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Association of smoking with activity of ankylosing spondylitis – systematic review and meta-analysis

Syventävien opintojen kirjallinen työ
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Fysiatria

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Meta-analyysin tarkoitus oli selvittää kirjallisuusnäyttö tupakoinnin ja selkärankareuman aktiivisuuden yhteydestä mittaamalla eroa tupakoijien ja tupakoimattomien välillä Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) -mittarilla.

Tietolähteinä käytettiin Medlinea, Embasea, Scopusta sekä Web of Science -tietokantoja, joista systemaattinen haku suoritettiin helmikuussa 2020. Artikkelit valittiin kahden itsenäisen ja riippumattoman arvioijan toimesta ja systemaattisen harhan riskiä arvioitiin NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies -työkalulla muokatusti. Tiedot haettiin ennaltamääritellyillä ehdoilla.

Katsauksen aineistoon valittiin 18 artikkelia jotka kaikki käsittelivät poikkileikkausotantoja. Yhteenlaskettu otos koostui 3.599 tupakoijasta sekä 3.591 tupakoimattomasta selkärankareumapotilaasta. Yksittäisten tutkimusten potilasmäärät vaihtelivat 18 ja 1.141 välillä, selkärankareumadiagnoosista kulunut aika myös vaihteli huomattavasti - kolmesta kahteenkymmeneen vuoteen.

Meta-analyysissä BASDAI-pisteiden yhteenlaskettu painotettu keskiarvo oli 0,6 (95% luottamusväli 0,42 – 0,78) tupakoimattomien hyväksi. Ero oli tilastollisesti merkitsevä, mutta se jäi BASDAI-mittarin pienimmän kliinisesti merkittävän eron (0,8 pistettä) alapuolelle.

Näyttöä kliinisesti merkittävästä korrelaatiosta tupakoinnin ja selkärankareuman aktiivisuuden välillä mitattuna BASDAI-pisteytyksellä ei ole löytynyt.

Avainsanat: selkärankareuma, tupakointi

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Tuomas Kulju[1], Juhani Juhola[2], Mikhail Saltychev[2]

[1] Department of Clinical Medicine, Faculty of Medicine, University of Turku, Finland

[2] Department of Physical and Rehabilitation Medicine, Turku University Hospital and University of Turku, Turku, Finland

Address for correspondence:

Mikhail Saltychev, Department of Physical and Rehabilitation Medicine, Turku University Hospital, PO Box 52, FI-20521, Turku, Finland

E-mail: mikhail.saltychev@gmail.com, Tel.: +358 50 438 1761, Fax: +358 2 313 3730

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ABSTRACT

Objective: To evaluate the evidence regarding the association of smoking and disease activity in patients with SA measured by difference between smokers and non-smokers in the BASDAI scores.

Data sources: Medline, Embase, Scopus, and Web of Science databases were searched in February 2020.
Study selection: The study selection was performed by two independent reviewers. The risk of systematic bias was assessed according to the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.
Data extraction: The data were extracted using a pre-defined standardized form.
Results: The search resulted in 714 records. The final sample consisted of 18 papers with cross-sectional data. The sample sizes varied from 18 to 1,141. There was a substantial variation in the time since SA inset – from three up to 20 years. Most of the included studies reported better BASDAI scores for non-smokers. The pooled sample consisted of 3,599 smokers and 3,591 non-smokers. The sizes of smokers' groups varied widely from 19 up to 1,141 patients. The pooled mean difference in BASDAI scores was 0.6 (95% CI 0.42 to 0.78) points in favor of non-smokers. The pooled result fell below the level of minimal clinically important difference (MCID) for BASDAI of 0.8 points. There was a significant heterogeneity: Q=50.9 (df=17) and I^2=67%.

Conclusions: Smoking seems to be associated with severity of SA only weakly and clinically insignificantly when measured by BASDAI.

