NOCTURNAL GASTROESOPHAGEAL REFLUX, ASTHMA AND SYMPTOMS OF OBSTRUCTIVE SLEEP APNEA: A LONGITUDINAL, GENERAL POPULATION STUDY

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1) How does this advance the field? This study’s prospective data from a general population indicates that nocturnal gastroesophageal reflux increases the risk of new onset of respiratory symptoms, asthma and obstructive sleep apnea symptoms. Prospective data on these associations have been lacking in the literature.

2) What are the clinical implications? This study suggests that nocturnal gastroesophageal reflux should be considered in patients with respiratory symptoms, asthma and obstructive sleep apnea as a possible contributing factor. It also supports the theory that nocturnal gastroesophageal reflux should be considered a distinct clinical entity.

Key words: Nocturnal, gastroesophageal reflux, lung function, asthma, obstructive sleep apnea
ABSTRACT

Background Nocturnal gastroesophageal reflux (nGER) is associated with asthma and obstructive sleep apnea (OSA). Our aim was to investigate whether nGER is a risk factor for onset of asthma and onset of respiratory and OSA symptoms in a prospective population based study.

Methods We invited 2640 subjects from Iceland, Sweden and Belgium for two evaluations over a nine years interval. They participated in structured interviews, answered questionnaires, underwent spirometries and methacholine challenge testing. nGER was defined by reported symptoms.

Results Subjects with persistent nGER (n=123) had an independent increased risk of new asthma at follow-up [OR (95% CI): 2.3 (1.1-4.9)]. Persistent nGER was independently related to onset of respiratory symptoms [OR (95% CI): 3.0 (1.6-5.6)]. The risk of developing symptoms of OSA was increased in subjects with new and persistent nGER [OR (95% CI): 2.2 (1.3-1.6) and 2.0 (1.0-3.7), respectively]. No significant association was found between nGER and lung function or bronchial responsiveness.

Conclusions Persistent symptoms of nocturnal gastroesophageal reflux contributes to the development of asthma and respiratory symptoms. New onset of OSA symptoms is higher among subjects with symptoms of nGER. These findings support that nGER may play a role in the genesis of respiratory symptoms and diseases.
Abbreviations:
GER = Gastroesophageal reflux, nGER = nocturnal GER, OSA = Obstructive sleep apnea, FEV1 = Forced expiratory volume in one second, PEF = Peak expiratory flow, ECRHS = European Community Respiratory Health Survey, ESS = Epworth sleepiness scale, FVC = Forced vital capacity, BHR = Bronchial hyperresponsiveness, BMI = Body mass index, PPI = Proton pump inhibitor, TLESR = Transient lower esophageal sphincter relaxation, COPD = Chronic obstructive pulmonary disease, OR = Odds ratio
INTRODUCTION

Heartburn is one of the most common symptoms experienced in the western world. It is usually caused by gastroesophageal reflux (GER), and affects 12% of the adult population on a weekly basis. Asthma is also a common disease with a prevalence of about 5%. Co-occurrence exists between GER and airway symptoms, and asthma and symptoms related to obstructive sleep apnea (OSA). Additionally, subjects with GER disease have been reported to have significantly lowered forced expiratory volume in one second (FEV1) and peak expiratory flow (PEF).

GER treatment has been shown to have a significant effect on pulmonary illnesses. Kiljander et al. observed that Esomeprazole 40 mg twice daily during 26 weeks improved pulmonary function and asthma-related quality of life in asthmatic patients with GER. This finding has been supported by others, but is not entirely consistent in the literature.

Recently, nocturnal GER (nGER) has become of special interest as a distinct clinical entity. It is considered to be more harmful than daytime GER, and has a greater risk of leading to respiratory complications. OSA patients are also more likely to have nGER, which by itself causes arousals during sleep and can therefore cause even more sleep impairment. However, all epidemiological studies on these associations have been cross-sectional and to our knowledge there is no prospective study investigating whether nGER induces respiratory disorders, including asthma and OSA.

