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Lifestyle Factors and Disease Activity Over Time in Early Axial Spondyloarthritis: The SPondyloArthritis Caught Early (SPACE) Cohort

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ABSTRACT. ***Objective.*** Our aim was to study the importance of baseline BMI, smoking, and alcohol consumption (AC) for disease activity (DA) over 1 year in early axial spondyloarthritis (axSpA), stratified by sex.

Methods. In the SPondyloArthritis Caught Early cohort (patients with chronic back pain onset at age < 45 yrs, with pain for ≥ 3 months and ≤ 2 yrs), the Ankylosing Spondylitis Disease Activity Score (ASDAS) was recorded at inclusion, 3, and 12 months. All patients included in the analysis had axSpA based on a high physician's level of confidence at baseline. Differences in ASDAS over 1 year by BMI (normal < 25 kg/m^2, overweight 25–29.9 kg/m^2, and obese ≥ 30 kg/m^2), smoking history (never/previous/current), and AC (none, 0.1–2 units/week, 3–5 units/week, and ≥ 6 units/week) at baseline were estimated using mixed linear regression models.

Results. There were 344 subjects (mean age of 30.3 yrs; 49.4% men). In women, obesity was associated with 0.60 (95% CI 0.28–0.91) higher ASDAS compared to normal BMI. In both sexes, AC tended to be associated with lower DA over 1 year, with a significant association only in women with the highest AC (mean difference of –0.55, 95% CI –1.05 to –0.04). Smoking was associated with higher ASDAS over 1 year compared to never smoking in both sexes, although the difference reached statistical significance only in female former smokers. Results were similar in multivariable analysis, adjusted for all lifestyle factors and other confounders.

Conclusion. In early axSpA, BMI and smoking are associated with higher DA over 1 year, and AC with lower DA. The magnitude of the modest associations may differ between men and women.

Key Indexing Terms: alcohol consumption, body mass index, cigarette smoking, lifestyle, patient outcome assessment, spondylarthritis

Axial spondyloarthritis (axSpA) is associated with a substantial disease burden, which is comparable for patients with radiographic axSpA (r-axSpA) and nonradiographic axSpA.[1] In the era of tailored and targeted treatment decisions in patients with axSpA,[2,3] early identification of patients at risk of unfavorable disease outcomes, who might require specific interventions, is important. In this context, the effect of modifiable lifestyle factors on disease activity (DA) and other outcomes in axSpA, is of interest.

Modifiable lifestyle factors, such as cigarette smoking and alcohol consumption (AC), and lifestyle-related conditions such as obesity, are globally linked to considerable morbidity and

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mortality, as well as substantial personal burden and deep social and economic impact.[4,5,6]

In both the patients with early axSpA and with r-axSpA, cigarette smoking has been associated with more severe disease (i.e., cross-sectionally associated with higher DA scores, worse physical functioning, poorer quality of life (QOL); and longitudinally with spinal radiographic progression).[7,8,9,10] In early axSpA, smokers were also less likely to achieve remission and frequently had more inflammation on magnetic resonance imaging (MRI) of both the sacroiliac joints and the spine.[11] In contrast, AC has been associated with lower DA scores and better physical function compared with abstention in patients with axSpA.[12] Regarding the importance of BMI for DA and other outcomes in axSpA, the results are variable. Some studies indicate that obesity is associated with higher DA, impaired physical function and QOL, as well as lower response rates to biological treatment and spinal radiographic progression[13,14,15,16]; however, other studies found no association between BMI and DA.[17,18]

However, most of the results above derive from cross-sectional studies in later stages of the disease. There is a scarcity of studies exploring the effect of such modifiable lifestyle factors on DA and other disease-related outcomes over time and especially in patients with early axSpA. Such information could be important as a background for future intervention studies aiming to reveal the effect of lifestyle modification on DA.

The aim of the present study was therefore to investigate the importance of BMI, cigarette smoking, and AC at baseline for DA over 1 year in patients with early axSpA. The effect of modifiable lifestyle factors on DA over time was also investigated separately in men and women, based on observed sex differences in DA, clinical characteristics,[19,20] and in exposure to modifiable lifestyle factors[12,21,22] in patients with axSpA.

