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ORIGINAL ARTICLE

Smoking quantity determines disease activity and function in Chinese patients with ankylosing spondylitis

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Abstract

The objective of this study was to systemically and comprehensively evaluate the associations between smoking and disease outcomes in patients with ankylosing spondylitis (AS). Information on smoking, clinical features, and sociodemographic characteristics was collected by a questionnaire administered directly to the patient. Group differences were analyzed by *t* test or chi-square test. Logistic regression analysis was conducted with the Bath AS Disease Activity Index (BASDAI), Bath AS Functional Index (BASFI), C-reactive protein, and erythrocyte sedimentation rate as the dependent variables and different stratification of smoking duration, smoking intensity, and cumulative smoking as independent variables. In order to compare our results with previous studies, meta-analysis was performed to calculate standardized mean difference (SMD) for relationship between outcomes and smoking status. A total of 1178 AS patients were analyzed. Compared with non-smokers, the risk of having active disease (BASDAI ≥ 4) was higher in patients who smoked at least 15 years, or 15 cigarettes per day, or 15 pack-years (OR = 1.70 [1.06, 2.73], 1.75 [1.08, 2.82], and 1.97 [1.06, 3.67], respectively); and smokers had increasing risk of BASDAI ≥ 4 with increasing years of smoking, or cigarettes per day, or pack-years ($p_{\text{-trend}} = 0.010$, 0.008 and 0.006, respectively). The risk of having active disease was higher in patients who smoked at least 15 cigarettes per day or 15 pack-years (OR = 1.74 [1.06, 2.84] and 2.89 [1.56, 5.35], respectively), with increasing number of cigarettes per day and pack-years. Smokers had an increased risk of BASFI ≥ 4 ($p_{\text{-trend}} = 0.040$ and 0.007, respectively). By meta-analysis, current, former and ever smokers had significantly higher BASDAI (SMD = 0.34 [0.18, 0.48], 0.10 [0.01, 0.19], and 0.27 [0.20, 0.34], respectively) and BASFI (SMD = 0.35 [0.16, 0.55], 0.30 [0.22, 0.39], and 0.35 [0.21, 0.50], respectively) compared to non-smokers. Smoking is a risk factor for greater disease activity and worse functioning in AS patients.

Keywords Ankylosing spondylitis · Cumulative smoking exposure · Outcomes · Smoking duration · Smoking intensity

Introduction

Ankylosing spondylitis (AS) is one of the most common inflammatory chronic rheumatic diseases throughout the world. It characteristically causes chronic inflammatory back pain, spinal mobility restriction, and in many patients, eventual functional disability [1, 2]. Previous studies have reported the associations of ethnic, geographical, and socioeconomic factors with clinical features of AS [3]. It has been reported that different countries had different prevalences of AS: 0.24% in Europe, 0.17% in Asia, 0.59% in North America, 0.10% in Latin America, and 0.07% in Africa. In addition, male/female ratio of AS was also different (3.8 in Europe,

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2.3 in Asia, 6.0 in the USA, and 2.0 in Cuba). The prevalence of AS in China ranges between 0.11 and 0.37% [4–8]. The severity of AS, including disease activity, physical function and inflammation might be influenced by various genetic factors [9–11]. Also, environmental factors likely play an important role in disease progression [11].

Smoking is a severe public health problem in China and is one of the major environmental risk factors for rheumatoid arthritis (RA) [12–15]. Several reports have found some associations between smoking and disease outcomes in AS patients [16, 17]. Two studies observed that AS smokers had a significantly higher Bath AS Disease Activity Index (BASDAI) scores than that in non-smokers in Turkish and Egyptian patients [18, 19], while one report found that current but not former smokers had significantly higher BASDAI scores in Australians [20]. Several other studies reported that smoking had an adverse effect on functional ability in AS [17, 18, 20, 21]. However, there was no significant difference between smokers and non-smokers regarding the BASDAI score in Taiwanese and British patients [17, 21], and Gaber et al. [19] also showed that there was no significant difference between smokers and non-smokers with AS about the Bath AS Functional Index (BASFI) in Egyptian AS patients. In addition, a Norwegian study with 11.2-year-follow-up pointed that current but not former smoking was an important risk factor for AS (OR = 1.99, 95% CI = 1.28–3.11) [22].

Although several studies have analyzed the adverse effect of smoking, the main aspects of the research focused on either smoking status, or duration, or pack-year. Therefore, we aimed to (1) systemically evaluate smoking from different aspects (smoking status, duration, intensity [number of cigarettes per day] and cumulative smoking exposure [pack-years]) and disease outcomes (disease activity, physical function and inflammation) in Chinese AS patients and (2) compare our results of smoking and disease outcomes with previous reports in other studies by meta-analysis.

