Original Article

# Impact of Rhinitis on Work Productivity: A Systematic Review

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***What is already known about this topic?*** Information on the economic impact of allergic rhinitis on work productivity remains fragmented and therefore cannot be taken efficiently into account by the medical community and policy makers.

***What does this article add to our knowledge?*** This systematic review confirms that rhinitis impacts at-work productivity more than absenteeism and provides a summary estimate that may serve as guidance for physicians and public health interventions.

***How does this study impact current management guidelines?*** Physicians should draw more attention to the burden of allergic rhinitis on work productivity, and inform the patient of the possible occupational impacts of the condition and the benefits of treatment.

**BACKGROUND: Allergic rhinitis (AR) is increasingly acknowledged as having a substantial socioeconomic impact associated with impaired work productivity, although available information remains fragmented.**

**OBJECTIVE: This systematic review summarizes recently available information to provide a quantitative estimate of the burden of AR on work productivity including lost work time (ie, absenteeism) and reduced performance while working (ie, presenteeism).**

**METHODS: A Medline search retrieved original studies from 2005 to 2015 pertaining to the impact of AR on work productivity. A pooled analysis of results was carried out with studies reporting data collected through the validated Work Productivity and Activity Impairment (WPAI) questionnaire.**

**RESULTS: The search identified 19 observational surveys and 9 interventional studies. Six studies reported economic evaluations. Pooled analysis of WPAI-based studies found an estimated 3.6% (95% confidence interval [CI], 2.4; 4.8%) missed work time and 35.9% (95% CI, 29.7; 42.1%) had impairment in at-work performance due to AR. Economic evaluations indicated that indirect costs associated with lost work productivity are the principal contributor to the total AR costs and result mainly from impaired**

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*Abbreviations used*
*AR- Allergic rhinitis*
*ARIA- Allergic Rhinitis and its Impact on Asthma*
*CI- Confidence interval*
*COPD- Chronic obstructive pulmonary disease*
*IQR- Interquartile range*
*RCT- Randomized controlled trial*
*SD- Standard deviation*
*SE- Standard error*
*SPS- Stanford Presenteeism Scale*
*SR- Systematic review*
*WPAI-AS- Work Productivity and Activity Impairment questionnaire-Allergy Specific*

**presenteeism. The severity of AR symptoms was the most consistent disease-related factor associated with a greater impact of AR on work productivity, although ocular symptoms and sleep disturbances may independently affect work productivity. Overall, the pharmacologic treatment of AR showed a beneficial effect on work productivity.**
**CONCLUSIONS: This systematic review provides summary estimates of the magnitude of work productivity impairment due to AR and identifies its main determinant factors. This information may help guide both clinicians and health policy makers.**  **(J Allergy Clin Immunol Pract 2018;6:1274-86)**

***Key words:*** *Absenteeism; Allergy; Rhinitis; Work productivity; Presenteeism*

Allergic rhinitis (AR) is a global public health issue due to its high prevalence and its adverse impacts on sleep, cognitive functioning, mood, and associated comorbid conditions, such as asthma and sinusitis, and ultimately on quality of life and work and school performance.[1-3]

A number of reviews have highlighted the socioeconomic burden of AR in terms of impaired work productivity, including lost work time (ie, absenteeism) and reduced performance while working (ie, impaired presenteeism).[4-8] Blanc et al[9] first reported that reduction in self-rated job effectiveness was more common in individuals with rhinitis (36%) than among those with asthma (19%), whereas absenteeism was similar in both conditions. US population-based surveys have provided estimates of the annual number of workdays missed because of AR ranging from 0.03 to 0.8 per employed individual.[10-13] Goetzel et al[14] combined data on work productivity impairment from 3 large-scale US surveys and concluded that "allergy" (excluding asthma) was associated with an average 3.4% (range: 0.3% to 9.0%) productivity loss due to work absence and an average 10.9% (range: 8.3% to 14.5%) reduction in at-work performance. Even though an increasing number of studies of AR have included quantitative and validated measures of absenteeism and presenteeism,[15] to our knowledge, no systematic review (SR) of this area has yet been conducted. Therefore, available information on the impact of AR on work productivity remains fragmented and cannot be efficiently taken into account to guide clinical practice and public health interventions.

This SR aimed to synthesize and critically analyze the available information pertaining to the burden of AR on work productivity both in terms of absenteeism and impaired presenteeism to derive summary quantitative estimates of these effects. The secondary aim of this SR was to identify the factors that may affect, either negatively or positively, these productivity impairments.

## METHODS

### Protocol

This SR was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (www.prisma-statement.org).[16]

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Conflicts of interest: D. Price (all fees paid to Observational and Pragmatic Research Institute) is a board member for Aerocrine, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis, and Teva Pharmaceuticals; has received consultancy fees from Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Meda, Mundipharma, Napp, Novartis, Pfizer, Teva Pharmaceuticals, and Theravance; has received research support from UK National Health Service, British Lung Foundation, Aerocrine, AKL Ltd, AstraZeneca, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis, Pfizer, Respiratory Effectiveness Group, Takeda, Teva Pharmaceuticals, Zentiva, and Theravance; has received lecture fees from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Meda, Merck, Mundipharma, Novartis, Pfizer, Skyepharma, Takeda, and Teva Pharmaceuticals; has received fees for manuscript preparation from Mundipharma and Teva Pharmaceuticals; has received travel support from Aerocrine, Boehringer Ingelheim, Mundipharma, Napp, Novartis, Teva Pharmaceuticals, and AstraZeneca; has received payment for patient enrollment or completion of research from Chiesi, Teva Pharmaceuticals, Zentiva, and Novartis; has received payment for developing educational materials from Novartis and Mundipharma; has stock/stock options from AKL Ltd which produces phytopharmaceuticals; and owns 74% of the social enterprise Optimum Patient Care Ltd, UK, and 74% of Observational and Pragmatic Research Institute Pte Ltd, Singapore. A. L. Valero has received consultancy fees from FAES, Orion Pharma, Novartis, Sanofi, Stallergenes, Meda, GlaxoSmithKline, Chiesi, AstraZeneca, Zambon Esteve, Uriach, and VIFOR; and has received research support from Novartis, Leti, Uriach, and Meda. J. Bousquet has received personal fees for being on the scientific and advisory board for Almirall, Meda, Merck, MSD, Novartis, Sanofi-Aventis, Takeda, Teva, and Uriach; and has received lecture fees from Almirall, AstraZeneca, Chiesi, GSK, Meda, Menarini, Merck, MSD, Novartis, Sanofi-Aventis, Takeda, Teva, and Uriach. The rest of the authors declare that they have no relevant conflicts of interest.

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**TABLE I.** Observational surveys: summary findings

| Reference | Working AR adults | Severity of AR | Duration of AR | Questionnaire instrument | Work time missed (absenteeism) | Impairment in at-work productivity (presenteeism) |
|---|---|---|---|---|---|---|
| Collins et al, 2005[44] | 1472 | NA | NA | SPS | Mean (95% CI) missed work time: 0.9 h (0.7-1.1) in the last 4 wk (estimate: 9.9 d/y)* | Mean (95% CI) work impairment: 18.2 (17.5-18.8) |
| Bousquet et al, 2006[17] | 84 | Mild | IAR | WPAI-AS | 0 | Median (IQR) % work impairment: 20 (10-30) |
| | 66 | Mild | PAR | | 0 | Median (IQR) % work impairment: 20 (0-40) |
| | 894 | M/S | IAR | | 0 | Median (IQR) % work impairment: 40 (20-70) |
| | 1107 | M/S | PAR | | 0 | Median (IQR) % work impairment: 40 (20-62) |
| Lamb et al, 2006[18] | 4524 | NA | NA | WPSI | Average missed work time: 3.6 d/y | Unproductive work due to AR: 2.3 h/d when experiencing Sx |
| Stull et al, 2007[19] | 301 | NA | NA | WPAI-AS | Mean (SD) % missed work time: 6.8 (14.6) | Mean (SD) % work impairment: 40.0 (26.9) |
| Szeinbach et al, 2007[20] | 577 | NA | NA | 10-point scale | Average missed work time:1 h/wk (range: 0-32 h) (estimate: 5.5 d/y)* | NA |
| Valovirta et al, 2008[45] | 2287 | NA (AA: 42%) | PAR: 62% | Nonvalidated | Taking time off work in the past year due to AR: 26% | Work affected (unable to concentrate): average 49% |
| Meltzer et al, 2009[21] | 3831 | M/S: 66% | NA | Nonvalidated | • Mean (SD) entire workdays missed due to AR: 0.4 (2.0) past 4 wk (estimate: 4.4 d/y)† vs 0.2 (1.5) for non-AR (estimate: 2.2 d/y)*<br>• Mean (SD) partial workdays missed due to AR: 0.3 (1.9) past 4 wk vs 0.1 (1.4) for non-AR | NA |
| Van Cauwenberge et al, 2009[22] | 600 | NA | SAR: 59% | Nonvalidated | Absence from work, late arrival, or early departure: 27%, average 6 h work missed per symptomatic wk | Moderate or considerable effect of AR on concentration: 31% |
| Neffen et al, 2010[23] | 1088‡ | NA | SAR: 62% | Nonvalidated | Missed work because of AR (past 12 mo): 20% | Interference with work performance: 33%; 30% point decrease in work productivity related to AR |
| de la Hoz et al, 2012[25] | 134 | M/S: 61%‡ | NA | WPAI-generic | Adjusted mean (SE): 4.6 (1.1)% | Adjusted mean (SE): 23.5 (1.6)% |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Katelaris et al, 2011[26] | | 1043‡ | NA | SAR: 66% | Nonvalidated | Missed work because of AR (past 12 mo): 25% | Interference with work performance: 50%; 25% point decrease in work productivity related to AR |
| Demoly et al, 2011[40] | | 702‡ | NA (AA: 22%) | SAR: 51% | Nonvalidated | Sick leave at the time of physician visit: 5.1% for an average of 4.5 d | NA |
| Bhattacharyya, 2012[46] | NA | | NA | NA | Not detailed | Mean (SE) incremental workdays lost/y: 0.6 (0.4) vs non-AR participants | Proportion (SE) of participants with work limitation: 13.9 (1.0)% vs 10.4 (0.3) in non-AR participants; adjusted OR: 1.43 (95% CI: 1.2-1.7) |
| Keith et al, 2012[28] | | 1001‡ | NA (AA: 27%) | SAR: 51% | 3-point scale | NA | Reduced productivity during the allergy season: 2% very troublesome, 8% moderately troublesome |
| Meltzer et al, 2012[27] | | 2500‡ | NA (AA: 32%) | PAR: 56% | Nonvalidated | Missed work because of AR during the past 12 mo: 30% | Interference with work performance: 42%; 23% point decrease in work productivity related to AR |
| Bielory et al, 2014[29] | | 962 | NA | SAR: 78% | 100-point scale | Missed work because of AR (unknown period of time assessed): 3% | Reduced productivity by 26% points (from 91 to 65) when allergy Sx at their worst vs no Sx |
| Jantunen et al, 2014[41] | | 636 | NA | NA | 100-point scale | Mean (SD) missed work time: 0.8 (5.1) d/y | Mean (SD) % reduction in work productivity: 15.2 (14.5) % when Sx |
| Price et al, 2015[30] | | 691 | M/S: 75% (AA: 30%) | SAR: 100% | Categorical scale of impairment from 10% to 100% | Mean (SD) missed work time: 4.1 (16.4) d/y in M/S AR vs 2.5 (7.7) d/y in mild AR | • Decreased work performance >50% in 32.8% of M/S AR vs 12.2% of mild AR<br>• Decreased work performance on mean (SD) 37.7 (53.0) d/y in M/S AR vs 21.0 (29.9) d/y in mild AR. |
| Colas et al, 2016[43] | | 241 | Mild | NA | WPAI-AS | Mean (SD) % missed work time: 0.8 (1.6) (n = 18) | Mean (SD) % work impairment: 8.9 (11.7) (n = 18) |
| | | | M/S | NA | | Mean (SD) % missed work time: 1.9 (6.0) (n = 223) | Mean (SD) % work impairment: 16.9 (17.1) (n = 199) |