METHODS

Study population. For the purpose of the present analysis, the baseline, 3-month, and 12-month data from the SPondyloArthritis Caught Early (SPACE) cohort until June 2018 were used.[23] The SPACE cohort is an international, observational cohort, recruiting patients aged > 16 years with early chronic back pain (CBP) of a duration ≥ 3 months but ≤ 2 years, with an age of onset of < 45 years, seen in the outpatient clinical care of 14 participating centers in 4 countries. Patients were not eligible if they had another painful condition (not related to axSpA) that could interfere with the evaluation of the disease or result in an inability to comply with protocol requirements. Baseline evaluation included clinical and laboratory assessment, questionnaires, and MRI and plain radiographs of the sacroiliac joints and spine. Patients fulfilling the Assessment of Spondyloarthritis international Society criteria for axSpA or with an increased likelihood for axSpA, based on the existence of several prespecified SpA features, were then followed up after 3 and 12 months, and yearly thereafter.

Patients included in the current analysis had been given a diagnosis of axSpA by the examining rheumatologist with a level of confidence ≥ 6 on a 0–10 scale based on all the available information from the baseline evaluation, including imaging (Supplementary Table 1, available with the online version of this article).

Ethics. The SPACE study protocol was approved by the medical ethical committee of the Leiden University Medical Center (reference number P08.105), the regional committee for medical and health research ethics in South-East Norway (reference number 2014/426), the ethical committee "Azienda Ospedaliera di Padova" (reference number 2438P), and the regional research ethics committee in Lund, Sweden (reference number 2010/653). All participants provided informed consent according to the Declaration of Helsinki.

Outcome: disease activity over time. The main outcome was DA over 1 year, measured by the Ankylosing Spondylitis Disease Activity Score–C-reactive protein (ASDAS-CRP) at baseline, 3, and 12 months.[24,25] In order to further explore the nature of the relation between modifiable lifestyle factors and DA, the individual ASDAS components over 1 year served as separate secondary outcomes: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) question 2 (axial pain), BASDAI question 3 (peripheral joints symptoms), BASDAI question 6 (duration of morning stiffness), patient global assessment of DA (PtGA), and CRP.

Baseline covariates: modifiable lifestyle factors. Patients were classified based on BMI as normal weight (< 25 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥ 30 kg/m^2). Smoking status was reported as never, current, and previous. Current AC was categorized based on units of alcohol consumed weekly (median = 2, IQR 0–5) as: none (0 units/week), lowest (0.1–2 units/week), middle (3–5 units/week), and highest (≥ 6 units/week). Moderate AC (≤ 14 units/week) and high AC (> 14 units/week) as defined by the UK Department of Health[26] was not considered appropriate in our study, as only 10 patients (3.8%, 9 males) reported a high AC at baseline. The patients lacking information regarding AC (23%) made up a separate category.

Statistical analysis. The demographic, clinical, lifestyle, and socioeconomic characteristics of the patients at baseline were presented and stratified by sex, taking into account the distribution of continuous variables. Males and females were compared using appropriate statistical tests. The mean value of ASDAS and its individual components (median for CRP) at each visit were presented for the whole study population and stratified by sex.

Differences in DA over 1 year by baseline lifestyle factors were investigated through random coefficient analysis, using linear mixed models (SPSS Statistics 24, IBM Corp; Supplementary Data 1, available with the online version of this article).[27]