Our aim was to investigate in a nine-year prospective population-based study whether nGER is a risk factor for the onset of respiratory symptoms in relation to asthma and symptoms of OSA.
METHODS

The present study is an international, population-based cohort study, a nine-year prospective follow-up of 2640 randomly selected subjects from Reykjavik, Iceland, Gothenburg and Uppsala, Sweden, and Antwerp, Belgium who participated in the European Community Respiratory Health Survey (ECRHS). All participating subjects in ECRHS I were invited for ECRHS II. They participated in a structured interview, answered questionnaires, underwent spirometry, methacholine challenge studies, measurements of height and weight, and gave blood samples for analyses of specific and total IgE. The study was approved by the local ethics committees in all participating centres (National Bioethics Committee of Iceland: VSNb2010090010/03.1; The Regional Ethical Committee of Uppsala University: Ups 99-313; The Advisory Committee for Medical Ethics of the University of Antwerp, Belgium: 99/021).

The same definition of nGER was used both at baseline and follow-up nine years later. nGER was defined based on the occurrence of heartburn or belching after lying down. All subjects reporting nocturnal reflux symptoms (from less than once a week to almost every night) were classified as having nGER. The subjects were divided into four groups based on their answer at baseline and follow-up: never nGER, nGER at baseline, nGER at follow-up and persistent nGER (nGER at both baseline and follow-up). The participants were asked specifically about usage of medications for acid reflux in the preceding month.

Subjects were considered to have asthma if they reported having been diagnosed with asthma by a physician plus having asthma-related symptoms in the last 12 months. Yes/no-questions were posed about respiratory symptoms at any time in the last 12 months: wheezing, nocturnal chest tightness, shortness of breath at rest and after exercise, nocturnal shortness of breath and nocturnal cough. Subjects who had had any of these respiratory symptoms in the last 12 months were additionally classified as having “any respiratory symptom”. Participants defined with asthma, or reporting a particular symptom at follow-up but not at baseline, were defined as having an onset of asthma or respiratory symptoms during the study period.

Symptoms of OSA were estimated by a questionnaire and defined as self-reported snoring, apneas, or daytime sleepiness. The same questions were used at baseline and follow-up. Those reporting observed snoring or daytime sleepiness more than twice a week, or observed apneas
once a week or more, were considered to have the corresponding symptom. Those with any of
the above-mentioned symptoms were additionally classified as having “any OSA symptom”. For
a more OSA-specific analysis of these symptoms, those with new snoring and/or apnea plus new
daytime sleepiness were also analysed together.

In the follow-up participants also answered the Epworth sleepiness scale (ESS).\textsuperscript{15} A score of 10
or higher was considered as significant daytime sleepiness. ESS was not used when analysing
onset of OSA symptoms as it was not available at baseline.

Smoking history was investigated by asking subjects at baseline and follow-up whether they
were current smokers, ex-smokers or never-smokers. Based on this information the subjects were
classified into Never-smoker, Ex-smoker, Quitter, and Smoker.

The maximum forced expiratory volume in one second (FEV1) and maximum forced vital
capacity (FVC) from five technically acceptable blows were determined.\textsuperscript{16} FEV1/FVC was
calculated from these maximum values. Predicted values for FEV1, FVC and FEV1/FVC were
calculated on the basis of the European Coal and Steel Union reference values.\textsuperscript{17} A change in
lung function was calculated as the change per year in percent of predicted values between the
two studies.

A methacholine challenge was carried out using a dosimeter (Mefar, Brescia, Italy). The starting dose
was 0.002 mg followed by several dose steps up to an accumulated dose of 1 mg. A change in
bronchial responsiveness was expressed as a change in slope per year of follow-up.\textsuperscript{18} Bronchial
hyperresponsiveness (BHR) was defined as a fall in FEV1 of ≥ 20% following an accumulated dose of
1 mg methacholine.\textsuperscript{19}

Blood samples were collected for the measurement of total and specific serum IgE using the
Pharmacia CAP System (Pharmacia Diagnostics, Uppsala, Sweden). Specific IgE was measured
at baseline against \textit{Dermatophagoides pteronyssinus}, cat, birch, timothy grass and \textit{Cladosporium
herbarum}. The detection of specific IgE of ≥ 0.35 kU/l was used as a definition of sensitization
to a specific allergen. Atopy was defined as sensitization to at least one of the investigated
allergens.
Statistical analysis

All statistics were calculated with STATA 11.0 software, version intercooled (Stata Corporation, College Station, Texas). Associations were analysed by chi square test and linear and logistic regressions. Adjusted calculations were done by adjusting for gender, age, location, smoking history at follow-up, body mass index (BMI) at base-line and change in BMI. A p-value of < 0.05 was considered statically significant.
RESULTS
A total of 1761 subjects (response rate 66.7%) were investigated at baseline and followed up after nine years (Figure 1). The characteristics of the participants are presented in table 1. Subjects with new or persistent nGER had a higher baseline BMI (p<0.001), used more anti-reflux medication, and those with persistent nGER were slightly older. No significant differences were found regarding gender, change in BMI, smoking or atopy.