*(continued)*

**TABLE I.** *(Continued)*

| Reference | Working AR adults | Severity of AR | Duration of AR | Questionnaire instrument | Work time missed (absenteeism) | Impairment in at-work productivity (presenteeism) |
|---|---|---|---|---|---|---|
| | | NA | IAR | | Mean (SD) % missed work time: 1.6 (4.4) (n = 64) | Mean (SD) % work impairment: 8.3 (8.8) (n = 56) |
| | | NA | PAR | | Mean (SD) % missed work time: 1.9 (6.2) (n = 177) | Mean (SD) % work impairment: 19.0 (18.0) (n = 161) |

*AA*, Associated asthma; *AR*, allergic rhinitis; *CI*, confidence interval; *IAR*, intermittent AR; *IQR*, interquartile range; *M/S*, moderate/severe AR; *OR*, odds ratio; *PAR*, persistent AR; *SAR*, seasonal AR; *SD*, standard deviation; *SE*, standard error; *SPS*, Stanford Presenteeism Scale; *Sx*, symptoms; *WPSI*, Work Productivity Short Inventory; *WPAI-AS*, Work Productivity and Activity Impairment questionnaire-Allergy Specific.
*Estimate based on an 8-h work day, 5 workdays per week, and 220 workdays per year.
†Severity assessed using the Clinical Global Impression (CGI) generic scale.
‡Unknown working status.

**Eligibility criteria.** We screened all original studies with an English abstract containing information on work productivity and/or indirect costs of rhinitis and published between January 2005 and December 2015. Case series, review articles, and model-based economic evaluations were excluded. We did not consider studies published before 2005 as they have already been reviewed previously.[4]

**Information sources and search strategy.** The online database PubMed was searched using the following keywords: work [and] productivity [and] rhinitis; WPAI [and] rhinitis; productivity [and] rhinitis; and costs [and] work [and] rhinitis. Other databases were not searched, but we used the alternative strategy of sending the list of retrieved publications to an international panel of 11 experts in the field of allergy from 10 countries (Table E1, available in this article's Online Repository at www.jaci-inpractice.org) asking them if they were aware of any other relevant published or unpublished data. In addition, the publications cited in the reference lists of the retrieved studies as well as review articles were carefully scrutinized to ensure that no original published data had been missed in the original search.

**Selection of studies.** The 41 retrieved papers were screened for eligibility by 2 independent reviewers (JB and OV) followed by full text evaluation of the 35 articles that met the initial inclusion criteria (see Figure E1 this article's Online Repository at www.jaci-inpractice.org). Twelve studies were excluded because of methodological issues or missing data (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). This process left 23 remaining studies.[17-39] The expert panel feedback identified 4 additional studies that were included in the analysis.[40-43] Another 3 relevant publications were retrieved through the analysis of citations lists.[44-46]

**Data collection process.** The data from the 30 included studies were extracted in a standardized manner and verified by 2 authors (OV and JB) using a list of predefined variables (Table E3, available in this article's Online Repository at www.jaci-inpractice.org). The authors were contacted whenever possible to obtain additional information unavailable in the original publication.[30,36,41,43]

**Assessment of the quality of selected studies.** The studies were classified into 3 categories: (1) observational surveys; (2) interventional studies; and (3) economic evaluations of the impact of AR on work productivity. Bias in the observational surveys was evaluated using the Newcastle-Ottawa Quality scale for assessing the quality of cohort studies in meta-analyses (www.ohri.ca/programs/clinical_epidemiology/oxford.htm). The risk of bias in randomized controlled trials (RCTs) was assessed using the descriptive Cochrane Collaboration's "Risk of bias" tool.[47]

## Data analysis

Data of studies using the Work Productivity and Activity Impairment-Allergy Specific (WPAI-AS) instrument were pooled to estimate the magnitude of the work productivity impairment related to AR. The WPAI-AS was selected as the outcome measure for this pooled analysis because it has been extensively validated in a large variety of health disorders[15,48,49] (http://www.reillyassociates.net/WPAI_References.html) and was the most commonly used instrument in the retrieved studies. The WPAI instrument produces 3 outcome measures of work disability: (1) the work time missed due

**TABLE II.** Interventional studies: work productivity impairment at baseline assessment

| Reference | Duration of AR | Severity of AR | Intervention group | No. of participants | % work time missed (absenteeism)* | % impairment in at-work productivity (presenteeism)* | % overall work impairment* |
|---|---|---|---|---|---|---|---|
| Okubo et al, 2005[31] | SAR | M/S | Fexofenadine | 79 | Mean (SD): 1.1 (4.5) | Mean (SD): 39.1 (27.6) | Mean (SD): 39.4 (27.9) |
| | | | Placebo | 89 | Mean (SD): 0.3 (1.7) | Mean (SD): 36.6 (25.8) | Mean (SD): 36.7 (25.9) |
| Fairchild et al, 2007[33] | SAR | M/S | Olopatadine NS 0.6% | 293 | NA | NA | Mean (SD): 48.5 (24.7) |
| | | | Olopatadine NS 0.4% | 303 | NA | NA | Mean (SD): 45.0 (26.3) |
| | | | Placebo | 297 | NA | NA | Mean (SD): 44.1 (25.2) |
| Bousquet et al, 2009[34] | PAR: 62% | M/S: 72% | ARIA guidelines | 339 | 0 | Median (IQR): 30 (20-50) | Median (IQR): 30 (20-50) |
| | | | Free-choice | 342 | 0 | Median (IQR): 30 (10-50) | Median (IQR): 30 (10-50) |
| Bousquet et al, 2009[35] | IAR | M/S | Desloratadine | 262† | NA | NA | Mean (SEM): 46.4 (2.4) |
| | | | Placebo | 256† | NA | NA | Mean (SEM): 41.4 (2.3) |
| Bousquet et al, 2010[36] | PAR | M/S | Desloratadine | 301† | NA | NA | Mean (SEM): 48.0 (2.4) |
| | | | Placebo | 261† | NA | NA | Mean (SEM): 47.0 (2.3) |
| Mansfield, 2010[37] | SAR | M/S | Levocetirizine | 235 | Mean (SD): 4.5 (12.9) | Mean (SD): 51.8 (24.2) | Mean (SD): 52.9 (24.9) |
| | | | Placebo | 233 | Mean (SD): 3.5 (9.8) | Mean (SD): 49.0 (24.2) | Mean (SD): 49.9 (24.6) |
| Meltzer et al, 2010[38] | PAR | M/S | Mometasone NS | 20 | Mean (range): 4.7 (0-33.3) | Mean (range): 5.9 (2.0-9.0) | NA |
| | | | Placebo | 9 | Mean (range): 4.4 (0-20.0) | Mean (range): 5.9 (3.0-9.0) | NA |
| Segall et al, 2010[39] | SAR | M/S | Levocetirizine | 216 | Mean (SD): 3.8 (11.2) | Mean (SD): 51.6 (24.1) | Mean (SD): 52.5 (24.6) |
| | | | Placebo | 227 | Mean (SD): 3.3 (9.4) | Mean (SD): 49.3 (24.0) | Mean (SD): 50.1 (24.3) |

*AR*, Allergic rhinitis; *ARIA*, Allergic Rhinitis and its Impact on Asthma; *IAR*, intermittent AR; *IQR*, interquartile range; *M*, mild AR; *M/S*, moderate/severe AR; *NA*, not available; *NS*, nasal spray; *PAR*, persistent AR; *SAR*, seasonal AR; *SD*, standard deviation.