Materials and methods

Study subjects and data collection

The questionnaire was collected in ten rheumatology departments in the hospitals of Shanghai, Taizhou, Taixing, and Wuxi in China since September of 2010. As of July of 2016, 1359 patients who fulfilled the modified New York criteria (1984) [23] were enrolled and interviewed using questionnaire administered by trained rheumatologists or investigators on site. Patients who did not have smoking information were excluded. This study was approved by the Ethics Committees of the School of Life Sciences of Fudan University, and informed consent was obtained from each participant.

The questionnaire included sociodemographic (such as age, sex, education, and smoking history) and clinical characteristics (such as disease duration, BASDAI, BASFI, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and drug treatments). Furthermore, specific information on smoking including smoking status, smoking duration, and average number of cigarettes per day was also collected. Patients were categorized into non-smokers and ever (former + current) smokers by smoking status. The number of pack-years was calculated (one pack-year = 20 cigarettes per day for 1 year) and divided into three subgroups (0 pack-year, < 15 pack-year, and ≥ 15 pack-year according to cumulative smoking dose) [21], and patients with AS were categorized in three subgroups according to smoking intensity (0 cigarette per day, < 15 cigarettes per day, and ≥ 15 cigarettes per day) [24]. In addition, the patients were also divided into another three groups (0 year, < 15 years, and ≥ 15 years) according to smoking duration. Disease activity and physical function were assessed using the BASDAI [25] and BASFI [26], respectively. A higher score indicated greater disease activity (BASDAI) and adverse functional status (BASFI). In addition, patients were defined as having greater disease activity when the BASDAI was greater than or equal to four [25]; similarly, patients were defined as having an adverse functional status when the BASFI was greater than or equal to four [26]. An elevated ESR was determined when it was higher than 15 mm/h for males and 20 mm/h for females, respectively [27]; CRP was defined as elevated when it was higher than 8 mg/L. Treatment with non-steroidal anti-inflammatory drugs (NSAIDs) were defined as the use of any dose of NSAIDs during previous 3 months. Treatments with any disease-modifying anti-rheumatic drugs (DMARDs) or with any tumor necrosis factor (TNF) blocker were defined as the use of any of these drugs in previous 6 months, and patients with AS took any of the above medicines were defined as "drug treatments" (used as a binary variable). Current smokers were defined as daily smoking of any number of cigarettes, cigars, or pipes.

Literature search

We searched PubMed and China National Knowledge Internet to find relevant studies published before July 2016 using the search terms "ankylosing spondylitis" or "AS" combined with "smoke," "smokers," "smoking," or "pack-year." Studies were selected if they met the following criteria: (1) they represented an original article, (2) they examined the association of smoking with at least one of the four disease outcomes (BASDAI, BASFI, ESR, or CRP), and (3) titles, abstracts, and full articles were independently screened by two investigators. For every study, the information regarding published data (first author's, year of publication, journal of publication

and the studied population), number and average age of AS cases, and conclusions were extracted.

Statistical analysis

In this analysis, continuous and categorical variables were present as mean with standard deviation (SD) and frequency (%), respectively. Group differences were analyzed by *t* tests for continuous variables and chi-square tests for categorical variables. Logistic regression was conducted to measure the odd ratios (OR) of different clinical parameters. Clinical manifestations and laboratory test results (such as greater disease activity, adverse functional status, elevated CRP and ESR) were considered as the dependent variables. The different stratification of smoking duration, smoking intensity, and cumulative smoking was defined as independent variables. Gender, age, and drug treatments were considered as covariate variable in multivariable logistic regression. *p* values for trend (two-sided) were derived from trend tests.

In addition, a meta-analysis was conducted to compare our results with previous reports. A meta-regression model was used to explore source of heterogeneity among studies and the *Q* statistic was examined to determine any heterogeneity [28]. Stratified analyses were also performed according to different populations. In meta-analysis, P values for heterogeneity over 0.1 illustrated no heterogeneity among studies, and for this case we used a fixed-effect model with inverse variance method to calculate the standardized mean difference (SMD) [29]. When *p* values for heterogeneity were less than 0.1, the DerSimonian and Laird method random-effect model was utilized [30]. Through creating funnel plots qualitatively and as measured by Begg's [31] and Egger's [32] test, publication biases were examined quantitatively. If the mean disease outcomes (BASDAI, BASFI, CRP and ESR) were not available, the median would be used instead. Similarly, IQRs would be used if SDs were not given. Medians and IQRs were transformed to mean and SDs according to published methods [33]. In case the means (SD) and medians (IQR) were not provided, the studies were excluded in analysis.

All data was carried out by SPSS 22.0 and R (Version 3.2.2: www.r-project.org/). All statistical tests were two-tailed, and a *p* value of < 0.05 was determined as statistically significant.