In the main analyses, ASDAS over 1 year was used as the dependent variable. First, we analyzed 3 univariable models assessing BMI, smoking status, and AC at baseline separately. Second, we performed multivariable analyses that included BMI, smoking status, and AC at baseline simultaneously, adjusted for each other and further adjusted for relevant confounders: age; sex; level of formal education (as a measure of socioeconomic status at baseline); and current treatment with nonsteroidal antiinflammatory drugs (NSAIDs), conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), and biologic DMARDs (bDMARDs; present/absent) as time-dependent covariates. Education level was dichotomized as low/middle (elementary school, low-level secondary vocational school, midlevel secondary general school, or midlevel vocational school) or high (high-level secondary general school, high-level vocational school, or university). All models were also stratified by sex in accordance with our a priori hypothesis and aim. In every model, we tested the inclusion of a random intercept, a random slope, and the combination of both. Goodness-of-fit statistics and specifically the Akaike information criterion were used to choose the model that fit the data best. Each model was tested to ensure that the assumptions of regression analysis using linear mixed models were not violated. In the secondary analysis, the individual ASDAS components were used in separate multivariable models as dependent variables. In the model with CRP as the dependent variable, the distribution of residuals was not normal. Therefore, the $\log_{10}$ of CRP (mg/L) + 1was used as the dependent variable, with 1 added because undetectable CRP levels had been assigned a value of 0.

Patient and public involvement. Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

RESULTS

Descriptive statistics (baseline). In total, 344 patients attended

Table 1. Baseline demographic, clinical, lifestyle, and socioeconomic characteristics.

	All, n = 344	Males, n = 170	Females, n = 174	*P*
Age, yrs, mean (SD)	30.3 (7.7)	29.2 (7.5)	31.3 (7.7)	0.01
Male sex	170 (49.4)	NA	NA	NA
Duration of CBP, months, mean (SD)	13.3 (6.9)	13.1 (6.9)	13.6 (6.9)	0.57
IBP[a]	251 (73.0)	125 (73.5)	126 (72.4)	0.82
HLA-B27 positive[a]	218 (64.5)	124 (75.2)	94 (54.3)	< 0.001
IBD[a]	24 (7.0)	10 (5.9)	14 (8.0)	0.43
AAU[a]	42 (12.2)	22 (12.9)	20 (11.5)	0.68
PsO[a]	64 (19.0)	24 (14.5)	40 (23.3)	0.04
Peripheral arthritis[a]	82 (23.9)	41 (24.1)	41 (23.7)	0.93
Sacroiliitis according to mNY criteria	44 (17.1)	28 (23.5)	16 (11.5)	0.01
ASDAS, mean (SD)	2.5 (1.0)	2.4 (1.0)	2.6 (0.9)	0.06
BASDAI (0–10), mean (SD)	4.1 (2.1)	3.6 (2.0)	4.5 (2.1)	< 0.001
CRP, mg/L, median (IQR)	4 (2.8–7.0)	4 (2.2–7.2)	3.7 (2.9–7.0)	0.58
ESR, mm/h, median (IQR)	9 (5–19)	6.5 (2–17.3)	11 (7–21)	0.002
BMI, kg/m^2				< 0.001
Normal weight (< 25)	208 (65.0)	102 (63.7)	106 (66.3)	
Overweight (25–29.9)	75 (23.4)	51 (31.9)	24 (15.0)	
Obese (≥ 30)	37 (11.6)	7 (4.4)	30 (18.8)	
Smoking				0.02
Never	194 (59.9)	89 (55.6)	105 (64.0)	
Previous	78 (24.1)	36 (22.5)	42 (25.6)	
Current	52 (16.0)	35 (21.9)	17 (10.4)	
Alcohol consumption, units/week				< 0.001
None	76 (22.1)	24 (14.1)	52 (29.9)	
Lowest (0.1–2)	93 (27.0)	38 (22.4)	55 (36.1)	
Middle (3–5)	39 (11.3)	25 (14.7)	14 (8.0)	
Highest (≥ 6)	57 (16.6)	46 (27.1)	11 (6.3)	
Missing	79 (23.0)	37 (21.8)	42 (24.1)	
High level of education	222 (69.2)	108 (67.9)	114 (70.4)	0.64
Current treatment				
NSAIDs	265 (77.0)	128 (75.3)	137 (78.7)	0.45
csDMARDs	37 (10.8)	15 (8.8)	22 (12.6)	0.25
bDMARDs	16 (4.7)	8 (4.7)	8 (4.6)	0.96