*Assessed using the Work Productivity and Activity Impairment-Allergy Specific (WPAI-AS) questionnaire.

†Unknown working status.

**TABLE III.** Pooled analysis of the impact of rhinitis on work productivity: estimates weighted for variance

| | Absenteeism, %* | | | | Impaired presenteeism, %* | | | | Overall work productivity impairment, %* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study type | N studies (references) | N strata | N participants | Mean % (95% CI) | N studies (references) | N strata | N participants | Mean % (95% CI) | N studies (references) | N strata | N participants | Mean % (95% CI) |
| All studies | 6[19,25,31,37,39,43] | 8 | 1666 | 3.6 (2.4; 4.8) | 8[17,19,25,31,34,37,39,43] | 15 | 4563 | 35.9 (29.7; 42.1) | 11[17,19,25,31,33-37,39,43] | 22 | 6535 | 39.4 (34.8; 44.0) |
| By study design: | | | | | | | | | | | | |
| Observational | 3[19,25,43] | 3 | 676 | 4.3 (1.0; 7.7) | 4[17,19,25,43] | 7 | 2803 | 28.6 (19.8; 37.5) | 4[17,19,25,43] | 7 | 2802 | 29.3 (21.3; 37.4) |
| Interventional | 3[31,37,39] | 5 | 990 | 3.2 (1.9; 4.4) | 4[31,34,37,39] | 8 | 1760 | 42.2 (34.9; 49.6) | 7[31,33-37,39] | 15 | 3733 | 44.2 (39.9; 48.4) |
| By disease pattern: | | | | | | | | | | | | |
| IAR/SAR | 4[31,37,39,43] | 6 | 1054 | 2.9 (1.8; 4.0) | 5[17,31,37,39,43] | 9 | 2113 | 37.5 (23.8; 51.3) | 7[17,31,33,35,37,39,43] | 14 | 3523 | 41.2 (33.7; 48.6) |
| PAR | 1[43] | 1 | NA | NA | 3[17,34,43] | 5 | 2015 | 28.0 (19.8; 36.2) | 4[17,34,36,43] | 7 | 2522 | 33.7 (26.4; 40.9) |
| By disease severity: | | | | | | | | | | | | |
| Mild AR | 1[43] | 1 | NA | NA | 2[17,43] | 3 | 168 | 16.3 (8.9; 23.7) | 2[17,43] | 3 | 168 | 16.5 (9.6; 23.5) |
| M/S AR | 5[25,31,37,39,43] | 7 | 1347 | 3.1 (2.1; 4.1) | 7[17,25,31,34,37,39,43] | 12 | 4094 | 38.1 (31.5; 44.8) | 10[17,25,31,33-37,39,43] | 19 | 6066 | 41.4 (36.7; 46.0) |

*AR*, Allergic rhinitis; *CI*, confidence interval; *IAR*, intermittent AR; *M/S*, moderate/severe AR; *NA*, not appropriate; *PAR*, persistent AR; *SAR*, seasonal AR.
*Assessed using the Work Productivity and Activity Impairment-Allergy Specific (WPAI-AS) questionnaire.

to a specific health condition (ie, absenteeism); (2) the productivity impairment while working due to the specific health condition (ie, impaired presenteeism); and (3) the overall work impairment that is the sum of absenteeism and impaired presenteeism.[15,48] These metrics are expressed as percentages (from 0% to 100%), with higher percentages indicating greater impairment. These were reported as noninteger summary values with a measure of variability for the distribution (eg, a mean and standard deviation [SD] or a median and interquartile range [IQR]) that varied among the studies.

Baseline preintervention data that were reported separately by treatment versus control group in RCTs contributed separately to the pooled estimate, and, whenever relevant, stratified data by the pattern of AR (ie, seasonal/intermittent vs persistent) or disease severity (mild vs moderate-to-severe) also contributed separately to the overall pooled estimates.

For each WPAI metric (ie, absenteeism, presenteeism, and overall productivity impairment), the overall or subsets of pooled estimates of the mean value with its corresponding 95% confidence interval (95% CI) were calculated by weighting for the variance of each contributing value included in the estimate using a random effect approach, because heterogeneity among studies was high in all pooled estimated. Because individual studies could report either the standard error (SE), SD, or IQR, the sample variance of each reported metric was derived by applying the following formulae as appropriate: $V = n \times SE^2$, $V = SD^2$, or $V = (IQR/1.35)^2$, assuming normal distributions. Those sample variances were further transformed into the variances of the mean dividing by n, thus taking into account the size of the various studies.

Pooling was not possible for absenteeism in persistent and mild AR because only a single study/stratum was applicable. We also excluded from the pooled analyses data for the stratum of observations for the placebo group in 1 interventional study[31] because it reported an extreme variance estimate that could not be verified. Pooled analyses were performed with arithmetic calculations of spreadsheet-entered data in Excel. A pooled analysis of the effects of treatment interventions on work productivity could not be conducted because data were not collected using the WPAI-AS[32] or were not appropriately reported.[31,33,37-39]

As a further approach to pooled estimates that did not presume a normal distribution of the mean values for absenteeism, presenteeism, or overall impaired productivity, we re-estimated these using a hierarchical modeling Bayesian meta-analytic approach. This allowed us to presume a Beta distribution for these data, given probabilities bounded between 0 and 1. Each outcome was modeled with 1 million draws using Stan software (http://mc-stan.org/).

## RESULTS

The 30 selected studies included 19 observational surveys[17-23,25-30,40,41,43-46] and 9 interventional studies.[31-39] Six studies reported economic evaluations,[18,24,32,41-43] among which 3 were also identified among the observational surveys[18,41,43] and 1 among interventional studies.[32]

### Characteristics of observational surveys

The surveyed populations, diagnostic criteria, and reported outcomes of the 19 observational surveys are summarized in Table I and Table E4 (available in this article's Online Repository at www.jaci-inpractice.org). The criteria and results of quality assessment are detailed in Table E5 (available in this article's Online Repository at www.jaci-inpractice.org).

**Populations.** The participants with AR were recruited from various population sources (Table E4, available in this article's Online Repository at www.jaci-inpractice.org). Six studies compared AR individuals with referent groups without AR derived from the same population,[18,21,22,25,44,46] but adjustment for confounding demographic characteristics and multimorbidity was performed in only 2 studies.[25,46]

**Characteristics of AR.** The diagnosis of AR was documented using various criteria as detailed in Table E4 (available in this article's Online Repository at www.jaci-inpractice.org). Ascertainment of allergen sensitization through skin-prick tests and/or serum-specific IgE antibodies was used as a diagnostic criterion in only 3 surveys[25,40,43] and reported to be present in 41% to 55% of the participants with AR in 3 other studies.[17,19,26]

Five observational surveys provided the proportion of participants with moderate-to-severe AR (61% to 93%) (Table I).[17,21,25,30,43] Work productivity was reported separately for mild and moderate-to-severe AR in only 2 studies.[17,43] Eleven studies reported the duration of AR symptoms.[17,22,23,26-30,40,43,45] The proportion of persistent AR among these studies ranged from 0% to 72%. Data on work productivity were provided separately for persistent and intermittent AR in only 2 studies.[17,43]

**Outcomes.** Seven surveys collected data on the impact of AR on work productivity using validated instruments (Table I): the WPAI instrument either in its specific version for allergic diseases (WPAI-AS)[17,19,30,43] or in its generic version,[25] the Stanford Presenteeism Scale (SPS),[44] and the Work Productivity Short Inventory questionnaire.[18] The recall periods assessed by these questionnaires were 7 days, 4 weeks, and 12 months, respectively. In one prospective cohort study of participants with AR recruited in a random sample of specialized clinics in Spain, the WPAI-AS questionnaire was administered quarterly over a 1-year period.[43] The remaining observational surveys collected information on the impact of AR on work productivity using diverse nonvalidated instruments.

### Characteristics of interventional studies

**Populations.** Eight of the nine interventional studies (Table II and Table E6, available in this article's Online Repository at www.jaci-inpractice.org) were RCTs evaluating the effects of AR medications on work productivity.[31-33,35-39] One study was a pragmatic, investigator-randomized design and compared the treatment of AR based on the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines with a "free-choice" strategy.[34] For 2 studies that failed to provide the number of enrolled participants who were currently employed, work and school productivity impairments could not be differentiated.[35,36] Quality assessment of interventional studies is presented in Table E7 (available in this article's Online Repository at www.jaci-inpractice.org).