Asthma and respiratory symptoms
Subjects with persistent nGER had significantly more new-onset asthma than subjects without nGER (Table 2). This association remained statistically significant after adjusting for gender, age, location, follow-up time, smoking history, BMI at baseline and change in BMI [adjusted OR (95% CI): 2.33, (1.12-4.87)] (Figure 2). Persistent nGER was also independently related to new onset of daytime and nocturnal respiratory symptoms such as wheezing with breathlessness, chest tightness and cough (Figure 3). Taken together, the adjusted risk for developing any respiratory symptom during the study period was significantly higher among subjects with persistent nGER than subjects without nGER (Table 3).

Obstructive sleep apnea symptoms
New onset of OSA symptoms was significantly more common in subjects with new or persistent nGER (Table 4). For all symptoms except daytime sleepiness, new onset was most common among subjects with persistent nGER, albeit only a little higher than among subjects with new nGER. The combination of new snoring and/or apneas together with new daytime sleepiness was most common among subjects with persistent nGER. Subjects with former nGER had a similar risk of new onset of OSA symptoms as subjects without nGER. These associations remained significant after adjusting for gender, age, location, follow-up time, smoking history, BMI at baseline and change in BMI (Table 3). Those with new or persistent nGER had a higher ESS score than subjects without nGER (Table 4, Figure 4), and this remained significant after adjusting for gender, age, location, follow-up time, smoking history, BMI at baseline and change in BMI.

Spirometry and bronchial hyperresponsiveness
On follow-up after nine years, spirometry was performed in 1417 persons and methacholine
challenge in 976 persons. No significant association was found between nGER status and change
in FEV1, FVC or FEV1/FVC (Table 5). The prevalence of new onset of BHR during the study
period was, however, significantly higher in subjects with persistent nGER (Table 5). This
association was not statistically significant after adjusting for age, gender, location, follow-up
time, smoking history, BMI at baseline and change in BMI [adjusted OR (95% CI): 2.01 (0.81-
4.96)].

**Interactions**

Interaction analyses were done while simultaneously adjusting for location, age, gender, follow-
time, smoking history, baseline BMI and change in BMI. The association between new nGER
and new OSA symptoms was stronger among men than women [OR (95% CI): 5.6 (1.9 – 16.6)
vs. 1.4 (0.8 – 2.6), p_{interaction} = 0.03]. The association between persistent nGER and new
respiratory symptoms was stronger among women than men [OR (95% CI): 21.6 (2.8 – 163.2)
vs. 1.7 (0.8 – 3.6), p_{interaction} = 0.02]. No other significant interactions in the associations between
nGER status and respiratory symptoms, lung function or OSA symptoms were found for atopy,
obesity, smoking, BMI, location or gender.

Among those with new nGER, those who were using anti-reflux medication had a significantly
lesser decrease in FVC than those who were not [coef. (95% CI): 0.33 (0.01, 0.65) vs. -0.19 (-
0.38, 0.01), p_{interaction} = 0.03]. There were no significant differences in change in FEV1, BHR,
prevalence of onset of asthma, respiratory or OSA symptoms between anti-reflux medicating or
non-medicating subjects with persistent nGER (data not shown).

**Participants and non-participants**

Participants at follow-up were less likely to be smokers at baseline (31.8 vs. 44.8%, p<0.001)
and had a slightly higher mean age [33.7 (7.2) vs 32.7 (6.9) years, p<0.001]. No difference was
found regarding gender or BMI between participants and non-participants.
DISCUSSION

This prospective follow-up study shows that subjects with persistent nGER were about two times more likely to report an onset of asthma and respiratory symptoms at follow-up after nine years compared to participants who never had nGER. Symptoms of OSA were also much more likely to occur during the study period amongst subjects with new onset or persistent nGER. The association between new nGER and new OSA symptoms was stronger among men than women, but the association between persistent nGER and new respiratory symptoms was stronger among women than men.