Results

Results of our own data: smoking is a risk factor for greater disease activity and worse functioning in Chinese AS patients

A total of 1359 patients with AS were enrolled in our study. After excluding 181 patients who did not have smoking information, the remaining 768 (65.20%) non-smokers, 114 (9.67%) former, and 296 (25.13%) current smokers with AS were analyzed in this study. Sociodemographic and clinical characteristics of patients are shown in Table 1. Males comprised 73.24% of the patients. The average age and age at

Table 1 Baseline characteristics of Chinese AS patients ($N = 1178$)

Parameter	Mean (SD) or *n* (%)
Age, year (SD)	36.57 (12.78)
Males (%)	834 (73.24%)
BMI (kg/m^2) (SD)	22.69 (3.41)
Onset age (years) (SD)	29.25 (11.48)
Disease duration (years) (SD)	7.33 (7.51)
HLA-B27 (+) (%)	752 (88.67%)
ESR (mm/h) (SD)	28.53 (26.80)
ESR elevated (%)	403 (56.01%)
CRP (mg/L) (SD)	20.77 (27.86)
CRP elevated (%)	420 (78.95%)
BASDAI (SD)	2.71 (1.97)
BASDAI ≥ 4 (%)	211 (23.11%)
BASFI (SD)	1.80 (2.18)
BASFI ≥ 4 (%)	169 (16.00%)
Drug treatments (%)	642 (60.00%)
NSAİDs/DMARDs (%)	483 (75.23%)
TNF blocker (%)	159 (24.76%)
Smokers	410 (34.80%)
Males (%)	403 (98.29%)
Females (%)	7 (1.71%)
Smoking status	
Non-smokers (%)	768 (65.20%)
Current smokers (%)	296 (9.67%)
Former smokers (%)	114 (25.13%)
Smoking intensity (cigarettes/day)	
0 (%)	768 (68.82%)
(0–15) (%)	216 (19.35%)
≥ 15 (%)	132 (11.83%)
Smoking duration (years)	
0 (%)	768 (68.82%)
(0 (15) (%)	203 (18.19%)
≥ 15 (%)	145 (12.99%)
Cumulative smoking (pack-years)	
0 (%)	768 (68.82%)
(0–15) (%)	283 (25.36%)
≥ 15 (%)	65 (5.82%)

Data are presented as mean ± standard deviation or *n* (%). Drug treatments: including NSAIDs, DMARDs, immunosuppressive drugs and TNF blockers

BMI body mass index, *HLA* human leukocyte antigen, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, BASFI Bath Ankylosing Spondylitis Functional Index, ESR erythrocyte sedimentation rate, CRP C-reactive protein

disease onset were 36.57 ± 12.78 and 29.25 ± 11.48 years old, respectively. The disease duration was 7.33 ± 7.51 years, and 88.67% patients were HLA-B27 positive. The comparison between smoking and non-smoking AS patients is shown in Table 2. Compared with non-smokers, more former smokers had an elevated ESR ($p = 0.031$) and BASFI ≥ 4 ($p = 0.019$), while both current and ever smokers had a higher BASDAI score ($p = 0.001$ or 0.003) and higher frequencies of BASDAI ≥ 4 ($p < 0.001$ or $p = 0.002$) and BASFI ≥ 4 ($p = 0.022$ or $p = 0.004$) compared to non-smokers.

Associations between smoking and disease outcomes are shown in Table 3, revealing the crude and adjusted analytical results of smoking associated with disease outcomes. Independent variables tested in multivariate logistic regression models included age, gender, and drug treatment. Increased smoking intensity, smoking duration, and cumulative smoking exposure were all associated with higher disease activity ($p_{\text{-trend}} < 0.001$) and poorer functioning ($p_{\text{-trend}} < 0.001$) in the unadjusted model.

The association between smoking duration and disease outcome was conducted (Table 3). Compared with non-smokers, the risk of high disease activity was greatest in patients who smoked at least 15 years (OR = 1.70, 95% CI 1.06–2.73, $p < 0.05$), followed by 0–15 years (OR = 1.58, 95% CI 1.04–2.39, $p < 0.05$). With increasing years of smoking, smokers had increasing risk of greater disease activity compared with non-smokers ($p_{\text{-trend}} = 0.010$). Nevertheless, there was no association between functional status and smoking duration ($p_{\text{-trend}} = 0.118$).

In addition, the adjusted model (adjusted for age, gender and drug treatment) was also conducted in further analyses (Table 3). Compared with non-smokers, the risk of greater disease activity was highest in patients who smoked at least 15 cigarettes/day (OR = 1.75, 95% CI 1.08–2.82, $p < 0.05$), followed by 0–15 cigarettes/day (OR = 1.56, 95% CI 1.05–2.33, $p < 0.05$). Smokers had increasing risk of higher disease activity with increasing smoking intensity ($p_{\text{-trend}} = 0.008$). In addition, the physical function of AS patients was also influenced by smoking intensity. Compared with non-smokers, the OR of poorer function was 2.34 (95% CI 1.51–3.63, $p < 0.001$) in patients who smoked at least 15 cigarettes/day, and increased smoking intensity predicted an increased risk of worse functioning ($p_{\text{-trend}} = 0.040$).