**Characteristics of AR.** Sensitization to relevant allergens was ascertained in all participants with AR, although the tested allergens were not detailed in 4 studies.[33,35,36,38] Five RCTs evaluated participants with "seasonal AR"[31,33,37,39] and 1 RCT included participants with "intermittent AR."[35] Symptom severity at baseline was categorized according to a symptom score in 6 RCTs and to the ARIA grades in 1 study,[34] and was not specified in 1 study.[33] The majority (n = 7) of the 9 RCTs enrolled participants with moderate-to-severe AR at baseline (Table E6, available in this article's Online Repository at www.jaci-inpractice.org).[31,32,35-39]

**Outcomes.** The impact of AR on work productivity was assessed using the WPAI-AS questionnaire in 8 RCTs (Table II).

### Absenteeism

Seven observational surveys reported that 3% to 30% of participants "missed work time due to AR,"[22,23,26,27,29,40,45] but failed to provide any quantitative estimate of absenteeism (Table I). Six observational surveys provided quantitative estimates of missed work time expressed as an absolute number of hours or days lost over variable intervals of time (Table I).[18,20,21,30,41,44] These estimates ranged from 0.8 to 9.9 workdays lost per year. The Medical Expenditure Panel Survey estimated a 0.6 incremental workday missed per year in participants with AR after controlling for sociodemographic characteristics, smoking, and multimorbidity.[46]

The pooled analysis of 6 WPAI-based studies (1666 participants) provided an overall pooled estimate of 3.6% (95% CI, 2.4; 4.8%) missed work time due to AR (Table III).[19,25,31,37,39,43] The re-estimated pooled value using Bayesian modeling was 3.5% (95% CI, 2.6; 4.7%). Stratified by observational versus interventional design, the pooled estimates were 4.3% and 3.2%, respectively (Table III). The pooled values for each stratum using Bayesian modeling were all within 0.1% of the original estimates (data not shown).

### Presenteeism

Seven observational surveys reported that 10% to 50% of participants with AR experienced "work limitation" related to AR (Table II).[22,23,26-28,30,45] Seven observational surveys assessed quantitatively the impact of AR on work productivity using various nonvalidated indices[18,23,26,27,29,30,41] (Table II).

The pooled analysis of impaired presenteeism included 8 studies using the WPAI-AS instrument (4563 participants) and provided an estimated 35.9% (95% CI, 29.7; 42.1%) impairment in work performance due to AR (Table III).[17,19,25,31,34,37,39,43] The re-estimated pooled value using Bayesian modeling was 35.8% (95% CI, 30.2; 41.7%). In stratified analyses, pooled estimates were higher for interventional versus observational studies (42.2% vs 28.6%); seasonal versus persistent AR (37.3% vs 28.0); and moderate-to-severe versus mild AR (38.1% vs 16.3%) (Table III). The differences between strata increased by a maximum of 0.4% substituting the estimates yielded through Bayesian modeling (data not shown).

### Overall work productivity

The pooled analysis of 11 studies using the WPAI-AS questionnaire (6536 participants) found an estimated 39.4% (95% CI, 34.8; 44.0%) impairment in overall work productivity due to AR (Table III).[17,19,25,31,33-37,39,43] The re-estimated pooled value using Bayesian modeling was 39.4% (95% CI, 35.1; 43.8%). Differences between strata were in the same direction and similar to those observed for impaired presenteeism, with the widest gap observed in overall work productivity being 24.9% comparing moderate-to-severe versus mild AR (Table III). This gap was only slightly narrower (24.3%) using Bayesian estimates (data not shown).

**TABLE IV.** Interventional studies: impact of treatment on work productivity

| Reference | Duration of AR | Severity of AR | Intervention group | N participants | Impact on missed work time (absenteeism) | Impact on at-work productivity (presenteeism) | Impact on overall work impairment |
|---|---|---|---|---|---|---|---|
| Okubo et al, 2005[31] | SAR | M/S | Fexofenadine<br>Placebo | 79<br>89 | NA | Mean difference vs baseline:<br>• Treated = −5.6%<br>• Placebo = +3.2% | Mean difference vs baseline:<br>• Treated = −5.5%<br>• Placebo = +3.4% |
| Bousquet et al, 2005[32] | PAR | M/S | Levocetirizine<br>Placebo | 186<br>196 | Mean (95% CI) no. of missed work d/mo:<br>• Treated = 0.2 (0.1-0.3)<br>• Placebo = 0.4 (0.3-0.8) | Mean (95% CI) work impairment, d/mo:<br>• Treated = 0.7 (0.5-0.9)<br>• Placebo =1.0 (0.8-1.3) | Mean (95% CI) total work days lost, days per mo:<br>• Treated = 0.9 (0.7-1.1)<br>• Placebo = 1.49 (1.2-2.0) |
| Fairchild et al, 2007[33] | SAR | M/S | Olo 0.6%<br>Olo 0.4%<br>Placebo | 293<br>303<br>297 | NA | NA | Mean difference vs baseline:<br>• Olo 0,6%: −15.2%<br>• Olo 0,4%: −13.0%<br>• Placebo: −7.4% |
| Bousquet et al, 2009[34] | PAR: 62% | M/S: 72% | ARIA<br>Free-choice | 339<br>342 | Missed % work time:<br>• ARIA group = 0<br>• Free-choice group = 0 | Median (IQR) difference vs baseline:<br>• ARIA group = −20 (−35; 0)%<br>• Free choice group = −10 (−30; 0)% | Median (IQR) difference vs baseline:<br>• ARIA group = −20 (−40; 0)%<br>• Free choice group = −10 (−30; 0)% |
| Bousquet et al, 2009[35] | IAR | M/S | Desloratadine<br>Placebo | 262<br>256 | NA | NA | Mean (SEM) difference vs baseline:<br>• Treated = −15.0 (2.8)%<br>• Placebo = −5.7 (2.7)% |
| Bousquet et al, 2010[36] | PAR | M/S | Desloratadine<br>Placebo | 301<br>261 | NA | NA | Mean (SEM) difference vs baseline:<br>• Treated = −15.9 (2.8)%<br>• Placebo = −11.9 (2.7)% |
| Mansfield, 2010[37] | SAR | M/S | Levocetirizine<br>Placebo | 235<br>233 | Mean (SD) % work time missed at baseline and endpoint:<br>• Treated = 4.5 (12.9); 1.2 (4.9)<br>• Placebo = 3.5 (9.8); 2.3 (8.8)Mean (95% CI) % difference vs placebo at endpoint: −1.4 (−2.6; −0.2) | Mean (SD) % work impairment at baseline and endpoint:<br>• Treated = 51.8 (24.2); 37.8 (21.4)<br>• Placebo = 49.0 (24.2); 40.9 (24.1)Mean (95% CI) % difference vs placebo at endpoint: −4.6 (−8.3; −0.9) | Mean (SD) % impairment in overall work productivity:<br>• Treated = 52.9 (24.9); 38.2 (21.8)<br>• Placebo = 49.9 (24.6); 40.9 (24.1)Mean (95% CI) % difference vs placebo at endpoint: −4.4 (−8.2; −0.6) |
| Meltzer et al, 2010[38] | PAR | M/S | Mometasone<br>Placebo | 20<br>9 | Mean difference vs baseline:<br>• Treated = −2.2%<br>• Placebo = +5.8% | Mean difference vs baseline:<br>• Treated = −1.9%<br>• Placebo = −0.1% | NA |
| Segall et al, 2010[39] | SAR | M/S | Levocetirizine<br>Placebo | 216<br>227 | NA | NA | Adjusted mean difference between groups = −4.44% |

*AR*, Allergic rhinitis; *ARIA*, Allergic Rhinitis and its Impact on Asthma; *CI*, confidence interval; *IAR*, intermittent AR; *IQR*, interquartile range; *M/S*, moderate/severe AR; *NA*, not available; *Olo*, Olopatadine nasal spray; *PAR*, persistent AR; *SAR*, seasonal AR.

**TABLE V.** Estimated costs of lost work productivity due to rhinitis

| Reference | Study design | Monetary unit (y) | Average daily wage* | Cost of absenteeism, mean per patient per year | Cost of presenteeism, mean per patient per year | Total cost of lost work productivity, mean per patient per year | Direct medical costs, mean per patient per year |
|---|---|---|---|---|---|---|---|
| Bousquet et al, 2005[32] | RCT of levocetirizine vs placebo (6 mo), 5 EU countries; 2001-2002 | € (2002) | 106.76 | | | | |
| | Levocetirizine group | | | 153.96 | 589.20 (3.8)† | 743.16 (3.4)† | 218.16 |
| | Placebo group | | | 406.80 | 948.12 (2.3)† | 1354.92 (13.5)† | 100.44 |
| Lamb et al, 2006[18] | Survey of 8267 US employees (WPSI, 12 mo); 2001-2002 | US$ (2002) | 274.00 | 182.99 | 409.56 (2.2)† | 592.58 | NA |
| Kim et al, 2010[24] | Population survey based on Korean NHIC data; 2007 | US$ (2009) | 82.51 | 11.53 | NA | NA | 49.10 |
| Jantunen et al, 2014[41] | Nationwide questionnaire panel survey, Finland; 2013 | € (2011) | 141.00 | 111.40 | 511.80 (4.6)† | 623.20 | NA |
| Cardell et al, 2016[42] | Questionnaire-based survey of a random population sample, Sweden; 2014 | € (2014) | NA | 78.0 | 672.8 (8.6)† | 750.8 (3.6)‡ | 210.3 |
| Colas et al, 2016[43] | Questionnaire-based survey of 498 AR participants recruited in a national random sample of 101 specialized clinics; follow-up of 12 mo; Spain; 2009 | € (2010) | NA | 90.19 | 1682.71 (18.7)† | 1772.90 (3.2)‡ | 553.80 |

*AR*, Allergic rhinitis; *NHIC*, National Health Insurance Corporation; *RCT*, randomized controlled trial; *WPSI*, Work Productivity Short Inventory questionnaire.
*National average of workers' daily wage used by investigators to calculate the cost components of AR.
†Cost of presenteeism/cost of absenteeism ratio.
‡Total cost of lost productivity/direct medical cost ratio.

