<Z | *.060* | .140 | .439 | .180 | 1 |

**Table E3: Cross sectional associations of DHEAS z-score with lung function measures, airflow limitation (FEV1/FVC<LLN) and restrictive pattern on spirometry (FVC<LLN and FEV1/FVC>LLN) in ECRHS-2 and ECRHS-3.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  |  | **Continuous Z-score** | **Low\* DHEA-S vs.higher** |
|  | n | Mean ± SD | Beta† (95% CI)  | p | Beta† (95% CI)  | p |
| **FEV1** (% of predicted) |  |  |  |  |  |  |
| ECRHS-2 | 2,037 | 2962 ± 510 | *0.59 (-0.00,1.18)* | *.052* | **-1.86 (-3.48,-0.24)** | **.024** |
| ECRHS-3 | 1,479 | 2574 ± 501  | *0.73 (-0.04,1.49)* | *.062* | **-2.42 (-4.55,-0.28)** | **.027** |
| **FVC** (% of predicted) |  |  |  |  |  |  |
| ECRHS-2 | 2,002 | 3675 ± 588 | 0.43 (-0.11,0.97) | .116 | **-1.55 (-3.03,-0.07)** | **.041** |
| ECRHS-3 | 1,458 | 3392 ± 593  | 0.23 (-0.46,0.92) | .508 | *-1.78 (-3.71,0.15)* | *.078* |
| **FEV1/FVC** (% of predicted) |  |  |  |  |  |  |
| ECRHS-2 | 1,954 | 80.6 ± 6.6 | 0.21 (-0.13,0.55) | .233 | -0.50 (-1.44,0.43) | .290 |
| ECRHS-3 | 1,458 | 75.9 ± 6.5 | **0.51 (0.11,0.92)** | **.013** | -0.69 (-1.83,0.45) | .236 |
|  |  | %  | RR† (95% CI)  | p | RR† (95% CI) | p |
| **Restrictive pattern**  |  |  |  |  |  |
| ECRHS-2 | 1,963 | 4.3%  | 0.82 (0.62,1.08) | .158 | 1.60 (0.96,2.67) | .071 |
| ECRHS-3 | 1,551 | 4.0%  | 0.89 (0.65,1.20) | .434 | 1.61 (0.81,3.20) | .172 |
| **Airflow limitation**  |  |  |  |  |  |
| ECRHS-2 | 1,954 | 6.3%  | 1.03 (0.89,1.19) | .698 | 1.02 (0.65,1.77) | .880 |
| ECRHS-3 (pre-BD) | 1,458 | 10.1%  | **0.80 (0.70,0.92)** | **.002** | **1.73 (1.22,2.79)** | **.001** |
| ECRHS-3 (post-BD) | 1,406 | 5.4%  | **0.78 (0.69,0.88)** | **<.001** | **1.66 (1.14,2.42)** | **.008** |

All spirometric measures are pre-bronchodilator (pre-BD), except for ECRHS-3 post-BD airflow obstruction. n: subjects with complete data on all covariates; RR: rate ratio; \*low DHEAS: z-score < -1; †models adjusted for: age, height, smoking habits, exposure to passive smoking, BMI, schooling, physical activity, menopausal status.

**Table E4. Cross-sectional associations of DHEAS z-score with lung function measures, stratified by age and menopausal status.**