The present study suggests that gastroesophageal reflux is a risk factor for developing asthma. However, we did not find a significant effect of nGER treatment on the study outcomes, except for a lesser decrease in FVC among new nGER subjects who were on treatment compared to those without treatment. The reason for the lack of association to nGER treatment may be due to the fact that our data collection on nGER treatment did not differ between the type of medication used, the dosage or total treatment time. Therefore, all participants who had used any GER medication in the preceding month of any frequency were classified as having nGER treatment, making the nGER treatment group rather diffuse. Some studies, but not all, have reported that GER treatment with proton pump inhibitors (PPIs) improves asthma-related quality of life and may even improve respiratory function. These effects have mostly been minor, which has led some to conclude that GER is not a major trigger for asthma. However, our results indicate that the new onset of asthma is greater than twofold among those with prevalent nGER compared to those without nGER, even after adjusting for common confounding factors. We therefore hypothesize that the modest effects of GER treatment on asthma might rather be explained by a relative irreversibility of GER-induced airway damage. Indeed, as many have pointed out, PPIs do not stop reflux but rather make it less acidic, and can thereby only limit but not eliminate the potential damage to the airways. Additionally, those with more severe GER are usually excluded from these treatment studies. When all of the above is taken into consideration, it must be considered possible that nGER can be implicated in the pathogenesis of asthma in a subgroup of patients.
Subjects with persistent nGER were roughly twice as likely to develop any respiratory symptoms under the study period as those without nGER, even after adjusting for confounding factors. This is in accordance with other studies, which report associations between GER and chronic cough, asthma and various upper respiratory tract symptoms.\textsuperscript{3,23,24} Two mechanisms have mainly been proposed in this context. First, microaspiration of gastric acid can cause bronchoconstriction, thereby predisposing to respiratory symptoms and asthma. Second, bronchospasm can be caused by a vagal reflex that is triggered by gastric acid in the distal esophagus.\textsuperscript{25} The present results add prospective data to these known associations, thereby strengthening theories on causality in these associations.

We found that nGER increases the risk of developing symptoms of OSA, supporting the conclusion that nGER may play a role in the genesis of OSA. Even though we found increase in BMI also to be a risk factor for the development of symptoms of OSA, the association with nGER was independent of changes in BMI. Also, since the prevalence of OSA increases with age, especially in the age groups studied in this nine years prospective study, the confounding effects of ageing predisposing to OSA must be considered. As the new onset of OSA symptoms was twice as common in the nGER groups compared to those without nGER, even after adjusting for age, aging alone cannot explain the increase in OSA symptoms in the nGER groups. Therefore an independent effect of nGER on causation of OSA must be considered. This is in agreement with results from another epidemiological study on the association between nGER and symptoms of OSA.\textsuperscript{24} Since OSA is caused by upper airway narrowing and recurrent, intermittent upper airway collapse,\textsuperscript{26} edema in the upper airway caused by nGER has been hypothesized to play a role in the OSA pathogenesis, but this remains to be studied further.\textsuperscript{27}

Other studies report that OSA might induce nGER, as reflux is more common among OSA patients and treatment of OSA with continuous positive airway pressure effectively diminishes nGER symptoms.\textsuperscript{28} A few mechanisms have been suggested in support of a causal relationship. Contrary to former belief, nocturnal reflux is not caused by negative intrathoracic pressure during apneic episodes, as recent studies have reported the lower esophageal sphincter contracts during apneic episodes and thereby inhibits gastric acid reflux.\textsuperscript{29-31} Rather, nGER is more likely caused by transient lower esophageal sphincter relaxation (TLESR).\textsuperscript{30} These TLESRs are more common in OSA patients than in a normal population and could explain the relationship between
OSA and nGER. In agreement with Shepherd et al., we hypothesize that the repeated stress of negative intrathoracic pressure in OSA patients on the lower esophageal sphincter may strain it to the point where it starts losing its tonus intermittently and thereby generates more TLESRs.