## Comorbid ocular symptoms impacting work productivity

Two studies reported that ocular symptoms (conjunctivitis) in addition to nasal symptoms were associated with a more detrimental effect on work productivity[20] or "professional effectiveness."[22] One of these studies also documented an independent adverse effect of sleep disturbance and low health-related quality of life on work productivity.[20]

## Impact of pharmacologic treatment

Overall, RCTs reported a beneficial effect of the pharmacologic treatment of AR on work productivity (Table IV).[31,39] One study showed that treatment based on ARIA guidelines significantly improved absenteeism and presenteeism as compared with a "free-choice" treatment.[34]

## Comparison with other health conditions

A formal comparison of the work impairment due to AR with other chronic diseases could not be performed because the SR identified only 3 relevant surveys that used different outcome measures. Using the SPS, Collins et al[44] found that the mean work time missed (0.9 hour [95% CI: 0.7-1.1]) in the last 4 weeks and work performance impairment (18.2% [95% CI: 17.5-18.8%]) related to AR were similar to those attributed to asthma, arthritis, diabetes, heart and circulatory problems, and musculoskeletal disorders. Lamb et al[18] reported that the estimated mean total productivity loss per employee during the last year, including the number of days missed and the number of unproductive hours, was significantly higher for AR compared with 10 other chronic conditions, including high stress, migraine, depression, arthritis/rheumatism, anxiety disorders, respiratory infections, hypertension, diabetes, asthma, and coronary heart disease. Using the generic WPAI, de la Hoz et al[25] found that absenteeism was similar in AR (adjusted mean ± SE, 4.6 ± 1.1%) compared with diabetes (4.2 ± 1.7%) and hypertension (2.1 ± 1.5%) but significantly lower than in symptomatic depression (31.7 ± 2.6%). AR was associated with a significantly higher overall loss of productivity (adjusted mean ± SE, 26.6 ± 1.8%) than hypertension (8.8 ± 2.5%) and diabetes (16.7 ± 2.8%), but it was lower than in symptomatic depression (59.5 ± 4.3%).

## Economic evaluations

Six studies assessed the economic costs of lost work productivity related to AR (Table V).[18,24,32,41-43] Overall, these economic evaluations indicated that the costs of impaired presenteeism were 2.2- to 18.7-fold higher than those of absenteeism, whereas the total costs of lost productivity (ie, absenteeism plus impaired presenteeism) were 3.2- to 13.5-fold higher than the direct medical costs. The indirect costs resulting from lost work productivity represented 76% to 93% of the total AR costs.

A Swedish population-based questionnaire survey[42] showed that the cost of moderate-to-severe persistent AR was 4-fold higher than mild persistent AR. A prospective 1-year cohort study found that the mean indirect costs resulting from presenteeism were approximately 1.9-fold higher in moderate-to-severe AR compared with mild AR and 2.3-fold higher in participants with persistent AR compared with those with intermittent AR.[43] The cost of absenteeism did not differ according to the severity or duration of AR symptoms. In persistent

AR, the costs of absenteeism and presenteeism due to AR were significantly reduced in participants treated with levocetirizine as compared with placebo.[32]

## DISCUSSION

### Summary of evidence

The pooled analysis of WPAI-based studies identified in this SR showed that AR is associated with a substantial adverse impact on the productivity at work (ie, presenteeism) with an estimated 35.9% (95% CI, 29.7; 42.1%) impairment, whereas the impact on absenteeism was minimal (3.6% [95% CI, 2.4; 4.8%]). These figures are similar to previous estimates of absenteeism, whereas estimates of impaired productivity at work are higher than those reported in previous US surveys that used various instruments to quantify the impact of AR on work productivity.[10-14] The estimates derived in this SR are however in line with those reported by 2 recently published WPAI-based studies conducted in Asian health care settings that documented mean (SD) overall productivity impairment due to AR of 32% (26%) and 40% (29%).[50,51]

Overall, this SR indicated that the level of impaired productivity due to AR is at least similar to that reported in many other chronic diseases.[18,25,44] The recent Asian studies cited previously further confirm that overall work productivity is more impaired by rhinitis than asthma (33 [30]% vs 20 [25]%) and chronic obstructive pulmonary disease (COPD) (17 [27]% vs 15 [23]%).[50,51] In addition, our pooled estimate of the overall productivity impairment due to AR (39.4% [95% CI, 34.8; 44.0%]) is in line with the mean percentage impairment provided by a recent SR of WPAI-based studies in various chronic health disorders: depression (29%; range: 15% to 43%); COPD (31%; range: 19% to 42%); irritable bowel syndrome and constipation (36%; range: 21% to 51%); and arthritis (45%; range: 21% to 69%).[49] However, in this SR, the studies on asthma and "allergies" were pooled together and included only 2 studies on rhinitis.[17,48] Nevertheless, the impact of seasonal or intermittent AR is likely to be of more limited duration than other chronic diseases.

This SR confirmed that more severe AR is associated with a more detrimental impact on work productivity,[17,19,21,22,25,30,41,43] with a substantial difference of 24.9% and nonoverlapping 95% CIs between the pooled estimates of moderate-to-severe versus mild disease. These findings are further substantiated by a recent study showing a correlation between the WPAI-AS score and the overall intensity of AR symptoms assessed using a visual analog scale.[52] In addition, this SR indicated that associated conjunctivitis and sleep disturbances could have a detrimental effect on work productivity independently from nasal symptoms.[20,22] The aggravating role of ocular symptoms was further substantiated by an observational survey of patients with AR recruited by primary care physicians and specialists that, however, was not eligible for inclusion in this SR because detailed WPAI questionnaire data were not reported.[53] This study demonstrated that ocular symptoms were associated with a greater impact on absenteeism and productivity while at work, even after adjustment for the severity of nasal symptoms. A number of observational surveys in this SR reported on sleep problems related to AR,[17,19-21,23,26,27,40,45] but they failed to investigate the specific impact of sleep disorders on work productivity, with the exception of the study by Szeinbach et al.[20] These findings—if further confirmed—may have clinical implications because ocular symptoms and sleep disturbances are highly prevalent among patients with AR and are often underestimated by health care providers.[1,54,55] Greater awareness of these symptoms and their potential effects may help physicians to identify subjects with an increased risk of impaired work productivity and to target their treatment to reduce the work and economic impact of AR.

Although a formal meta-analysis of the effects of the pharmacological treatment of AR was not appropriate to the data available, the RCTs identified through this SR showed an overall beneficial effect of oral antihistamines and nasal sprays on work productivity. These findings are in line with a critical review of studies published before 2003 showing that treatment with nonsedating antihistamines reduces the productivity losses due to AR.[56]

Earlier population-based studies conducted in the USA provided a wide range of estimates of the indirect costs of AR, ranging from 7%[11] to 25%[10] of the total costs. Unfortunately, few studies have assessed both absenteeism and presenteeism.[6] The current SR indicates that: (1) the indirect costs associated with lost work productivity are the principal component of the total AR costs and result mainly from the costs of presenteeism and (2) the indirect costs of AR appear to be greater than or similar to those resulting from many other chronic diseases traditionally considered as being more important from a medical perspective.

### Limitations

Methodological weaknesses of this SR should be considered for interpreting its estimates of the burden of AR on work productivity. First, the pooled estimates of the impact of AR on work productivity were derived from a limited number of studies based on the validated WPAI instrument. These studies were heterogeneous in their findings that we addressed by relying on random effect modeling for pooled estimates. Moreover, additional analyses using a Bayesian approach stipulating a Beta rather than normal distribution of mean values yielded pooled estimates that were not substantially different from a standard meta-analytic approach. Many observational surveys used nonvalidated measures of at-work productivity. For example, most reports of the effects of pharmacological interventions presented data in a form that could not be utilized in a pooled analysis. The findings from these non-WPAI studies were only descriptively assessed and summarized.

Second, IgE sensitization to aeroallergens was not systematically documented in the majority of observational surveys. Thus, the findings derived from these surveys are likely to be relevant not only to AR, but also to other forms of rhinitis.

Third, most available studies had a substantial, although unquantifiable, potential for bias toward the selection of participants with more severe AR. The subjects with AR participating in population or patient panels[21-23,26-30,41] and "convenience" samples surveys[18,45] might be those who were more prone to report a higher impact of the disease. Individuals who seek primary health care[17,19,25,40,43] or managed care[20] are unlikely to accurately represent the whole population of individuals suffering from AR. Only 5 of the 19 observational surveys provided information on the severity of AR,[17,21,25,30,43] and data on work productivity impairment associated with mild AR were available in only 2 studies.[17,43] Moderate-to-severe AR seemed to be overrepresented in observational surveys as compared with existing

population-based data (eg, 29% to 40%[54,57]); the proportion of participants with moderate-to-severe AR ranged from 61% to 93% in the 5 surveys that provided this information.[17,21,25,30,43] In addition, RCTs are inherently affected by a selection bias toward more severe and/or symptomatic AR because, in these studies, only participants with a moderate-to-severe disease were enrolled. This may explain why the pooled estimates of overall productivity (Table III) were higher for interventional compared with observational studies, underscoring that differences in study design, including subject selection, can effect disability estimates despite using the same WPAI instrument.