Values are expressed as n (%) unless otherwise indicated. [a] According to ASAS definition. ASAS: Assessment of Spondyloarthritis international Society; ASDAS: Ankylosing Spondylitis Disease Activity Score; AAU: acute anterior uveitis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; bDMARD: biologic disease-modifying antirheumatic drug; CBP: chronic back pain; CRP: C-reactive protein; csDMARD: conventional synthetic disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; IBD: inflammatory bowel disease; IBP: inflammatory back pain; mNY: modified New York; NA: not applicable; NSAID: nonsteroidal antiinflammatory drug; PsO: psoriasis.

the baseline visit, of whom 170 (49.4%) were male (Table 1). All of the participating SPACE centers contributed patients to the present study (Supplementary Table 2, available with the online version of this article). The mean age at first visit was 30.3 (SD 7.7) years and females were slightly older than males (Table 1). The mean duration of CBP at baseline was 13.3 (SD 6.9) months and the back pain was of inflammatory character in 251 (73.0%) patients. The majority of the patients were positive for HLA-B27, significantly more in male than female patients, while only a minority (17.1%), mainly males, had radiographically evident sacroiliitis (Table 1).

Information on BMI, smoking, and AC was missing in 7%, 5.8%, and 23% of the patients at baseline. Thirty-seven (11.6%) patients were obese at baseline; females were more often obese than males (18.8% vs 4.4%). One hundred thirty (40.1%) patients had been ever smokers, with current smoking being more common in men and previous smoking in women. The majority of patients (189, 54.9%) reported some AC, with higher frequencies in men, both overall and for the highest consumption category (≥ 6 units/wk). A high level of education had been achieved by 69.2% of the patients, without significant difference between sexes (Table 1).

At the first visit, the mean ASDAS (2.5, SD 1.0) and BASDAI (4.1, SD 2.1) scores indicated a high DA state. Females had a higher ASDAS score, BASDAI score, and erythrocyte sedimentation rate (ESR), but not CRP, compared to males (Table 1, Figure 1). As expected, the majority of patients (77.0%) were treated with NSAIDs and only 4.7% had an ongoing treatment with bDMARDs at baseline (Table 1).

Descriptive statistics (follow-up). Of the 344 patients attending the baseline visit, 305 and 283 patients, respectively, also attended the 3- and 12- month visits. Details on the number of patients who missed ≥ 1 visits are given in Supplementary Table 3 (available with the online version of this article).