Cumulative smoking exposure was also analyzed (Table 3). Compared with non-smokers, the risk of greater disease activity was higher in group with 0–15 and ≥ 15 pack-years (OR = 1.68, 95% CI 1.21–2.35, $p < 0.01$; OR = 2.37, 95% CI 1.34–4.20, $p < 0.01$, respectively), a greater number of pack-years predicted an increased risk of higher disease activity ($p_{\text{-trend}} < 0.001$), and the risk of functional impairment in patients who smoked at least 15 pack-years was 2.89 (95% CI 1.56–5.35, $p < 0.001$) compared with non-smokers. With greater number of pack-years, smokers had increasing risk of functional impairment ($p = 0.007$). However, an association of smoking with higher risk of elevated CRP or ESR was not observed (Table 4).

Meta-analysis showed that smokers have higher BASDAI and BASFI SCORES than non-smokers in AS patients

According to the filtering criteria illustrated in Supplemental Fig. 1, nine published studies [11, 16, 17, 19, 21, 34–37] and our unpublished data set were included in meta-analysis. Among them, six were from Europe [11, 21, 34–37], two were

Table 2 Comparison of outcome variables between smokers and non-smokers in AS patients

	Non (768)	Former (114)	p^a	Current (296)	p^a	Ever (410)	p^a
BMI[b] (kg/m^2)	22.51 (3.35)	23.00 (3.47)	0.335	23.00 (3.52)	0.748	23.00 (3.50)	0.646
Onset age[b]	29.03 (11.63)	31.73 (12.57)	0.986	28.86 (10.55)	0.410	29.66 (11.22)	0.501
Disease year[b]	6.65 (7.17)	8.77 (8.68)	0.962	8.48 (7.65)	0.362	8.56 (7.95)	0.452
ESR (mm/h)[b]	28.87 (27.34)	33.44 (30.79)	0.658	26.58 (23.11)	0.134	27.92 (25.83)	0.178
ESR elevated	275 (54.03%)	56 (66.67%)	0.031	112 (56.57%)	0.543	168 (59.57%)	0.132
CRP (mg/dL)[b]	20.13 (29.60)	20.73 (24.50)	0.219	22.45 (24.38)	0.401	21.95 (24.37)	0.212
CRP elevated	388 (78.70%)	66 (79.52%)	0.866	150 (79.37%)	0.849	216 (79.41%)	0.818
BASDAI[b]	2.57 (1.87)	2.82 (2.10)	0.421	3.06 (2.12)	0.001	2.99 (2.12)	0.003
BASDAI ≥ 4	136 (20.21%)	22 (22.68%)	0.573	78 (31.08%)	< 0.001	100 (28.74%)	0.002
BASFI[b]	1.67 (2.13)	2.32 (2.34)	0.221	1.94 (2.23)	0.630	2.05 (2.26)	0.429
BASFI ≥ 4	104 (15.45%)	25 (22.12%)	0.019	57 (19.39%)	0.022	82 (20.15%)	0.004

BMI body mass index, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein

[a] Compared to non-smokers

[b] Adjusted for age, gender, and drug treatments. Data are presented as mean (SD) or *n* (%)

Table 3 Logistic regression analysis of smoking associated with disease outcomes in AS patients

	BASDAI ≥ 4		BASFI ≥ 4	
	OR[a] (95% CI)	OR[b] (95% CI)	OR[a] (95% CI)	OR[b] (95% CI)
Smoking duration (years)				
0	Ref	Ref	Ref	Ref
(0–15)	1.50 (1.02, 2.20) *	1.58 (1.04, 2.39) *	1.24 (0.81, 1.90)	1.26 (0.79, 2.02)
≥ 15	2.32 (1.54, 3.49) ***	1.70 (1.06, 2.73) *	2.47 (1.62, 3.75) ***	1.45 (0.88, 2.37)
P for trend	< 0.001	0.010	< 0.001	0.118
Smoking intensity (cigarettes/day)				
0	Ref	Ref	Ref	Ref
(0–15)	1.69 (1.17, 2.43) **	1.56 (1.05, 2.33) *	1.36 (0.91, 2.05)	1.12 (0.71, 1.77)
≥ 15	2.04 (1.32, 3.17) ***	1.75 (1.08, 2.82) *	2.34 (1.51, 3.63) ***	1.74 (1.06, 2.84) *
P for trend	< 0.001	0.008	< 0.001	0.040
Cumulative smoking (pack-years)				
0	Ref	Ref	Ref	Ref
(0–15)	1.68 (1.21, 2.35) **	1.56 (1.07, 2.26) *	1.29 (0.89, 1.87)	1.08 (0.71, 1.65)
≥ 15	2.37 (1.34, 4.20) **	1.97 (1.06, 3.67) *	4.14 (2.40, 7.14) ***	2.89 (1.56, 5.35) ***
P for trend	< 0.001	0.006	< 0.001	0.007

Ref reference, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *OR* odds ratio