The key strengths of this study were the prospective nature of the study, the high number of participants and the acceptable response rate. Even so, a few methodological issues need to be discussed. First, our definition of the nGER groups was based on self-reported heartburn, marked as less than once a week or more, without any objective diagnostic tests. This might have led to an overrepresentation of nGER among the participants, and thereby reducing the possible effects of nGER on the outcomes, but also served to increase the power in the statistical analyses. Therefore, we also ran all the calculations with nGER defined as heartburn at least once a week or more, which is considered reasonably specific. Based on this definition the group with persistent nGER group consisted of 34 subjects. In all aspects, the results were very similar to those reported above, although sometimes not reaching the same statistical significance as for the nGER groups we use (data not shown). We therefore conclude that the wide definition of nGER used in our research did not confound the results of our study. Second, the data on OSA were only subjective, as we were not able to collect objective data such as performing a polysomnography on this large group of participants. Third, the use of questionnaires translated in each country from the original English carries the risk of a translation bias. However, we consider this risk to be small, as the questions were all checked via back-translation and tested for translation bias. The questions regarding nGER were based on a former, thoroughly validated questionnaire. Finally, since many variables were studied in this research, the risk of a type I error must be considered. However, as there was a common trend in the results, where the symptom prevalence increased between the study groups similarly for various symptoms, the risk of a type I error must be considered small.

In conclusion, persistent nocturnal gastroesophageal reflux contributes to the development of asthma and respiratory symptoms. The risk of new onset of OSA symptoms is also higher among subjects with nGER. These findings further support the conclusion that nGER may play a role in the genesis of respiratory symptoms and diseases.
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Author Contributions

Guarantor of the manuscript: Christer Janson.

O.I.E. and A.B. wrote the main paper. T.G. and C.J. designed the study. C.J., K.T., T.G., W.D.B. were responsible for data collection at the respective centers. T.G., C.J., K.T., A.B., S.D., J.W. and O.I.E. analysed the data. All authors discussed the results and contributed to the manuscript at all stages.
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FIGURE LEGENDS

Figure 1. A flow diagram over selection of cases in ECRHS II.

Figure 2. Odds ratios and 95% confidence intervals for the association between new-onset asthma and nocturnal gastroesophageal reflux (nGER), adjusted for gender, age, location, smoking history at follow-up, body mass index (BMI) at baseline and change in BMI (never nGER as a reference group).

Figure 3. Odds ratios and 95% confidence intervals for the association between new-onset of respiratory symptoms and persistent nocturnal gastroesophageal reflux (nGER) compared to never nGER, adjusted for gender, age, location, smoking history at follow-up, body mass index (BMI) at baseline and change in BMI.

Figure 4. Epworth Sleepiness Scale score between nGER groups. *p-value <0.001 (chi square test, compared to never nGER)
Table 1: Population characteristics in relation to nGER (mean (SD) and %)

<table>
<thead>
<tr>
<th></th>
<th>Never nGER (n = 1298)</th>
<th>Former nGER (n = 139)</th>
<th>p-value*</th>
<th>New nGER (n = 201)</th>
<th>p-value*</th>
<th>Persistent nGER (n = 123)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline, years - Mean (SD)</td>
<td>33.5 (7.2)</td>
<td>34.0 (6.8)</td>
<td>0.45</td>
<td>34.1 (6.8)</td>
<td>0.23</td>
<td>35.0 (7.3)</td>
<td>0.03</td>
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<td>Male gender - %</td>
<td></td>
<td>46.1</td>
<td>46.0</td>
<td>0.99</td>
<td>42.8</td>
<td>51.2</td>
<td>0.28</td>
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<tr>
<td>Baseline BMI, kg/m² - Mean (SD)</td>
<td>23.3 (3.3)</td>
<td>23.9 (3.3)</td>
<td>0.07</td>
<td>24.0 (3.4)</td>
<td>0.02</td>
<td>25.4 (4.4)</td>
<td>&lt;0.001</td>
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<td>Change in BMI, kg/m² - Mean (SD)</td>
<td>1.9 (2.2)</td>
<td>1.5 (2.4)</td>
<td>0.14</td>
<td>2.1 (2.1)</td>
<td>0.25</td>
<td>2.1 (2.7)</td>
<td>0.38</td>
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<tr>
<td>Anti-reflux medication† - %</td>
<td>6.7</td>
<td>13.0</td>
<td>0.01</td>
<td>41.9</td>
<td>&lt;0.001</td>
<td>57.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atopy at baseline - %</td>
<td>28.8</td>
<td>30.0</td>
<td>0.78</td>
<td>23.9</td>
<td>0.18</td>
<td>30.2</td>
<td>0.75</td>
</tr>
<tr>
<td>Smoking: - %</td>
<td></td>
<td></td>
<td>0.05</td>
<td>0.87</td>
<td>0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>44.2</td>
<td>36.7</td>
<td></td>
<td>47.2</td>
<td></td>
<td>36.1</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>21.6</td>
<td>17.3</td>
<td></td>
<td>20.6</td>
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<td>27.9</td>
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<tr>
<td>Quitter</td>
<td>12.9</td>
<td>17.3</td>
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<td>12.6</td>
<td></td>
<td>11.5</td>
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<tr>
<td>Smoker</td>
<td>21.3</td>
<td>28.8</td>
<td></td>
<td>19.6</td>
<td></td>
<td>24.6</td>
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</table>