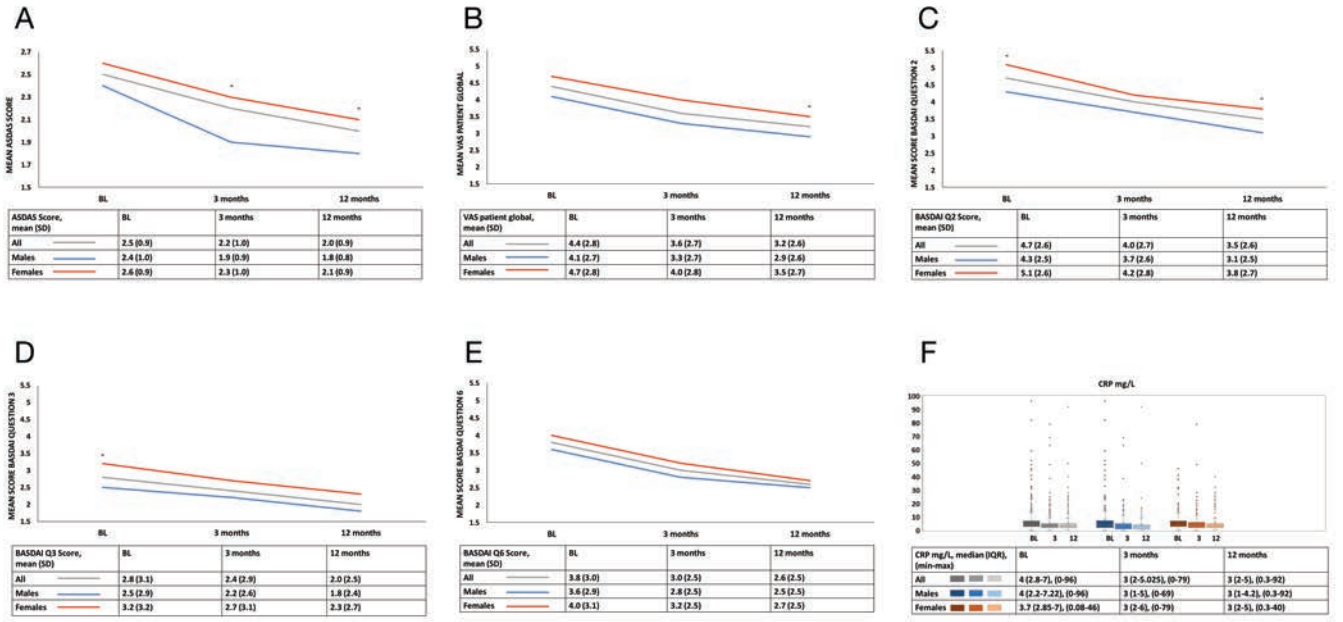

Figure 1. Disease activity scores over the first year of follow-up. (A) Mean ASDAS score, (B) mean patient global assessment of DA, (C) mean score BASDAI Q2 (spinal pain), (D) mean score BASDAI Q3 (peripheral joint symptoms), (E) mean score BASDAI Q6 (duration of morning stiffness), and (F) median CRP (mg/L). *$P < 0.05$ for comparison between males and females. ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BL: baseline; CRP: C-reactive protein; DA: disease activity; Q: question; VAS: visual analog scale.

Most patients (n = 214) had an ASDAS score at all 3 visits. Seventy-five patients had only 2 ASDAS scores and 48 patients had only 1 ASDAS score during the 12-month period, whereas 7 patients did not provide any ASDAS score (Supplementary Table 3, available with the online version of this article).

There was improvement in ASDAS, and all the ASDAS components, over 1 year. (Figure 1A–F) During the follow-up, the ASDAS score and the scores of the individual ASDAS components, with the exception of CRP, were higher in women, but improved to an equal extent in both sexes (Figure 1A–F).

ASDAS over time. In univariable models, patients that were obese at baseline had on average a 0.51 (95% CI 0.23–0.80) higher ASDAS score over 1 year compared to patients with normal BMI. Obese female patients had on average a 0.60 (95% CI 0.28–0.91) higher ASDAS score over 1 year compared to those with normal BMI, whereas no significant association was observed in men. (Table 2)

Cigarette smoking was also associated with higher ASDAS over 1 year. Male current smokers and female previous smokers had on average 0.31 (95% CI −0.01 to 0.62) and 0.31 (95% CI 0.03–0.59), respectively, higher ASDAS scores over 1 year compared with patients who never smoked.

Any level of AC was consistently associated with lower ASDAS over 1 year, compared to those with no AC, in both sexes (Table 2). However this association reached statistical significance only in female patients in the highest category of AC (≥ 6 units/wk) (mean difference −0.55, 95% CI −1.05 to −0.04).

In the multivariable model, including age, all modifiable lifestyle factors, education, and treatment over time, the point estimates were slightly different from the univariable models, but the observed associations remained statistically significant (Table 2). Obesity in females was still associated with on average 0.40 (95% CI 0.06–0.73) higher ASDAS over 1 year, compared with normal BMI. Female previous smokers had on average a 0.38 (95% CI 0.09–0.67) higher ASDAS score over 1 year compared to never smokers. For AC, the point estimates also remained similar, with a significant negative association with ASDAS in women consuming ≥ 6 units/week (−0.57, 95% CI −1.08 to −0.06).

Secondary analysis. Obesity was not significantly associated with any of the patient-reported outcomes (PROs) over time, overall (Supplementary Table 4, available with the online version of this article) or stratified by sex (Table 3), but obese female patients had on average higher CRP over 1 year compared with those with normal BMI (Table 3). The scores of the 3 individual BASDAI questions over time were positively associated with smoking in female patients but not in males (Table 3). The highest category of AC had a negative association with spinal pain score and peripheral joint symptoms score (Supplementary Table 4) in particular in women (Table 3).