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

[a] Unadjusted

[b] Adjusted for age, gender, and drug treatments

Table 4 Logistic regression analysis of smoking associated with disease inflammation in AS patients

	ESR elevated		CRP elevated	
	OR[a] (95% CI)	OR[b] (95% CI)	OR[a] (95% CI)	OR[b] (95% CI)
Smoking duration (years)				
0	Ref	Ref	Ref	Ref
(0–15)	1.00 (0.61, 1.63)	1.30 (0.77, 2.17)	0.98 (0.66, 1.45)	1.04 (0.68, 1.58)
≥ 15	1.11 (0.66, 1.87)	1.05 (0.57, 1.92)	1.59 (1.03, 2.45)	1.07 (0.65, 1.78)
p for trend	0.737	0.619	0.073	0.765
Smoking intensity (cigarettes/day)				
0	Ref	Ref	Ref	Ref
(0–15)	0.99 (0.62, 1.57)	1.17 (0.72, 1.93)	1.06 (0.73, 1.54)	0.98 (0.65, 1.47)
≥ 15	1.15 (0.65, 2.03)	1.22 (0.66, 2.26)	1.54 (0.96, 2.47)	1.20 (0.72, 2.02)
p for trend	0.704	0.440	0.103	0.570
Cumulative smoking (pack-years)				
0	Ref	Ref	Ref	Ref
(0–15)	0.95 (0.63, 1.43)	1.31 (0.73, 1.76)	1.04 (0.74, 1.44)	0.96 (0.66, 1.39)
≥ 15	1.84 (0.70, 4.82)	1.75 (0.64, 4.79)	3.19 (1.44, 7.10) **	2.12 (0.91, 4.91)
p for trend	0.492	0.292	0.035	0.332

Ref reference, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *OR* odds ratio

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

[a] Unadjusted

[b] Adjusted for age, gender and drug treatments

from China [16, 17], and one was from Egypt [19] (Supplemental Table 1).

Comparison of BASDAI between smokers and non-smokers by meta-analysis

The meta-analysis of BASDAI scores in selected studies is shown in Fig. 1. Compared with non-smokers, significantly higher BASDAI scores were observed in ever smokers (SMD = 0.27, 95% CI 0.20–0.34). When stratified the AS patients into Chinese group and Caucasian group, the analysis showed similar results (SMD = 0.24, 95% CI 0.13–0.34; SMD = 0.31, 95% CI 0.21–0.41, respectively). In addition, current and former smokers had significant higher BASDAI scores than non-smokers (SMD = 0.34, 95% CI 0.18–0.49; SMD = 0.10, 95% CI 0.01–0.19, respectively).

Comparison of BASFI between smokers and non-smokers by meta-analysis

The meta-analysis of BASFI scores in the selected studies is shown in Fig. 2. Compared with non-smokers, significantly higher BASFI scores were observed in ever smokers (SMD = 0.35, 95% CI 0.21–0.50). AS patients were divided into Chinese and Caucasian groups, and analysis showed similar results (SMD = 0.22, 95% CI 0.12–0.33; SMD = 0.44, 95% CI 0.34–0.54, respectively). Current and former smokers had significant higher BASFI scores than non-smokers (SMD = 0.35, 95% CI 0.16–0.55; SMD = 0.30, 95% CI 0.22–0.40, respectively).

No statistically significant difference between smokers and non-smokers by meta-analysis

In a meta-analysis, no statistically significantly different levels of ESR (SMD = 0.00, 95% CI − 0.11–0.10) and CRP (SMD = 0.00, 95% CI − 0.31–0.30) were found between ever smokers and non-smokers (Fig. 3).

Publication bias

Publication bias was examined qualitatively by funnel plots and estimated by Begg's and Egger's tests. The p values were 0.86 (BASDAI) and 0.17 (BASFI) in Egger's test and 0.19 (BASDAI) and 0.86 (BASFI) in Begg's test. Therefore, no publication bias existed in our study.

Discussion

In this study, we have systemically studied the relationship between smoking and outcomes in patients with AS from different aspects (smoking status, duration, intensity, and cumulative smoking exposure). Our comprehensive analysis of smoking in AS patients indicated that longer smoking duration is associated with higher risk of greater disease activity, and smokers have increasing risk of greater disease activity with increasing smoking years. Higher smoking intensity and cumulative smoking exposure are associated with higher risk of greater disease activity and worse dysfunction in AS patients, and smokers have an increased risk of greater disease activity and worse functional status with increasing smoking intensity and cumulative smoking exposure.