INTRODUCTION

Smoking is widely recognized as a risk factor for such connective tissue disorders as rheumatoid arthritis and systemic lupus erythematosus. It has been associated with disease activity and severity, response to therapy, and mortality rate by several reviews (Harrison 2002, Stolt, Bengtsson et al. 2003, Baka, Buzas et al. 2009, Onozaki 2009, Sugiyama, Nishimura et al. 2010, Klareskog, Malmstrom et al. 2011, Serra-Bonett and Rodriguez 2011, Chang, Yang et al. 2014, Lee, Bae et al. 2014, Jiang, Li et al. 2015, Anderson, Meyer et al. 2016, Speyer and Costenbader 2018, Vittecoq, Richard et al. 2018, Ishikawa and Terao 2020).

The correlation between smoking and ankylosing spondylitis (SA) is less studied. Smoking has been reported to be associated with earlier SA onset, disease activity, deteriorated functioning and quality of life, more severe radiographic inflammatory and structural lesions (Wendling and Prati 2013, Villaverde-Garcia, Cobo-Ibanez et al. 2017, Akar, Kaplan et al. 2018). That association may have a dose-dependent manner. The effects of smoking in SA may be related to the elevated level of inflammation, which is seen e.g. by a higher concentration of C-reactive protein, citrullinated vimentin, and metalloproteinases – a predictive factor for SA radiographic progression. Additionally, smoking may negatively affect bronchopulmonary and cardiovascular functions, which are already impaired by SA. Only a few reviews have previously focused on the effect of smoking in SA (Wendling and Prati 2013, Villaverde-Garcia, Cobo-Ibanez et al. 2017, Akar, Kaplan et al. 2018). Of them, one review was narrative (Wendling and Prati 2013) and only one review employed meta-analysis focusing on radiographic outcomes (Akar, Kaplan et al. 2018). A single previous systematic review has concentrated on clinically measured effects of smoking in SA. That review has suggested that smoking is associated with more severe pain, worse general health status, disease activity, physical immobility, and poorer quality of life (Villaverde-Garcia, Cobo-Ibanez et al. 2017). That review did not include a meta-analysis and graded the level of evidence as poor expressing also concern on inability to separate the effect of smoking from confounding factors. Thus, there is a lack of systematically evaluated evidence on the association of smoking with SA activity.

Several approaches have been introduced to assess the activity of SA (Garrett, Jenkinson et al. 1994), the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) being amongst the most validated and reliable scales (Madsen, Rytter et al. 2010). The BASDAI is often considered to be a golden standard for the task. The objective of this systematic review was to evaluate the evidence regarding the association of smoking and disease activity in patients with SA measured by difference between smokers and non-smokers in the BASDAI scores.

METHODS

Inclusion and exclusion criteria (PICO)

- Population: Adults with ankylosing spondylitis. Excluded: spondylitis related to other conditions e.g. other connective tissue disorders, Crohn disease etc. Patients were considered as smokers if they were current or previous smokers.
- Papers: Any design. Papers published in academic peer-reviewed journals, English language, abstract available. Excluded: theses, conference proceedings, case reports etc.
- Exposure: smoking defined as smoking in present or in the past regardless of duration or quantity
- Comparison: non-smoking status defined as never smoked.
- Outcome: difference between groups in disease activity measured by the BASDAI scale.

The initial intention was to include a wider variety of outcome measures such as changes in radiological progression, disease activity, function, and quality of life. However, this approach had to be abandoned after the selection based on full texts: there were 43 papers on the subject employing great spectrum of different and mostly incomparable outcomes. At that point, the decision was made to proceed with difference between groups in disease activity measured by the BASDAI scale as a single outcome.