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | Continuous DHEA-S z-score | Low DHEA-S vs. higher |
|  | Obs. | Beta† (95% CI)  | p | Beta‡ (95% CI)  | p |
| **FEV1** (% of predicted) |  |  |  |  |  |
| Age < 48 | 1844 | 0.45 (-0.23,1.13) | .201 | *-1.69 (-3.49,-0.11)* | *.066* |
| Age >= 48# | 1926 | *0.65(-0.00,1.31)* | *.051* | **-2.00 (-3.89,-0.11)** | **.038** |
| Pre-menopause | 1663 | **0.79 (0.08,1.51)** | **.029** | **-1.88 (-3.76,-0.01)** | **.049** |
| Post-menopause# | 1663 | 0.54 (-0.13,1.21) | .116 | **-2.21 (-4.13,-0.28)** | **.024** |
| *Post-menopause excluding HRT users* | 1372 | *0.65 (-0.11,1.41)* | *.094* | **-2.56 (-4.74,-0.38)** | **.022** |
|  |  |  |  |  |  |
| **FVC** (% of predicted) |  |  |  |  |  |
| Age < 48 | 1844 | 0.07 (-0.57,0.70) | .837 | -0.66 (-2.29,0.97) | .602 |
| Age >= 48# | 1926 | 0.44 (-0.15,1.04) | .145 | **-2.47 (-4.17,-0.76)** | **.005** |
| Pre-menopause | 1663 | 0.16 (-0.50,0.82) | .635 | -0.73 (-2.45,0.99) | .407 |
| Post-menopause# | 1663 | 0.35 (-0.26,0.95) | .258 | **-2.32 (-4.04,-0.61)** | **.008** |
| *Post-menopause excluding HRT users* | 1372 | 0.38 (-0.31,1.06) | .280 | **-2.29 (-4.24,-0.33)** | **.020** |
|  |  |  |  |  |  |
| **FEV1/FVC ratio** (% of predicted) |  |  |  |  |  |
| Age < 48 | 1844 | 0.33 (-0.07,0.73) | .103 | -0.98 (-2.03,0.07) | .068 |
| Age >= 48# | 1926 | 0.28 (-0.08,0.64) | .123 | 0.04 (-1.00,1.07) | .942 |
| Pre-menopause | 1663 | **0.61 (0.21,1.01)** | **.003** | **-1.10 (-2.16,-0.04)** | **.042** |
| Post-menopause# | 1663 | 0.26 (-0.12,0.64) | .175 | -0.25 (-1.34,0.83) | .648 |
| *Post-menopause excluding HRT users* | 1372 | 0.35 (-0.08,0.78) | .109 | -0.44 (-1.67,0.80) | .487 |
|  |  |  |  |  |  |

FEV1: Forced expiratory volume in 1 second, FVC: Forced vital capacity, HRT: hormonal replacement treatment.

#Test for interaction by age at study, or by menopausal status for the association between z-score DHEAs and lung function outcomes did not show any significant interaction (p>0.05)