Beyond these limitations, studies based on self-reporting may be affected by recall failure and attribution bias (eg, confusion about whether AR is the cause of the work impairment). Few available studies attempted to disentangle the impact of AR from that resulting from comorbid conditions, particularly asthma and rhinosinusitis, although these conditions may increase the adverse impact on work productivity.[58,59] Only 2 observational surveys took into account the potential confounding demographic characteristics and comorbidities in the analysis of their results.[25,46]

Another major limitation derives from the fact that the impact of seasonal AR cannot be estimated on an annual time framework. The WPAI-AS questionnaire is one of the best validated tools to assess absenteeism and presenteeism in AR.[15,48] The WPAI-AS questionnaire is applied for a 7-day recall period in an attempt at minimizing the recall bias. However, most studies evaluating specifically individuals with seasonal AR were interventional studies based on the WPAI-AS that were conducted during the relevant pollen season and failed to provide information on the total duration of the symptomatic period,[31,33,37,39] whereas work impairment has been significantly correlated with outdoor pollen and mold levels in individuals with AR.[60,61] Apps running on smartphone devices can help gather real-time information on daily work performance and AR symptoms over longer periods of time and, accordingly, should further reduce recall bias and make it possible to estimate more accurately the cumulative impact of seasonal and intermittent AR on work productivity.[62]

## CONCLUSIONS

This SR indicates that AR is substantially impairing at-work productivity (presenteeism) but only minimally absenteeism, although further studies assessing daily work productivity and severity of symptoms at the same time over prolonged periods and comparing with other chronic diseases are needed to better characterize the impact of AR. Nevertheless, the findings of this SR should increase the awareness of the medical community on the impact of AR on work productivity and provide an evidence-base to assist health care payers and policy makers implementing interventions to reduce the socioeconomic burden of AR.

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## ONLINE REPOSITORY

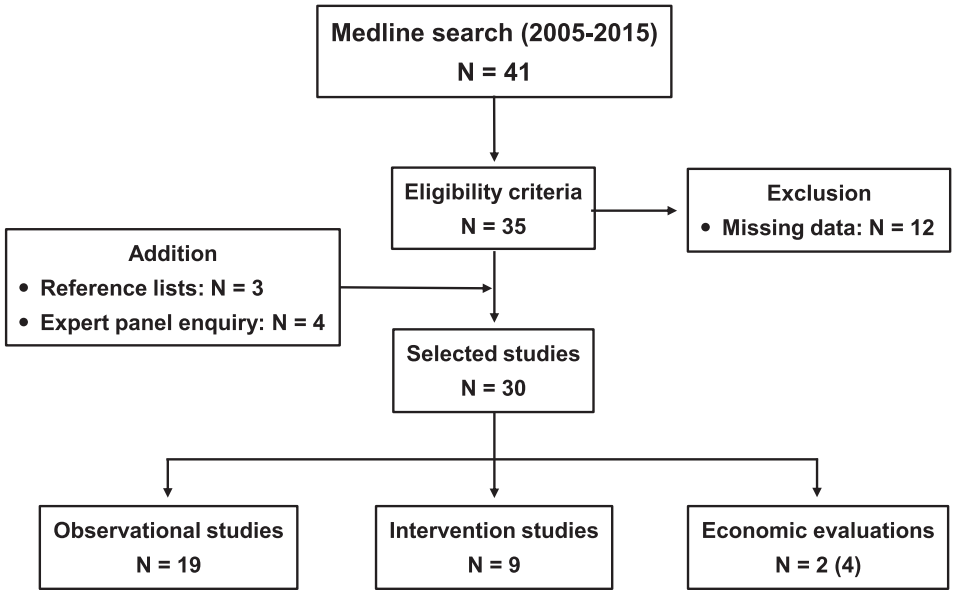


**FIGURE E1.** Flowchart of the retrieval and selection of included studies. The 6 economic evaluations of the impact of allergic rhinitis on work productivity included 3 studies that were also considered in observational surveys and one in interventional studies.

**TABLE E1.** List of surveyed experts

| Expert | Affiliation, country |
|---|---|
| Agache Ioana | Faculty of Medicine, Transylvania University, Brasov, Romania |
| Bachert Claus | Upper Airways Research Laboratory, ENT Dept, Ghent University Hospital, Ghent, Belgium |
| Cardell Lars-Olaf | Department of Ear, Nose, and Throat Diseases, Karolinska University Hospital, Stockholm, Sweden |
| Demoly Pascal | Department of Respiratory Diseases, Montpellier University Hospital, Montpellier, France |
| Fonseca Joao | Center for Health Technology and Services Research - CINTESIS, Faculdade de Medicina, Universidade do Porto; and Allergy Unit, CUF Porto Instituto & Hospital, Porto, Portugal |
| Haahtela Tari | Skin and Allergy Hospital, Helsinki University Hospital, Helsinki, Finland |
| Jantunen Juha | South Karelia Allergy and Environment Institute, Tiuruniemi, Finland |
| Kalayci Ömer | Pediatric Allergy and Asthma Unit, Hacettepe University School of Medicine, Ankara, Turkey |
| Price David | Observational and Pragmatic Research Institute, Singapore, Optimum Patient Care, Cambridge, UK, and Academic Centre of Primary Care, University of Aberdeen, Aberdeen, UK |
| Samolinski Boleslaw | Department of Prevention of Environmental Hazards and Allergology, Medical University of Warsaw, Warsaw, Poland |
| Valero Antonio Luis | Pneumology and Allergy Department Hospital Clínic, Clinical & Experimental Respiratory Immunoallergy, IDIBAPS, Barcelona, Spain |

**TABLE E2.** Studies excluded from analysis

| Reference | Study design | Methodological issues |
|---|---|---|
| Kakutani et al, 2005[E1] | Observational study of 512 workers with AR due to Japanese cedar pollen during the pollen season | • Article in Japanese with only abstract, tables, and figures in English |
| Saleem et al, 2009[E2] | Retrospective review of medical files of 169 patients seen by a single physician over a 30-mo period; assessment of the effect of treatment with various drugs | • Lack of clear definition of clinical outcomes<br>• Duration of treatment and follow-up not reported<br>• Duration of assessment of lost productivity not reported |
| Stull et al, 2009[E3] | Prospective survey of patients recruited during outpatient primary care or specialists office visits at 42 sites in the USA | • Same population as reported by Stull et al,[E4] 2007, without additional information on work productivity |
| Hellgren et al, 2010[E5] | Postal questionnaire sent to a randomized sample of adult population (n = 4000) stratified by gender and area of residence in Sweden | • No distinction between AR (only 12% of the sample) and the common cold |
| Sullivan et al, 2010[E6] | Cost-effectiveness analysis of treatment with desloratadine vs placebo in persistent AR | • Estimates of lost productivity derived from another clinical trial by Bousquet et al[E7] |
| Virchow et al, 2011[E8] | Cross-sectional study of 750 patients recruited by GPs or specialists comparing patients with AR with and without ocular symptoms (May-June 2008); 4 European countries | • Lack of detailed data on work productivity |
| Thorn et al, 2011[E9] | Online survey in 409 of 1920 eligible patients with AR (79%) or urticaria identified from 343 GP practices across Norway comparing the effectiveness of generic cetirizine/loratadine with previous second-generation antihistamines | • Lack of detailed data on work productivity in AR |
| Bousquet et al, 2013[E10] | Analysis of correlations between symptom improvement with desloratadine treatment and various indices (quality of life, work productivity, sleep) in 360 patients with AR derived from the study by Bousquet et al[E11] | • Lack of detailed data on work productivity (WPAI-AS scores) |
| Reinhold et al, 2013[E12] | Cost-effectiveness analysis of acupuncture in seasonal AR | • Lack of detailed data on work productivity |
| Zuberbier et al, 2014[E13] | Cost-of-illness evaluation of direct and indirect costs of allergic diseases in EU | • Data extrapolated from EU statistics and published medical literature<br>• Estimates for allergic diseases in general |
| Marcellusi et al, 2015[E14] | Cost-of-illness study of asthma and rhinitis in Italy | • Data extrapolated data from Italian epidemiologic studies and costs of health care<br>• Lack of evaluation of indirect costs for AR |
| Ostermann et al, 2015[E15] | Cost-of-illness study of 1137 patients with AR treated with homeopathy compared with control patients without homeopathy among a German health insurance company | • Lack of detailed data on work productivity specific to AR |

*AR*, Allergic rhinitis; *GP*, general practitioner; *WPAI-AS*, Work Productivity and Activity Impairment questionnaire-Allergy Specific.

**TABLE E3.** List of collected variables

| Variable | Definition |
|---|---|
| Study design | • Observational (prospective or retrospective), randomized controlled trial<br>• Economic evaluation of AR costs (cost-of-illness study, cost-effectiveness study) |
| Study settings | • Year and duration of the study<br>• Country |
| Nature of the cohort | • National/single center or multinational/multicenter<br>• Population-based, household panel, health care settings (general practice, specialist practice), managed care organization, patients panel, "convenience" samples of volunteers |
| Selection of the cohort | • Whole target population, random sample, nonrandomized sample, volunteers<br>• Participation rate |
| Control population | • Yes/no<br>• Nature of the controls: same source (yes/no) |
| Characteristics of the selected cohort | • Number of subjects, number of working subjects<br>• Mean age (no. of number of subjects aged >18 y), gender |
| Mode of data collection | • Questionnaire administered by health care professional, telephone interview, self-completed questionnaire<br>• Administrative data (database) |
| Ascertainment of AR | • Physician-based diagnosis, self-reported physician diagnosis, symptom-based diagnosis; database coding (ICD code)<br>• Currently treated or not<br>• Exclusion of cold/flu<br>• Allergy tests: skin-prick test and/or specific IgE performed or not performed or results not provided<br>• Allergy tests results used as a selection criterion (yes/no) and allergen(s) involved |
| Severity of AR | • ARIA classification (mild, moderate/severe)<br>• Symptom score and threshold used for inclusion |
| Duration of AR symptoms | • ARIA classification (intermittent, persistent), seasonal AR, perennial AR |
| Intervention | • Name and dosage of medication<br>• Description of other interventions |
| Assessment of work productivity | • Validated or nonvalidated questionnaire (description)<br>• Recall or assessment period |
| Outcomes of interest | • Work time missed (absenteeism)<br>• At-work productivity impairment (presenteeism)<br>• Overall work productivity impairment |
| Economic evaluation | • Cost of absenteeism<br>• Cost of presenteeism<br>• Direct health care costs |
| Comparison with other diseases | • Yes/no |
| Potential confounders taken into account | • Demographics (age, gender)<br>• Comorbidities (asthma, rhinosinusitis) |
| Data provided | • Mean/median values and measures of dispersion |
| Effects of disease-specific determinants on work productivity | • Severity and duration of AR symptoms<br>• Nature of nasal and ocular symptoms<br>• Effects of pharmacological treatment<br>• Other a posteriori identified factors |

*AR*, Allergic rhinitis; *ARIA*, Allergic Rhinitis and its Impact on Asthma; *ICD*, International Classification of Diseases.