DISCUSSION

In the present study, we have shown for the first time, to our knowledge, that BMI, cigarette smoking, and AC at baseline were modestly associated with DA over 1 year in patients with early axSpA. Interestingly, the patterns of these associations differed between males and females and for subcomponents of the ASDAS score.

Obesity was significantly and positively associated with ASDAS over time in females. The association between obesity and DA, measured by ASDAS, BASDAI, PtGA, CRP, or ESR,

Table 2. The estimated mean difference in ASDAS score over the first year of follow-up by baseline lifestyle factors.

Lifestyle Variable	Univariable Models			Multivariable Model[a]		
	All	Males	Females	All[b]	Males	Females
	N exposed = 315 / 320 / 337	N exposed = 158/ 157 / 166	N exposed = 157 / 163 / 171	N exposed = 298	N exposed = 148	N exposed = 150
BMI, kg/m^2						
Normal (< 25)	Ref	Ref	Ref	Ref	Ref	Ref
Overweight (25–29.9)	0.14 (–0.06 to 0.35)	0.10 (–0.16 to 0.36)	0.32 (–0.02 to 0.65)	0.17 (–0.04 to 0.38)	0.04 (–0.23 to 0.31)	0.31 (–0.02 to 0.64)
Obese (≥ 30)	0.51 (0.23–0.79)**	–0.01 (–0.61 to 0.60)	0.60 (0.28–0.91)**	0.33 (0.05–0.62)*	0.03 (–0.57 to 0.64)	0.40 (0.06–0.73)*
Smoking						
Never	Ref	Ref	Ref	Ref	Ref	Ref
Previous	0.19 (–0.02 to 0.40)	0.06 (–0.24 to 0.36)	0.31 (0.03–0.59)*	0.18 (–0.03 to 0.39)	0.01 (–0.30 to 0.31)	0.38 (0.09–0.67)*
Current	0.21 (–0.04 to 0.46)	0.31 (–0.01 to 0.62)	0.14 (–0.26 to 0.55)	0.24 (–0.03 to 0.50)	0.15 (–0.22 to 0.52)	0.28 (–0.12 to 0.67)
Alcohol, units/week[c]						
None	Ref	Ref	Ref	Ref	Ref	Ref
Missing	–0.15 (–0.40 to 0.11)	–0.15 (–0.57 to 0.27)	–0.07 (–0.39 to 0.25)	–0.06 (–0.32 to 0.21)	–0.03 (–0.49 to 0.43)	–0.07 (–0.41 to 0.27)
Lowest (0.1–2)	–0.18 (–0.42 to 0.06)	–0.27 (–0.68 to 0.14)	–0.07 (–0.36 to 0.23)	–0.03 (–0.28 to 0.21)	–0.10 (–0.54 to 0.35)	0.03 (–0.27 to 0.32)
Middle (3–5)	–0.39 (–0.69 to –0.09)*	–0.26 (–0.71 to 0.18)	–0.42 (–0.87 to 0.03)	–0.27 (–0.58 to 0.05)	–0.21 (–0.70 to 0.28)	–0.42 (–0.86 to 0.02)
Highest (≥ 6)	–0.36 (–0.63 to –0.09)*	–0.19 (–0.59 to 0.21)	–0.55 (–1.05 to –0.04)*	–0.28 (–0.57 to 0.01)	–0.22 (–0.64 to 0.20)	–0.57 (–1.08 to –0.06)*

Values are expressed as β (95% CI). N exposed is the number of patients included in each model (i.e., the univariable models on BMI, smoking, alcohol, respectively; and the multivariable models). Random coefficient analysis by linear mixed models was used for the estimates. All models include random intercept. β reflects the estimated mean difference in ASDAS over the first year. [a] BMI, smoking, and alcohol consumption were adjusted for each other and further adjusted for age, education level at baseline, and treatment with NSAIDs, csDMARDs, and bDMARDs as time-varying covariates. [b] Also adjusted for sex. [c] The number of missing data in univariable models: all = 76, males = 36, females = 40; number of missing data in multivariable model: all = 56, males = 28, females = 28). * $P < 0.05$. ** $P < 0.001$. ASDAS: Ankylosing Spondylitis Disease Activity Score; bDMARD: biologic disease-modifying antirheumatic drug; csDMARD: conventional synthetic disease-modifying antirheumatic drug; NSAID: nonsteroidal antiinflammatory drug.