We found that smoking was associated with greater disease activity in Chinese AS patients, which was consistent with previous studies [13, 18, 19, 21]. More specifically, current but not former smokers were associated with increased BASDAI scores, which are also reported in an Australian study of 126 AS patients [20]. In addition, increased smoking duration, smoking intensity, and cumulative smoking exposure were all associated with greater disease activity in our study ($p_{\text{-trend}} = 0.010$, 0.008 and 0.006, respectively). Mattey et al. found that smokers had a dose-response relationship with disease activity in 606 British AS subjects, and it was independent of several confounders (such as age, sex, disease duration and social deprivation) [21]. However, Chen et al. found that the disease activity of AS patients was not affected by smoking duration and cumulative smoking exposure based on a study of 35 smoking patients [17]. In our analysis, we collected 1178 AS patients and the analysis was conducted from different aspects (smoking duration, intensity and cumulative smoking exposure). Besides, similar results were also confirmed in our meta-analysis. Therefore, smoking was associated with greater disease activity in AS patients.

Functional impairment in AS patients was found in current and former smokers in our study; this may suggest irreversible impact of smoking on physical function. Until now, the relationship between smoking and BASFI was inconsistent in many studies. Chen et al. found that both smoking duration and cumulative smoking exposure were associated with physical function in 75 Taiwanese patients with AS [17]. Another study conducted in Australia found a positive relationship with current smoking, but not with cumulative smoking exposure in 126 AS patients [20, 38], while Mattey et al. found that cumulative smoking exposure was associated with higher risk of functional impairment in 606 British AS patients [21]. In our study, both increased smoking intensity and cumulative smoking exposure but not smoking duration were associated with an increased risk of functional impairment ($p_{\text{-trend}} < 0.001$). ESR and CRP levels were not significantly higher in ever smokers than those in non-smokers in logistic and meta-analysis, which was similar with previous studies [13, 35, 38].

Our study has several strengths. It represents the largest sample size of AS patients in the Chinese population with comprehensive clinical and demographic information; on the other hand, it has included information of drug treatment,