Data sources

Medline via PubMed, Embase, Scopus, and Web of Science. The search clause for the Medline search was:

("smoking" [Mesh] OR smoking OR tobacco OR cigarette OR cigar OR smoker) AND ("spondylitis, ankylosing"[Mesh] OR (ankylo*[TIAB] AND spondyl* [TIAB]) OR bechterew* [TIAB] OR marie-struempell [TIAB] OR "rheumatoid spondylitis" [TIAB] OR spondylarthritis [TIAB] OR spondyloarthritis [TIAB]) NOT (Review[ptyp] OR review [TI]) AND (hasabstract[text] AND English[lang])*

In order to avoid missing potentially relevant studies, the use of other limiters and filters was restricted and the authors relied instead on manual selection. Similar clauses were used when searching the other databases. The references of identified articles and reviews were also checked for relevance.

Selection strategy

The records identified from the data sources were stored using Endnote software (Endnote X7.8, Thomson Reuters). Using a build-in search engine of the Endnote software, duplicates, conference proceedings, theses, reviews, and case reports were deleted. Two independent reviewers screened the titles and abstracts of the remaining articles and assessed the full texts of potentially relevant papers (Figure 1). Disagreements between the reviewers were resolved by consensus or by a third reviewer.

Extraction strategy

The data needed for a quantitative assessment were extracted using a standardized form based on recommendations by the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green 2011). The form included: a first author name, a year of publication, a country, a sample, a gender distribution, the average age of patients, the duration of follow-up, and the estimates of main outcomes.

Assessment of the methodological risks of systematic bias

Two independent reviewers rated the risk of systematic bias using four criteria adopted from the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (NIH 2020). The assessment was based on the clarity of research question and study population, a power analysis, and the clarity of definition of smoking status. The risk of bias was dichotomized as "yes" vs. "no". Disagreements between the reviewers were resolved by consensus or by a third reviewer.

Main outcome measure – BASDAI

The BASDAI scale consists of six items: fatigue, spinal pain, arthralgia, enthesites (areas of localized tenderness where connective tissues insert into bone), and the duration and severity of morning stiffness. The items are rated on a Likert-like scale from zero to 10. The scores obtained for the duration and severity of morning stiffness are pooled into one score. The total score is a sum of five individual scores divided by five resulting in a possible range from zero (least activity) to 10 (most activity) points. Using a distribution-based method (appropriate for cross-sectional design used here by all of the included studies), the minimal clinically important difference (MCID) for BASDAI has previously been estimated around 0.8 points (van Tubergen, Black et al. 2015).

Statistical analysis (meta-analysis)

A random-effects model was used to quantify the pooled effect size of the included studies, which was a more fitting choice than a fixed-effect model considering the context of medical decisions making and generalizing the results beyond the selected samples. The results were presented as raw mean differences and accompanied by 95% confidence intervals (95% CIs). The heterogeneity was tested using the Q test and I^2 statistic. Heterogeneity was deemed present if Q was greater than the degree of freedom (number of studies – 1). The I^2 statistic described the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). The potential publication bias was assessed using the Egger's test (two-tailed *p*-value considered significant if =<0.05), and trim-and-fill correction was applied if needed. All calculations were performed using the Comprehensive Meta-Analysis CMA software, Version 3.0, available from www.meta-analysis.com.

RESULTS

The search resulted in 714 records (Figure 1). Of them, 103 records were assessed based on their titles and abstracts and 46 were assessed based on the full texts. The final sample consisted of 18 papers (Kaan and Ferda 2005, Reed, Dharmage et al. 2008, Mattey, Dawson et al. 2011, Chung, Machado et al. 2012, Chen, Chen et al. 2013, Fallahi, Jamshidi et al. 2013, Poddubnyy, Haibel et al. 2013, Gaber, Hassen et al. 2015, Ramiro, Landewe et al. 2015, Sakellariou, Anastasilakis et al. 2015, Zhang, Li et al. 2015, Jones, Ratz et al. 2017, Zhao, Challoner et al. 2017, Dülger, Karlıbel et al. 2018, Zhang, Wan et al. 2018, Dülger, Aykurt Karlibel et al. 2019, Karlibel, Dulger et al. 2019, Zhao, Jones et al. 2019). All of them reported cross-sectional data on smoking status and the BASDAI scores. The sample sizes varied from 18 to 1,141 and samples were predominated by male patients (Table 1). The average age varied from 30 up to 50 years. There was a substantial variation in the time since SA inset – from three up to 20 years. The most common source of the risk of systematic bias was absent study power analysis (Table 2). As smoking has often been a secondary outcome, the research question regarding smoking was clearly defined in half of the studies.