**Table E5. Baseline characteristics of participating women with valid spirometric measurements at follow-up (who were included in the longitudinal analyses) vs. women without (who were not included in the longitudinal analyses.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **With spirometric follow-up at ECRHS-3**n=1,216 | **Without spirometric follow-up at ECRHS-3**n=829 | **p-value**  |
| **Age,** years | 43.2 [28.0-56.8] | 43.6 [28.7-56.5] | .427 |
| **Smoking habits** |  |  | **<.001** |
| Non smokers  | 573 (47.1%) | 355 (42.8%) |  |
| Past smokers with <15py | 243 (20.0%) | 144 (17.4%) |  |
| Past smokers with ≥15py | 85 (7.0%) | 34 (4.1%) |  |
| Current smokers with <15py | 140 (11.5%) | 109 (13.2%) |  |
| Current smokers with ≥15py | 123 (10.1%) | 149 (18.0%) |  |
| Smokers with unknown py | 50 (4.1%) | 36 (4.3%) |  |
| *missing* | 2 (0.2%) | 2 (0.2%) |  |
| **Exposure to passive smoke in the last 12 months** |  |  | **.046** |
| No | 782 (53.0%) | 493 (59.5%) |  |
| Yes | 426 (35.0%) | 333 (40.2%) |  |
| *missing* | 8 (0.7%) | 3 (0.4%) |  |
| **Body mass index**,  |  |  | .984 |
| <25 kg/m2 | 706 (58.1%) | 488 (58.9%) |  |
| [25-30) kg/m2 | 357 (29.4%) | 234 (28.2%) |  |
| ≥30 kg/m2 | 152 (12.5%) | 106 (12.8%) |  |
| *missing* | 1 (0.1%) | 1 (0.1%) |  |
| **Age completed full time education** |  |  | .406 |
| 16years or younger | 198 (16.3%) | 159 (19.2%) |  |
| 17-20 years | 392 (32.2%) | 261 (31.5%) |  |
| 21years or older | 623 (51.2%) | 407 (49.1%) |  |
| *missing* | 3 (0.3%) | 2 (0.2%) |  |
| **Vigorous physical activity**  |  |  | **.004** |
| No | 681 (56.0%) | 526 (63.5%) |  |
| Yes | 516 (42.4%) | 292 (35.2%) |  |
| *missing* | 19 (1.6%) | 11 (1.3%) |  |
| **Menstrual Periods** |  |  | .244 |
| Regular | 734 (60.4%) | 465 (56.1%) |  |
| Never been regular | 68 (5.6%) | 52 (6.3%) |  |
| Recently irregular | 125 (10.3%) | 95 (11.5%) |  |
| Have stopped (>6 months)  | 261 (21.5%) | 203 (24.5%) |  |
| *missing* | 28 (2.3%) | 14 (1.7%) |  |
| **Use of corticosteroids in the last 12 months** |  |  | .262 |
| No | 736 (88.9%) | 1101 (90.5%) |  |
| Inhaled corticosteroids  | 66 (8.0%) | 88 (7.3%) |  |
| Oral corticosteroids | 17 (2.1%) | 21 (1.7%) |  |
| *missing* | 10 (1.2%) | 6 (0.5%) |  |
| **FEV1,** % of predicted | 99.8 ± 13.1  | 97.1 ± 13.9  | **<.001** |
| **FVC,** % of predicted | 100.5 ± 12.4 | 98.7 ± 12.8 | **.001** |
| **FEV1/FVC ratio,** % of predicted | 98.9 ± 7.8 | 97.9 ± 8.4 | **.006** |
| **Airway limitation** (FEV1/FVC<LLN) | 63 (5.2%) | 67 (8.1%) | **.008** |
| **Spirometric restrictive pattern** (FVC<LLN, FEV1/FVC≥LLN) | 36 (3.1%) | 45 (5.9%) | **.003** |
| **DHEA-S**, µM | 4.40 [0.16-15.6] | 4.18 [0.16-19.0] | .330 |
| **DHEA-S**, (z<1, %) | 129 (15.6%) | 172 (14.1%) | .375 |

ECRHS-2 participants who did not take part to ECRHS-3 (n=829) and were therefore excluded from longitudinal analyses were more likely to be active and passive smokers, were less physical active at baseline and had lower volumes on spirometry than those who participated to both ECRHS-2 and ECRHS-3 surveys (n=1,216) and who were included in the longitudinal analyses.

**Table E6: Associations of DHEAS z-scores with lung function decline.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  | Continuous Z-score |  | Low\* DHEAS vs.higher |  |
| **Lung function decline** | Obs. | Mean ± SD | Beta‡ (95% CI)  | p | Beta‡ (95% CI)  | p |
| **ΔFEV1** (%pred./year) | 1216 | -0.44 ± 0.77 | +0.01 (-0.04,0.05) | .771 | -0.07 (-0.21,0.05) | .241 |
| **ΔFVC** (%pred /year) | 1216 | 0.12 ± 0.78 | -0.03 (-0.08,0.02) | .224 | +0.04 (-0.09,0.17) | .546  |
| **ΔFEV1/FVC** (%pred /year) | 1216 | -0.33 ± 0.49 | **+0.04 (0.01,0.07)** | **.008** | **-0.13 (-0.22,-0.04)** | **.003** |

\*low DHEAS is defined as having Z-score < -1. ‡adjusted for age, schooling, BMI (all measured at baseline), ΔBMI between the two examinations, physical activity at baseline and follow-up, history of active and passive smoking between the two examinations, change in menopausal status