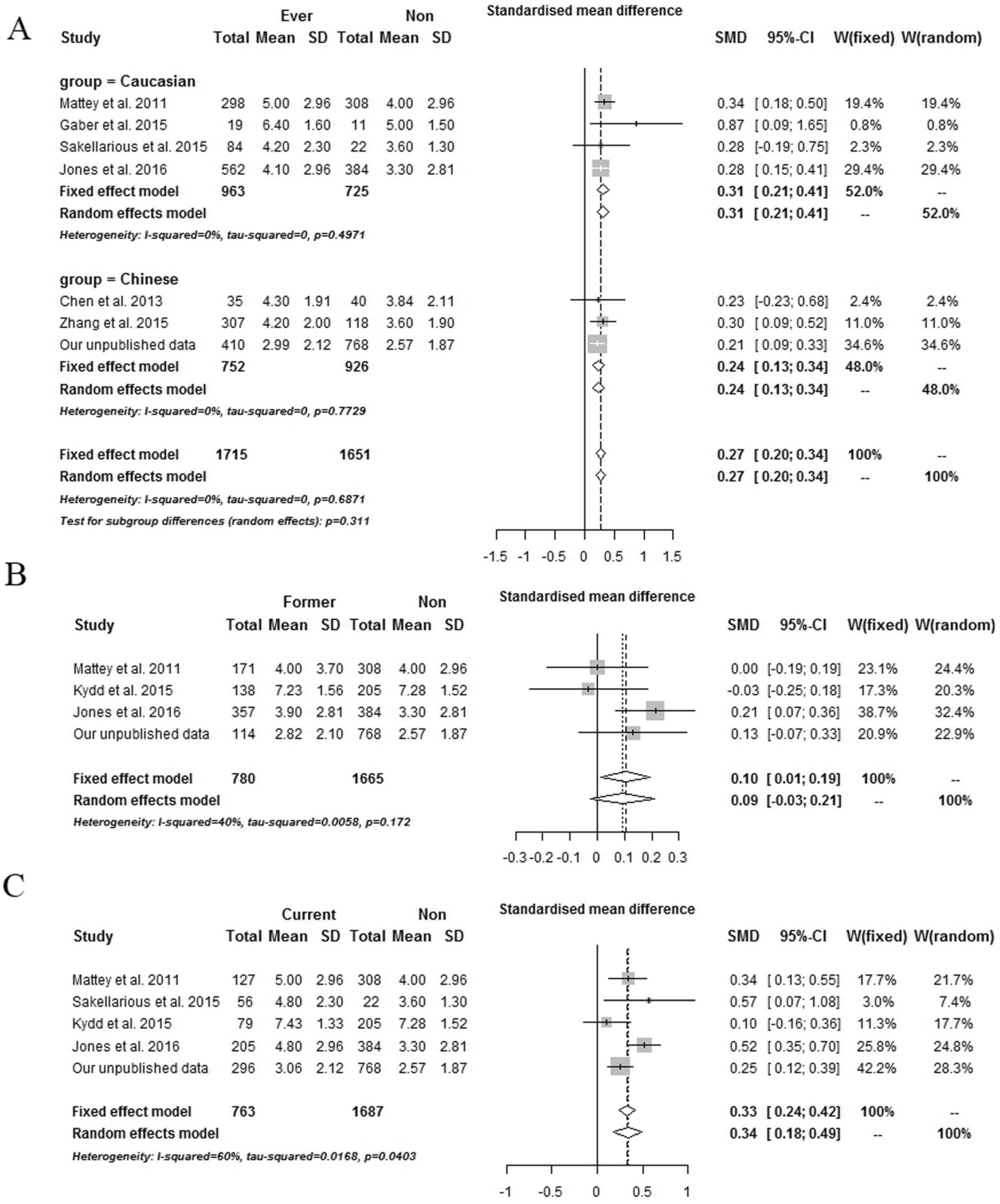

Fig. 1 Comparison of BASDAI between smokers and non-smokers in AS patients

especially TNF-α inhibitors [39] such as adalimumab [40–42], etanercept [43] and infliximab [44] which could improve disease activity and physical function. Interestingly, the effect of smoking on the efficacy of TNF blockers is