Most of the included studies reported better BASDAI scores for non-smokers although only eight studies resulted in clinically significant differences between groups (Figure 2). The pooled sample consisted of 3,599 smokers and 3,591 non-smokers. The sizes of smokers' groups varied widely from 19 up to 1,141 patients. The pooled mean difference in BASDAI scores was 0.6 (95% CI 0.42 to 0.78) points in favor of non-smokers. There was a significant heterogeneity – Q=50.9 (df=17). Of this heterogeneity, 67% (I^2) was coming from the variation of true effect size. There was not a significant risk of publication bias – Egger's *p*-value 0.77 without a need for a trim-and-fill correction.

DISCUSSION

This systematic review evaluated the evidence on correlation between smoking and disease activity in SA. The meta-analysis of 18 cross-sectional studies showed statistically significant difference between ever-smokers and never-smokers in activity level of SA measured by difference in the BASDAI scores. The difference fell, however, below the minimal clinically important difference of BASDAI. There was a substantial heterogeneity of the pooled effect.

This was the first meta-analysis on association between smoking and disease activity measured by the BASDAI. The results of this meta-analysis should be interpreted with caution. Meta-analysis is always an approximation. All the included study samples were cross-sectional. Therefore, no certain causality could be established. There was substantial heterogeneity between the included studies. The dichotomization of exposure as ever-smoking vs. never-smoking left the effects of smoking amount and the length of smoking history unclear. While the BASDAI is a reliable validated scale, the activity of such a complex condition as SA can hardly be explained by a single outcome.

The results of present review are in line with an earlier review, which has found evidence on only weak effect of smoking on pain level reporting correlation between current smoking and worse BASDAI scores in patients with SA (Villaverde-Garcia, Cobo-Ibanez et al. 2017). The present review was able to reveal this correlation in more details employing meta-analysis approach. Additionally, unlike previous reviews, the present study compared the pooled effect of smoking with the BASDAI MCID producing clinically interpretable results. Another review has found evidence on correlation between smoking and cumulative structural damage in SA – smokers have had significantly more syndesmophytes than never-smokers (Akar, Kaplan et al. 2018). That finding is incomparable with the results of present review, which left structural radiographic damage outside the scope.

There is a need for longitudinal research to reveal the potential causality in association of smoking with SA activity. Further research on pathophysiologic and molecular models of smoking effect in SA may introduce a plausible hypothesis behind the possible effect of smoking on SA activity. Additional research may reveal the effects of dose-dependency, time of quitting of smoking and pack-years measured by BASDAI as well as other outcomes.

Conclusions

Smoking seems to be associated with severity of SA activity only weakly and clinically insignificantly when measured by using the BASDAI scale.