**TABLE E4.** Characteristics of observational surveys

| Reference | Population and setting | Diagnosis of AR |
|---|---|---|
| Collins et al, 2005[E16] | 1,472 patients with AR (19%) of 7,797 workers of 5 locations of a chemical company; age: mean 43 y; self-completed Q; July 2002-November 2002; USA. Comparison vs employees with other diseases | Self-diagnosis; no data on allergy tests |
| Bousquet et al, 2006[E7] | 3,052 patients with AR recruited by 811 randomly selected GPs over 1 y; age: 18-80 y; self-administered Q; unknown timing; France. Severity and duration of AR taken into account | Physician-based diagnosis; 55.4% positive SPT or sIgE; 59.7% currently treated for AR Sx |
| Lamb et al, 2006[E17] | 8,267 volunteer employees recruited during health screenings at 47 employer locations; age: mean (SD), 41 (11.2) y; self-completed Q; December 2001-September 2002; USA. Comparison vs employees with other diseases | Self-reported Sx; no data on allergy tests |
| Stull et al, 2007[E4] | 404 patients with AR nonrandomly recruited in primary care or specialist (allergist or ENT) offices at 42 sites; age: ≥18 y; in-office self-completed Q; September-November 2005; USA | Physician-based diagnosis; 52% positive SPT and 48% evaluated for nasal congestion |
| Szeinbach et al, 2007[E18] | 2,065 patients with AR of a managed care organization; age: ≥18 y; postal self-completed Q; January 2000-December 2000; USA | ICD code; medical and prescription claims; no data on allergy tests |
| Valovirta et al, 2008[E19] | 3,562 patients with AR nonrandomly recruited among members of allergy patient organizations; age: NA; postal self-completed Q; unknown timing; 11 European countries (Patient Voice Allergy Survey) | Self-reported diagnosis (not known if physician based); no data on allergy tests |
| Meltzer et al, 2009[E20] | 3,831 patients with AR recruited in a national weighted household panel; age: 90.2% ≥18 y; postal self-completed Q; May-June 2004; USA. Comparison vs subjects without AR Sx | Self-reported Sx unrelated to cold or flu in the past 4 wk; no data on allergy tests |
| Van Cauwenberge et al, 2009[E21] | 1,201 eligible GPs from a panel of 2,817 GPs managed by a health care recruitment firm; age: 25-65 y; online Q; unknown timing; 8 countries (Australia, Brazil, Canada, France, Germany, Italy, Spain, UK). Comparison vs subjects without AR Sx | Self-diagnosis; no data on allergy tests |
| Neffen et al, 2010[E22] | 1,088 patients with AR randomly recruited from a 22,012-household panel*; age: ≥18 y; telephone and in-person interviews; February-April 2008; 8 Latin America countries (Allergies in Latin America Survey) | Self-reported physician diagnosis and either Sx or medication in the past 12 mo; no data on allergy tests |
| Katelaris et al, 2011[E23] | 1,043 patients with AR randomly recruited from a sample of 33,378-household panel*; age: ≥18 y; telephone and in-person interviews; December 2009-January 2010; 8 Asia Pacific countries (Allergies in Asia-Pacific Survey) | Self-reported physician diagnosis and either Sx or medication in the past 12 mo; positive SPT or sIgE in 41% of participants |
| Demoly et al, 2011[E24] | 902 patients recruited by 411 randomly selected GPs or allergists*; >12 y; unknown timing; France | Physician-based; positive SPT or sIgE |
| de la Hoz et al, 2012[E25] | 616 patients recruited in a national random sample of 74 primary care centers; age: >18 y; in-office self-completed Q; March-November 2005; Spain (CAPRI study). Comparison vs patients with other diseases adjusted using logistic regression analysis | Physician-based diagnosis, Sx for at least 2 y and T5SS >2/15; positive SPT or sIgE |
| Bhattacharyya, 2012[E26] | National household panel; age: mean 46.1 y; Q: computer-assisted personal interview (www.meps.ahrq.gov); 2007; USA (Medical Expenditure Panel Survey). Comparison vs population without AR adjusted for age, gender, race, ethnicity, education, insurance, region, marital status, and comorbidity index | ICD9 codes; no data on allergy tests |
| Keith et al, 2012[E27] | 1,001 patients with AR recruited by random-digit dialing of households nationwide*; age: ≥18 y; telephone interview; July 2006, Canada | Self-reported physician diagnosis or use of prescription/OTC medications to treat nasal Sx unrelated to cold or flu; no data on allergy tests |
| Meltzer et al, 2012[E28] | 2,933 patients with AR recruited random digit dialing of a 30,927-household panel*; age: ≥18 y; telephone interview; January 2006; USA (Allergies in America Survey) | Self-reported physician diagnosis and either Sx or medication in the last 12 mo; no data on allergy tests |
| Bielory et al, 2014[E29] | 2,046 patients with AR recruited from a national sample of landline and cell phone-only households; age:≥18 y; telephone interview; unknown timing; USA (Allergies, Immunotherapy, and Rhinoconjunctivitis Survey) | Self-reported physician diagnosis and Sx or use of prescription medication for allergies in the past 12 mo; no data on allergy tests |
| Jantunen et al, 2014[E30] | 635 patients with AR recruited from a nationwide panel of a market research company; age: 15-83 y; online Q; April 2013; Finland | Self-reported physician diagnosis; no data on allergy tests |

*(continued)*

**TABLE E4.** *(Continued)*

| Reference | Population and setting | Diagnosis of AR |
|---|---|---|
| Price et al, 2015[E31] | 1,000 patients with AR recruited from a nationwide patient panel database; age: ≥18 y; online Q; June-July 2011, UK | Self-reported physician diagnosis and current Sx; self-reported allergy tests |
| Colas et al, 2016[E32] | 498 patients with AR recruited in a national random sample of 101 specialized clinics; age: >18 y; in-office self-completed Q; April-December 2009; Spain (FERIN study). Severity and duration of AR and associated asthma taken into account | Physician-diagnosis; positive SPT or sIgE |

*AR*, Allergic rhinitis; *GP*, general practitioner; *ICD*, International Classification of Diseases; *NA*, data not available; *Q*, questionnaire; *SD*, standard deviation; *SPT*, skin-prick test; Sx: symptoms.
*Unknown working status.

**TABLE E5.** Quality assessment of observational surveys

| Reference | Representativeness of the cohort | Selection of control population | Case definition of AR | Ascertainment of outcome | Potential confounders taken into account | Completeness of data |
|---|---|---|---|---|---|---|
| | • 1 = whole target population, random sample<br>• 0 = volunteers, nonrandomized selected sample, no description of the derivation of the cohort | • 1 = same community<br>• 0 = volunteers, different source, no description of controls, no controls | • 1 = physician diagnosis, medical record; ICD code<br>• 2 = IgE-mediated sensitization to allergens<br>• 0 = self-report, no description | • 1 = secure record, validated questionnaire, structured interview<br>• 0 = nonvalidated questionnaire, no description | • 1 = demographic features, comorbidities, severity of rhinitis<br>• 0 = none | • 1 = number of employed subjects<br>• 2 = mean/median magnitude and measure of dispersion for absenteeism and presenteeism |
| Collins et al, 2005[E16] | 1 | 1 | 0 | 1 | 0 | 2 |
| Bousquet et al, 2006[E7] | 1 | 0 | 1 | 1 | 1 | 2 |
| Lamb et al, 2006[E17] | 0 | 1 | 0 | 1 | 0 | 1 |
| Stull et al, 2007[E4] | 0 | 0 | 1 | 1 | 0 | 2 |
| Szeinbach et al, 2007[E18] | 1 | 0 | 1 | 0 | 0 | 1 |
| Valovirta et al, 2008[E19] | 0 | 0 | 0 | 0 | 0 | 1 |
| Meltzer et al, 2009[E20] | 1 | 1 | 0 | 0 | 1 | 1 |
| Van Cauwenberge et al, 2009[E21] | 0 | 0 | 0 | 0 | 0 | 1 |
| Neffen et al, 2010[E22] | 1 | 0 | 0 | 0 | 0 | 0 |
| de la Hoz et al, 2012[E25] | 1 | 1 | 2 | 1 | 1 | 2 |
| Katelaris et al, 2011[E23] | 1 | 0 | 0 | 0 | 0 | 0 |
| Demoly et al, 2011[E24] | 1 | 0 | 2 | 0 | 0 | 0 |
| Bhattacharyya, 2012[E26] | 1 | 1 | 1 | 0 | 1 | 0 |
| Keith et al, 2012[E27] | 1 | 0 | 0 | 0 | 0 | 0 |
| Meltzer et al, 2012[E28] | 1 | 0 | 0 | 0 | 0 | 0 |
| Bielory et al, 2014[E29] | 1 | 0 | 0 | 0 | 0 | 1 |
| Jantunen et al, 2014[E30] | 0 | 0 | 0 | 0 | 0 | 2 |
| Price et al, 2015[E31] | 0 | 0 | 0 | 0 | 1 | 1 |
| Colas et al, 2016[E32] | 1 | 0 | 2 | 1 | 1 | 2 |

*AR*, Allergic rhinitis; *ICD*, International Classification of Diseases.