**Table E7. Cross-sectional associations of DHEAS z-score with restrictive pattern on spirometry** (FVC<LLN and FEV1/FVC>LLN) **and airflow obstruction** (FEV1/FVC<LLN). Results from main model and sensitivity analyses.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  | Continuous Z-score |  | Low\* DHEAS vs.higher |  |
|  | Obs. | Prevalent cases, n (%) | RR† (95% CI) | p-value | RR† (95% CI)  | p-value |
| **Restrictive pattern (FVC<LLN and FEV1/FVC>LLN)** |  |  |  |  |  |  |
| **Main model** | 3514 | 147 (4.2%) | 0.84 (0.68,1.04) | .101 | **1.62 (1.11,2.38)** | **.013** |
| w/o CS users1 | 3280 | 126 (3.8%) | 0.84 (0.67,1.05) | .128 | 1.48 (1.00,2.21) | .052 |
| w/o asthma2 | 3154 | 115 (3.7%) | 0.82 (0.66,1.03) | .086 | 1.58 (1.00,2.49) |  .050 |
| w/o current smokers3 | 2660 | 107 (4.0%) | **0.80 (0.67,0.95)** | **.011** | **1.66 (1.06,2.61)** | **.026** |
| w/o symptomatic sample4 | 2929 | 119 (4.1%) | 0.85 (0.66,1.09) | .194 | **1.56 (1.04,2.36)** | **.031** |
| **Airflow limitation (FEV1/FVC<LLN)** |  |  |  |  |  |  |
| **Main model** | 3770 | 303 (8.0%) | **0.90 (0.81,0.99)** | **.030** | **1.35 (1.08,1.69)** | **.008** |
| w/o CS users1 | 3479 | 240 (6.9%) | 0.92 (0.82,1.04) | .180 | 1.29 (0.92,1.81) | .135 |
| w/o asthma2 | 3027 | 173 (5.7%) | 0.93 (0.81,1.06) | .290 | 1.30 (0.91,1.85) | .153 |
| w/o current smokers3 | 2835 | 208 (7.3%) | 0.90 (0.79,1.02) | .096 | 1.33 (0.94,1.88) | .110 |
| w/o symptomatic sample4 | 3093 | 199 (6.4%) | 0.91 (0.77,1.08) | .274 | 1.26 (0.85,1.86) | .256 |

\*low DHEAS is defined as having Z-score < -1. †rate ratios adjusted for age, BMI, smoking history, passive smoke exposure, physical activity, schooling and menopausal periods. Obs : observations with complete information on all covariates. Statistically significant associations (p<.05) are shown in bold.

Sensitivity analyses were performed on (1) women who were not using corticosteroids; (2) women who did not report asthma; (3) non-smokers only; (4) after excluding women recruited as part of the symptomatic sample.

**Table E8: Associations of DHEAS z-scores with incidence of pre- and post-bronchodilator airway obstruction: sensitivity analyses.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Person-years | N incident (rates/1000) | Adjusted^ IRR (95% CI) for low DHEA-S\* vs. higher (reference)  | p-value |
| **Pre-bronchodilator airflow limitation incidence** |  |  |  |  |
| **Main model** | 12,243 | 60 (4.90) | **3.43 (1.91,6.14)** | **<.001** |
| w/o CS users | 11,317 | 46 (4.06) | **4.82 (2.53,9.18)** | **<.001** |
| w/o asthma | 11,058 | 44 (3.98) | **4.70 (2.45,9.01)** | **<.001** |
| w/o current smokers  | 9,161 | 37 (4.04)  | **2.86 (1.34,6.10)** | **.007** |
| w/o symptomatic sample | 10,370 | 49 (4.73) | **3.93 (2.05,7.52)** | **<.001** |
| **Post-bronchodilator airflow limitation incidence** |  |  |  |  |
| **Main model** | 11,942 | 22 (1.84) | **2.81 (1.05,7.53)** | **.040** |
| w/o CS users | 11,016 | 15 (1.36) | **4.24 (1.10,16.3)** | **.036** |
| w/o asthma | 10,812 | 13 (1.20) | 3.40 (0.86,13.4) | .080 |
| w/o current smokers  | 8,905 | 13 (1.57)  | **3.67 (1.03,13.0)** | **.044** |
| w/o symptomatic sample | 10,087 | 18 (1.78) | 2.00 (0.54,7.34) | .298 |

\*low DHEA-S is defined as having Z-score < -1. CS: corticosteroids, IRR: incidence rate ratio. ^adjusted for age and BMI at baseline, change in BMI, history of active smoking between the two examinations.

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