FIGURES AND TABLES

Figure 1. Search flow

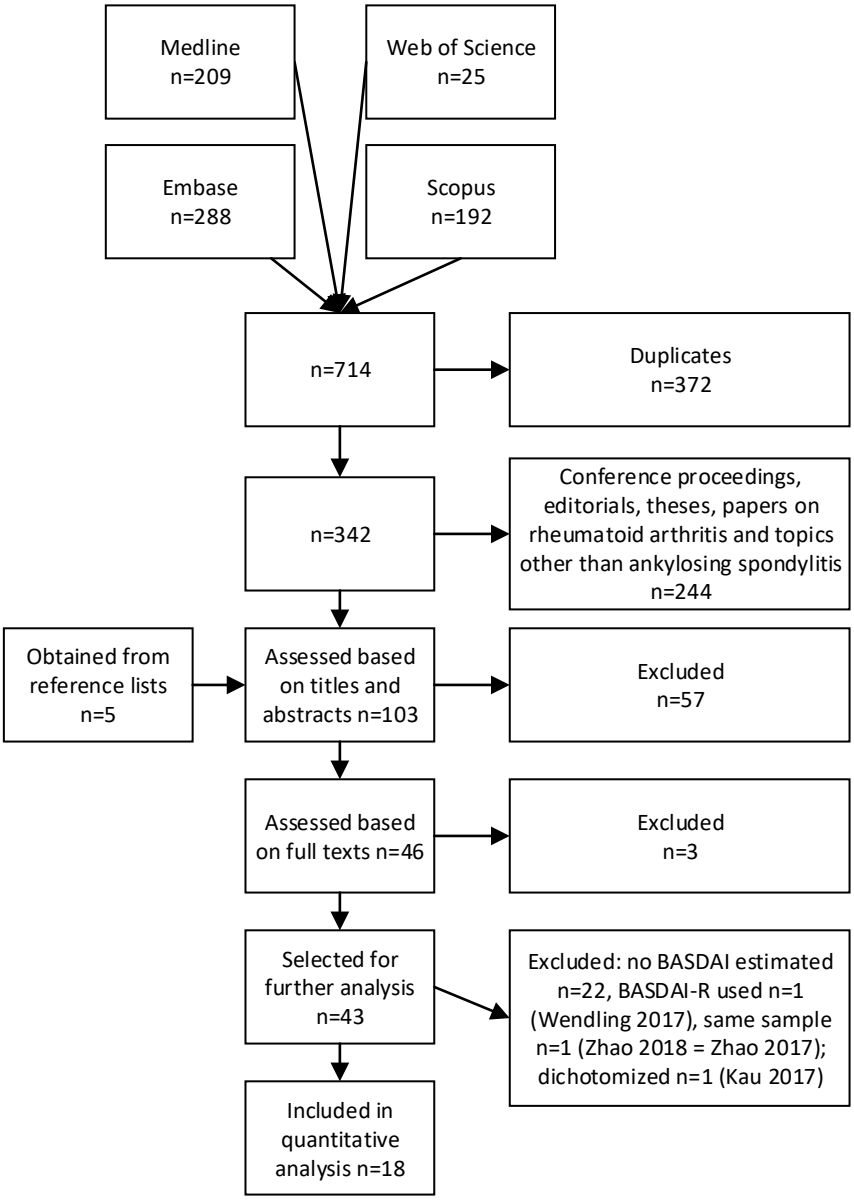

Figure 2. Forest plot of raw mean differences between smokers and non-smokers in disease activity measured by BASDAI scale.

Study name	Statistics for each study			Sample size		
	Difference in means	Lower limit	Upper limit	Smokers	Non-smokers	Relative weight
Poddubnyy 2013	-0.38	-1.00	0.24	71	139	5
Dulger 2019	-0.30	-1.37	0.77	40	31	2
Karlibel 2019	-0.10	-1.23	1.03	47	20	2
Dulger 2018	0.00	-1.00	1.00	54	38	3
Ramiro 2015	0.20	-0.55	0.95	49	78	4
Chung 2012	0.30	-0.02	0.62	241	413	9
Zhang 2018	0.42	0.18	0.66	410	768	10
Chen 2013	0.46	-0.46	1.38	35	40	3
Reed 2008	0.51	-0.21	1.23	58	68	4
Sakellariou 2015	0.60	-0.40	1.60	84	22	3
Zhang 2015	0.60	0.18	1.02	307	118	7
Fallahi 2013	0.61	0.52	0.70	47	113	12
Jones 2017	0.80	0.42	1.18	562	384	8
Mattey 2011	1.00	0.53	1.47	298	308	7
Zhao 2019	1.11	0.85	1.37	1141	890	10
Zhao 2017	1.15	0.34	1.96	112	126	4
Gaber 2015	1.40	0.24	2.56	19	11	2
Kaan 2005	1.44	0.80	2.08	24	24	5
	0.60	0.42	0.78	3599	3591	