Adapted from the Newcastle-Ottawa Quality scale for assessing the quality of nonrandomized studies in meta-analyses (www.ohri.ca/programs/clinical_epidemiology/oxford.htm).

**TABLE E6.** Characteristics of intervention studies

| Reference | Study design and setting | Population | No. of subjects |
|---|---|---|---|
| Okubo et al, 2005[E33] | RCT of fexofenadine 60 mg BID for 2 wk, peak cedar pollen season in Japan (February-March 2003); single-center, Japan | • SAR (cedar pollen)<br>• Severity: T4SS >4/12 with ≥ 2 individual Sx rated higher than moderate<br>• Age: 20-55 y; Sx for ≥2 y; positive sIgE; resident of the urban area of Tokyo | • Treated: 104 (79 working)<br>• Placebo: 102 (89 working) |
| Bousquet et al, 2005[E34] | RCT of levocetirizine 5 mg OD for 6 mo; unknown timing; multicenter, multinational (5 European countries) | • PAR<br>• Severity: T5SS >6/15<br>• Age: >18 y; no minimum duration of Sx; positive SPT or sIgE to HDM and 1 pollen (grass or *Parietaria*) | • Treated: 278 (186 working)<br>• Placebo: 273 (196 working) |
| Fairchild et al, 2007[E35] | RCT of Olopatadine nasal spray 0.6% (2 sprays per nostril BID) for 2 wk vs Olopatadine 0.4% vs placebo; "winter and fall allergy season"; multicenter, USA | • SAR (various pollens)<br>• Severity: no criteria for inclusion<br>• Age: ≥12 y; ≥2 y of "nonrecalcitrant AR"; positive SPT to the relevant pollen | • Olopatadine 0.6%: 406 (293 working)<br>• Olopatadine 0.4%: 418 (303 working)<br>• Placebo: 416 (297 working) |
| Bousquet et al, 2009[E36] | Pragmatic investigator-randomized, open-label parallel study comparing treatment according to ARIA guidelines* with "free choice treatment" for 2 wk; patients recruited by 405 specialists; March-July 2002; multicenter, France | • SAR (grass pollen)<br>• Severity at baseline†: mild IAR: 12%; moderate/severe IAR: 26%; mild PAR: 16%, moderate/severe PAR: 46%<br>• Age: ≥18 y; positive SPT and/or sIgE | • ARIA guidelines: 417 (339 working)<br>• Free choice treatment: 422 (342 working) |
| Bousquet et al, 2009[E37] | RCT of desloratadine 5 mg OD for 2 wk; September 2006-November, 2007; multicenter, multinational (15 countries) | • IAR<br>• Severity: T5SS ≥6/15<br>• Age: ≥12 y; Sx for ≥2 y; positive SPT to nonspecified allergens | • Treated: 262‡<br>• Placebo: 256‡ |
| Bousquet et al, 2010[E11] | RCT of desloratadine 5 mg OD for 12 wk; November 2006-November 2007; multicenter, multinational (15 countries) | • PAR<br>• Severity: T5SS ≥8/15<br>• Age: ≥12 y; Sx ≥ 2 y; positive SPT to nonspecified allergens | • Treated: 301‡<br>• Placebo: 261‡ |
| Mansfield et al, 2010[E38] | RCT of levocetirizine 5 mg OD for 2 wk, March-June 2008; multicenter; USA | • SAR (grass pollen);<br>• Severity: T5SS ≥7/15<br>• Age: 18-65 y; pharmacotherapy for >2 y; positive SPT | • Treated: 235 (working)<br>• Placebo: 233 (working) |
| Meltzer et al, 2010[E39] | RCT of mometasone furoate nasal spray, 200 mcg OD for 4 wk; unknown timing; single-center; USA | • PAR<br>• Severity: nasal congestion score ≥4/6 and TNSS ≥12/24<br>• Age: 18-60 y; Sx for ≥2 y with self-reported sleep disturbances; positive SPT to a "relevant perennial allergen" (nonspecified) | • Treated: 20 working<br>• Placebo: 9 working |
| Segall et al, 2010[E40] | RCT levocetirizine 5 mg OD for 2 wk; Spring 2008; multicenter; USA | • SAR (grass pollen)<br>• Severity: T5SS ≥7/15<br>• Age: 8-65 y; positive SPT | • Treated: 287 (216 working)<br>• Placebo: 290 (227 working) |

*AR*, Allergic rhinitis; *ARIA*, Allergic Rhinitis and its Impact on Asthma; *HDM*, house dust mite; *IAR*, intermittent AR; *PAR*, persistent AR; *RCT*, randomized controlled trial; *SAR*, seasonal AR; *SPT*, skin-prick test; *Sx*, symptoms; *T4SS*, total four symptoms score; *T5SS*, total five symptoms score; *TNSS*, sum of individual nasal symptoms (obstruction/blockage/congestion, drainage [anterior/posterior], nasal itch, and sneezing) rated on a 0-6 severity scale.

*Adapted ARIA guidelines: ebastine 10 mg OD in mild IAR; ebastine 10 mg OD in mild PAR; ebastine 10 mg BID in moderate/severe IAR; ebastine 10 mg BID and intranasal corticosteroid in moderate/severe PAR.

†Moderate/severe AR defined as a ≥50-mm visual analog score.

‡Unknown working status.

**TABLE E7.** Quality assessment of randomized controlled trials

| Reference | Selection bias | | Performance bias | Detection bias | Attrition bias and reporting bias | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Incomplete/selective outcome data | | | |
| | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Outcome | Baseline | Endpoint | Other sources of bias |
| Okubo et al, 2005[E33] | L Randomly allocated | U ND | L D-B; P-C | L* | Absenteeism<br>Presenteeism<br>Overall productivity | L<br>L<br>L | U (incomplete)<br>U (incomplete)<br>U (incomplete) | • Selection of moderate/severe AR<br>• Exclusion of nasal comorbidities |
| Bousquet et al, 2005[E34] | L Randomly allocated | U ND | L D-B; P-C | L* | Absenteeism<br>Presenteeism<br>Overall productivity | U (missing)<br>U (missing)<br>U (missing) | U (incomplete)<br>U (incomplete)<br>U (incomplete) | • Selection of moderate/severe AR<br>• Exclusion of respiratory comorbidities |
| Fairchild et al, 2007[E35] | L Randomly allocated | U ND | L D-B; P-C | L* | Absenteeism<br>Presenteeism<br>Overall productivity | U (missing)<br>U (missing)<br>L | U (missing)<br>U (missing)<br>U (incomplete) | • Selection of moderate/severe AR<br>• Exclusion of "known anti-histamine nonresponders" |
| Bousquet et al, 2009[E37] | L Investigator-randomized | U ND | L Open-label, physician blinded | L* | Absenteeism<br>Presenteeism<br>Overall productivity | L<br>L<br>L | L<br>L<br>L | • Comorbidities not excluded |
| Bousquet et al, 2009[E36] | L Randomly allocated | L Computer-generated | L D-B; P-C | L* | Absenteeism<br>Presenteeism<br>Overall productivity | U (missing)<br>U (missing)<br>L | U (missing)<br>U (missing)<br>L | • Selection of moderate/severe AR<br>• Comorbidities not excluded |
| Bousquet et al, 2010[E11] | L Randomly allocated | L Computer-generated | L D-B; P-C | L* | Absenteeism<br>Presenteeism<br>Overall productivity | U (missing)<br>U (missing)<br>L | U (missing)<br>U (missing)<br>L | • Selection of moderate/severe AR<br>• Comorbidities not excluded<br>• Exclusion if need of rescue medication |
| Mansfield et al, 2010[E38] | L Randomly allocated | U ND | L D-B; P-C | L* | Absenteeism<br>Presenteeism<br>Overall productivity | L<br>L<br>L | U (incomplete)<br>U (incomplete)<br>U (incomplete) | • Selection of moderate/severe AR<br>• Exclusion of respiratory comorbidities |
| Meltzer et al, 2010[E39] | L Randomly allocated | U ND | L D-B; P-C | L* | Absenteeism<br>Presenteeism<br>Overall productivity | U (incomplete)<br>U (incomplete) | U (incomplete)<br>U (incomplete)<br>U (missing) | • Selection of moderate/severe AR<br>• Comorbidities not excluded<br>• Exclusion of patients with sleep disturbance score <2 and AHI >30 |
| Segall et al, 2010[E40] | L Randomly allocated | U ND | L D-B; P-C | L* | Absenteeism<br>Presenteeism<br>Overall productivity | L<br>L<br>L | U (missing)<br>U (missing)<br>U (incomplete) | • Selection of moderate/severe AR<br>• Exclusion of asthma requiring maintenance treatment |

*AR*, Allergic rhinitis; *AHI*, apnea-hypopnea index; *D-B*, double-blinded study; *H*, high risk of bias; *L*, low risk of bias; *ND*, not detailed; *P-C*, placebo-controlled study; *U*, uncertain risk of bias.
Adapted from the Cochrane Collaboration's "risk of bias" tool (available from: www.handbook.cochrane.org).
*Lack of detailed information on the blinding procedures for outcome assessment (ie, work productivity), but the outcome measurement is unlikely to be influenced because it was performed using a validated self-completed questionnaire (ie, Work Productivity and Activity Impairment questionnaire).

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