SD = Standard Deviation, GER = Gastroesophageal Reflux, nGER = Nocturnal Gastroesophageal Reflux
*p-value calculated with “Never nGER” as a reference group
†Any use in the month before follow-up
Table 2: Respiratory symptoms with onset during study period in relation to nGER (%)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Never nGER (n = 1298)</th>
<th>Former nGER (n = 139)</th>
<th>p-value*</th>
<th>New nGER (n = 201)</th>
<th>p-value*</th>
<th>Persistent nGER (n = 123)</th>
<th>p-value*</th>
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</thead>
<tbody>
<tr>
<td>Wheeze</td>
<td>11.3</td>
<td>9.2</td>
<td>0.63</td>
<td><strong>18.7</strong></td>
<td>0.02</td>
<td><strong>22.2</strong></td>
<td>0.01</td>
</tr>
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<td>Wheeze and breathlessness</td>
<td>6.0</td>
<td>7.3</td>
<td>0.57</td>
<td>9.9</td>
<td>0.06</td>
<td><strong>16.0</strong></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wheeze when not having a cold</td>
<td>7.8</td>
<td>5.0</td>
<td>0.31</td>
<td>12.2</td>
<td>0.06</td>
<td><strong>15.7</strong></td>
<td>0.01</td>
</tr>
<tr>
<td>Nocturnal chest tightness</td>
<td>7.5</td>
<td>8.2</td>
<td>0.81</td>
<td>11.2</td>
<td>0.11</td>
<td><strong>17.1</strong></td>
<td><strong>0.003</strong></td>
</tr>
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<td>Breathlessness at rest</td>
<td>3.9</td>
<td>5.6</td>
<td>0.37</td>
<td>6.4</td>
<td>0.11</td>
<td>8.6</td>
<td>0.03</td>
</tr>
<tr>
<td>Breathlessness after exercise</td>
<td>9.1</td>
<td>10.9</td>
<td>0.54</td>
<td>10.9</td>
<td>0.44</td>
<td><strong>18.2</strong></td>
<td>0.01</td>
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<tr>
<td>Nocturnal attacks of breathlessness</td>
<td>3.1</td>
<td>4.8</td>
<td>0.31</td>
<td><strong>6.4</strong></td>
<td>0.03</td>
<td>7.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Nocturnal cough</td>
<td>19.5</td>
<td>22.6</td>
<td>0.56</td>
<td>23.1</td>
<td>0.35</td>
<td>36.1</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>New-onset asthma</td>
<td>5.4</td>
<td>7.3</td>
<td>0.41</td>
<td>8.5</td>
<td>0.11</td>
<td><strong>13.0</strong></td>
<td><strong>0.002</strong></td>
</tr>
<tr>
<td>Any resp. sympt.</td>
<td>49.0</td>
<td><strong>65.1</strong></td>
<td><strong>0.02</strong></td>
<td><strong>60.0</strong></td>
<td><strong>0.02</strong></td>
<td><strong>79.2</strong></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SD = Standard Deviation, mo = Month, yr = Year, GER = Gastroesophageal Reflux, nGER = Nocturnal Gastroesophageal Reflux
*p-value calculated with “Never nGER” as a reference group
<table>
<thead>
<tr>
<th></th>
<th>Any resp. sympt. - Adjusted OR (95% CI)</th>
<th>p-value</th>
<th>Any OSA sympt. - Adjusted OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never nGER</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Former nGER</td>
<td>1.7 (0.9 – 3.1)</td>
<td>0.11</td>
<td>1.5 (0.8 – 2.8)</td>
<td>0.21</td>
</tr>
<tr>
<td>New nGER</td>
<td>1.6 (1.0 – 2.5)</td>
<td>0.06</td>
<td>2.2 (1.3 – 3.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>Persistent nGER</td>
<td>3.0 (1.6 – 5.6)</td>
<td>&lt;0.001</td>
<td>2.0 (1.0 – 3.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>Change in BMI (per kg/m²)</td>
<td>1.1 (1.0–1.1)</td>
<td>0.09</td>
<td>1.1 (1.0 – 1.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.6 (0.5 – 0.8)</td>
<td>0.002</td>
<td>1.6 (1.2 – 2.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.0 (1.0 – 1.0)</td>
<td>0.36</td>
<td>1.0 (1.0 – 1.0)</td>
<td>0.30</td>
</tr>
<tr>
<td>Never smoker</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>1.2 (0.9 – 1.8)</td>
<td>0.26</td>
<td>1.1 (0.7 – 1.6)</td>
<td>0.63</td>
</tr>
<tr>
<td>Quitter</td>
<td>1.8 (1.1 – 2.9)</td>
<td>0.02</td>
<td>1.2 (0.7 – 1.9)</td>
<td>0.48</td>
</tr>
<tr>
<td>Smoker</td>
<td>3.7 (2.5 – 5.5)</td>
<td>&lt;0.001</td>
<td>1.7 (1.1 – 2.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Baseline BMI (per kg/m²)</td>
<td>1.1 (1.0 – 1.1)</td>
<td>0.03</td>
<td>1.0 (1.0 – 1.1)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