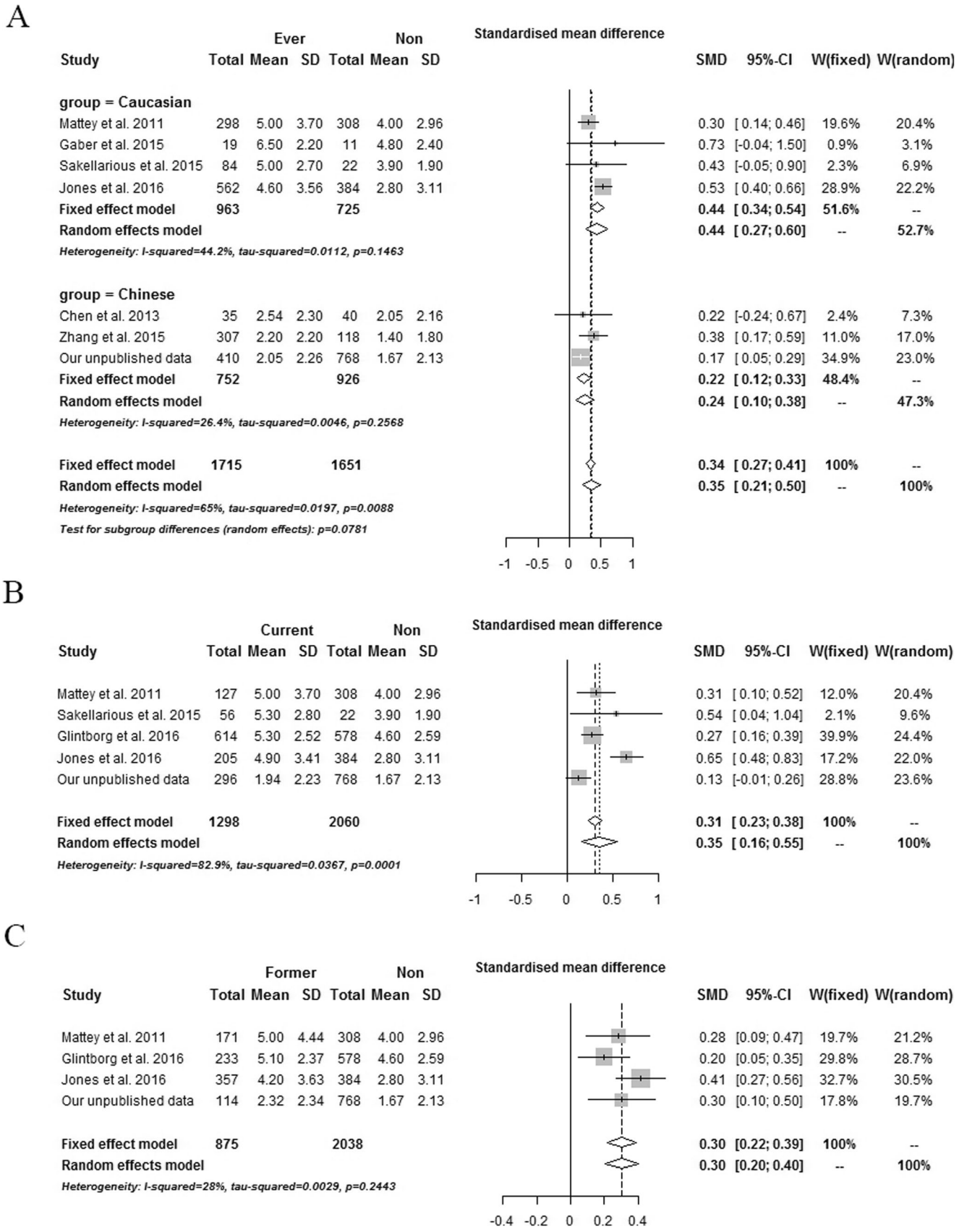

Fig. 2 Comparison of BASFI between smokers and non-smokers in AS patients

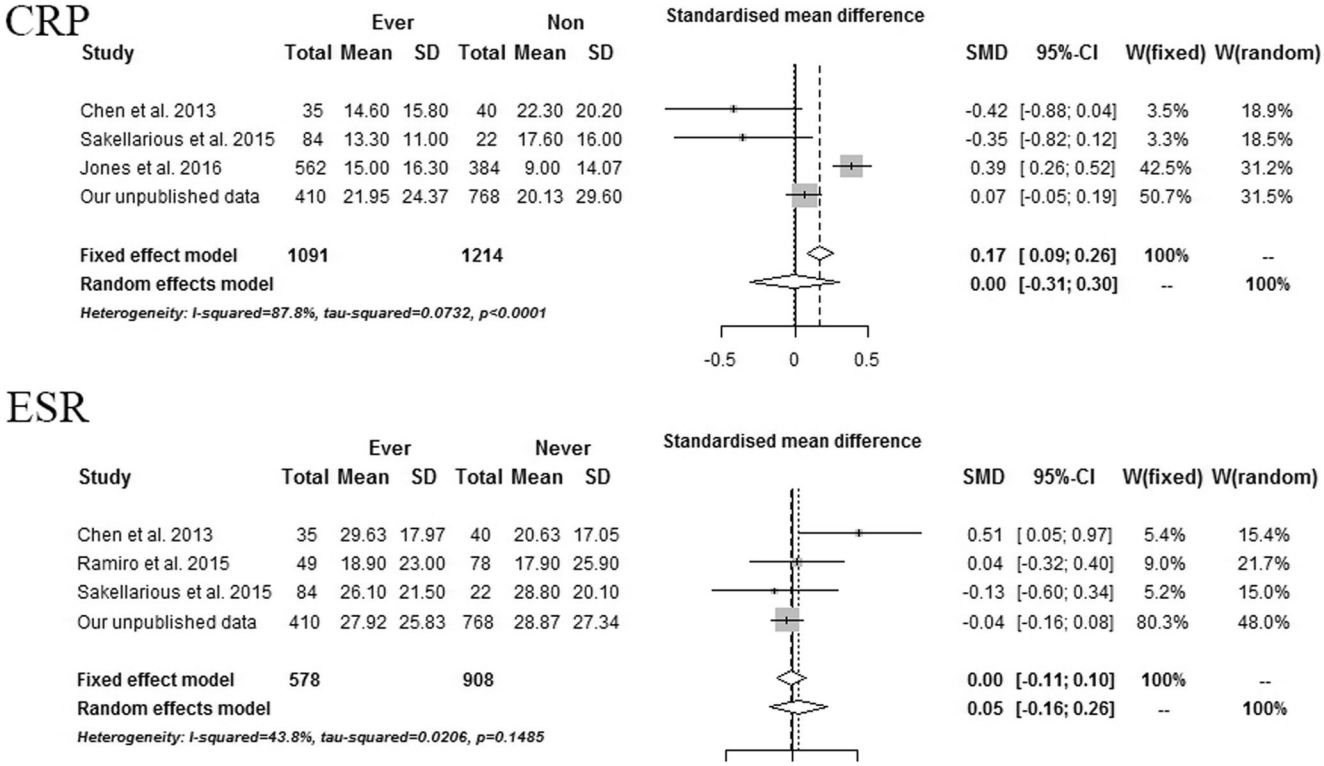

Fig. 3 Comparison of inflammatory markers between ever and non-smokers in AS patients

controversial. One report found that smoking did not influence TNF-α blocker response in Australia [34], while another study illustrated that smokers had poorer TNF blocker treatment response than non-smokers in Danish patients [36]. In order to address these contradictory data, drug treatment was adjusted in our multivariable logistic analysis, and the relationship between smoking and worse BASDAI as well as BASFI scores still remained. In addition, to avoid bias caused by different populations and small sample size, we summarized several previous researches via meta-analysis. However, our study has some limitations as well. Firstly, it is difficult to avoid recall bias when questioned about their disease and smoking status. Secondly, we cannot prove causality because of cross-sectional design in our study. Lastly, including more subjects might have provided a more powerful result in our meta-analyses.

Although several studies have analyzed the adverse effect of smoking, they primarily focused on different aspects of smoking (such as smoking status, or pack-years smoked, or smoking duration). In our study, we have systemically studied the relationship between smoking and outcomes in patients with AS from several different aspects (such as smoking status, duration, intensity and cumulative smoking exposure) using multivariable logistic regression. In addition, in order to compare our results with previous studies, meta-analysis was performed to calculate SMD for relationship between outcomes and smoking status. In conclusion, the adverse effect of smoking is mainly on the disease activity and physical function. In addition, the association of cumulative smoking exposure and smoking intensity with disease activity and physical function is also observed in our AS patients.

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Compliance with ethical standards

This study was approved by the Ethics Committees of the School of Life Sciences of Fudan University, and informed consent was obtained from each participant.

Disclosures None.

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