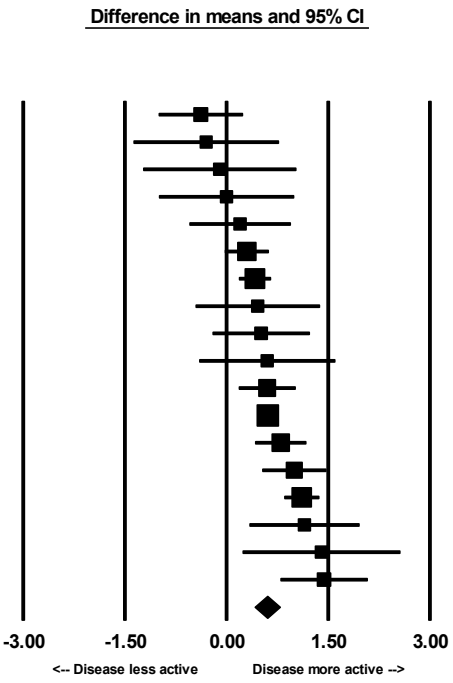

Table 1. Characteristics of the included studies

Study, year	Smokers			Non-smokers			Time since onset, years
	n	Women	Age	n	Women	Age	
Chen 2013	35	0%	35	40	0%	32	11
Chung 2012	241	49%	31[a]	413	57%	33[a]	1.5
Dülger 2018	40	28%	37	31	16%	38	4
Dülger 2019	54	17%	38	38	39%	40	11
Fallahi 2013	61	n/r[b]	38	99	n/r[b]	38	14.5
Gaber 2015	19	0%	29	11	0%	35	7.5
Jones 2017	562	25%	53	384	29%	51	16
Kaan 2005	24	50%	35	24	50%	35	3
Karlibel 2019	47	0%	33	20	0%	40	10
Kau 2017	77	1%	39	137	38%	40	8
Mattey 2011	298	n/r[b]	49	308	n/r[b]	49	15
Poddubnyy 2013	71	42%	34	139	53%	39	4
Ramiro 2015	49	18%	38	78	37%	42	20
Reed 2008	22	n/r[b]	45	104	n/r[b]	45	20
Sakellariou 2015	84	6%	42	22	6%	42	15.5
Zhang 2015	118	18%	29	307	18%	29	7.5
Zhang 2018	410	2%	37	768	63%	37	7.5
Zhao 2017	112	17%	46	126	31%	46	5
Zhao 2019	1141	29%	49	890	37%	48	20

[a] At onset; [b] Not reported

Table 2. Risk of systematic bias in the selected studies.

Study and outcome	Research question and objective clearly stated	Study population clearly defined	Sample size justified	Smoking status clearly defined
Chen 2013	Yes	Yes	No	Yes
Chung 2012	Yes	Yes	No	No
Dülger 2018	Yes	No	No	Yes
Dülger 2019	Yes	Yes	No	Yes
Fallahi 2013	Yes	Yes	No	Yes
Gaber 2015	No	No	No	Yes
Jones 2017	No	Yes	No	Yes
Kaan 2005	No	No	No	No
Karlibel 2019	No	No	No	Yes
Mattey 2011	Yes	Yes	No	Yes
Poddubnyy 2013	Yes	Yes	No	Yes
Ramiro 2015	No	Yes	No	No
Reed 2008	No	Yes	No	No
Sakellariou 2015	Yes	Yes	No	Yes
Zhang 2015	No	No	No	Yes
Zhang 2018	No	No	No	Yes
Zhao 2017	No	No	No	Yes
Zhao 2019	Yes	Yes	No	Yes

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