OR = Odds Ratio, CI = Confidence Interval, resp. sympt. = Respiratory Symptom, OSA sympt. = Obstructive Sleep Apnea Symptom, nGER = Nocturnal Gastroesophageal Reflux, BMI = Body Mass Index
<table>
<thead>
<tr>
<th>Table 4: Obstructive sleep apnea symptoms with onset during study period in relation to nGER (mean (SD) and %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New observed snoring - %</td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>New observed apneas - %</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>New daytime sleepiness - %</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>New snoring and/or apnea with new daytime sleepiness</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

*p-value calculated with “Never nGER” as a reference group
**Table 5: Lung function in relation to nGER (mean (SD) and %)**

<table>
<thead>
<tr>
<th></th>
<th>Never nGER (n = 1298)</th>
<th>Former nGER (n = 139)</th>
<th>p-value*</th>
<th>New nGER (n = 201)</th>
<th>p-value*</th>
<th>Persistent nGER (n = 123)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Change per year in percent predicted: - Mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1</td>
<td>-0.22 (0.89)</td>
<td>-0.34 (0.97)</td>
<td>0.18</td>
<td>-0.24 (1.01)</td>
<td>0.78</td>
<td>-0.26 (0.82)</td>
<td>0.68</td>
</tr>
<tr>
<td>FVC</td>
<td>-0.08 (1.02)</td>
<td>-0.15 (0.88)</td>
<td>0.47</td>
<td>-0.16 (1.23)</td>
<td>0.37</td>
<td>-0.08 (0.96)</td>
<td>0.98</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>0.000 (0.007)</td>
<td>-0.001 (0.005)</td>
<td>0.38</td>
<td>0.000 (0.007)</td>
<td>0.26</td>
<td>-0.001 (0.007)</td>
<td>0.60</td>
</tr>
<tr>
<td>New COPD (GOLD 1+) - %</td>
<td>2.4</td>
<td>1.8</td>
<td>0.73</td>
<td>3.9</td>
<td>0.27</td>
<td>1.0</td>
<td>0.39</td>
</tr>
<tr>
<td>New bronchial hyperreactivity - %</td>
<td>7.0</td>
<td>7.3</td>
<td>0.93</td>
<td>5.9</td>
<td>0.71</td>
<td><strong>14.8</strong></td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td>Slope change - Mean (SD)</td>
<td>-0.03 (0.28)</td>
<td>0.002 (0.26)</td>
<td>0.45</td>
<td>-0.01 (0.28)</td>
<td>0.61</td>
<td>0.03 (0.30)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

SD = Standard Deviation, GER = Gastroesophageal Reflux, nGER = Nocturnal Gastroesophageal Reflux, FEV1 = Forced Expiratory Volume in One Second, FVC = Forced Vital Capacity, GOLD = Global Initiative for Obstructive Lung Disease
*p-value calculated with “Never nGER” as a reference group
Figure 1

- 2640 participants in ECRHS I
- 2640 invited for ECRHS II
- 1761 participants in ECRHS II: 811 males, 950 females
- 879 non-participants
Figure 2
Figure 3