has also been demonstrated in previous cross-sectional studies of patients with axSpA and in a previous metaanalysis.[13,14,28] However, in a previous analysis on a subgroup of the present cohort, BMI was not significantly associated with ASDAS, although ASDAS was slightly higher (mean 4.2 vs 3.9) in overweight/obese patients (BMI ≥ 25 kg/m^2).[17] The different exposure definition, smaller sample size, cross-sectional design, and different case definition of that analysis preclude direct comparison with the present study.

In contrast with some cross-sectional studies,[13,14] there was no clear or significant association between obesity and the PROs included in ASDAS over time in the present study. On the other hand, obese female patients had on average significantly higher CRP over 1 year compared with those with normal BMI. This is in accordance with previous studies demonstrating a strong association between BMI and CRP in female patients with axSpA,[17] as well as in the general population.[29] This observation may be because of low-grade systemic inflammation in obese subjects, caused by proinflammatory signaling from the adipose tissue.[30,31] The mechanism behind the sex-specific association between obesity and CRP is not known, but differences in body fat distribution as well as the sex-specific endocrine properties of the adipose tissue may contribute.[29] In the present study, obesity was uncommon in male patients with axSpA; this may limit the statistical power to detect such an association in males.

In both sexes, cigarette smoking was associated with higher ASDAS over 1 year, but this association reached statistical significance only in previous female smokers. Because of the low proportion of current female smokers (10.4%) that limits the statistical power of this analysis, as well as the lack of information regarding smoking intensity and exact date of smoking cessation, these patterns should be interpreted with caution.

There was also a significant positive association between smoking and spinal pain over time in female patients. Smoking has been associated with pain in the general population. A history of cigarette smoking has been found to be associated with both widespread and regional pain, especially spinal pain.[32,33,34] Further, among patients with CBP, smokers have worse pain and less improvement of pain over time.[35] Smoking may be associated with higher pain intensity in females, but not in males,[36] although in a metaanalysis of cross-sectional and cohort studies, the prevalence of low back pain was increased in ever-smokers irrespective of sex.[34]

The AC in the present cohort was in general low to moderate. Moreover, higher levels of AC were more frequently observed in males than in females, as expected from the general population.[6] The lower levels of AC in our cohort compared to previous cohorts of patients with longstanding r-axSpA could be partly explained by the male predominance in the latter. Consumption of lower amounts of alcohol shortly after disease onset among patients who adopt a healthier lifestyle at this time may be another explanation. The high percentage of missing data regarding AC, which may preferentially derive from those with heavy drinking behaviors,[37] could also influence our results. However, the group with missing values in our analyses had point estimates for the main outcome that were quite similar to the group with low levels of AC.

The association between consumption of moderate amounts of alcohol and lower ASDAS is in accordance with previous

Table 3. Estimated mean difference in ASDAS components over the first year by baseline lifestyle factors, stratified by sex. Multivariable models[a].

Lifestyle Variable	BASDAI Q2 Spinal Pain		BASDAI Q3 Peripheral Joint Symptoms		BASDAI Q6 Duration of Morning Stiffness		PtGA		Log_{10} (CRP + 1)[b]	
	Males N exposed = 148	Females N exposed = 151	Males N exposed = 149	Females N exposed = 150	Males N exposed = 149	Females N exposed = 150	Males N exposed = 149	Females N exposed = 151	Males N exposed = 149	Females N exposed = 151
BMI (kg/m²)										
Normal (< 25)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Overweight (25–29.9)	0.26 (−0.48 to 0.99)	0.82 (−0.16 to 1.80)	−0.10 (−0.84 to 0.64)	0.60 (−0.45 to 1.66)	−0.15 (−0.94 to 0.63)	0.37 (−0.70 to 1.44)	0.12 (−0.66 to 0.90)	0.38 (−0.57 to 1.33)	−0.02 (−0.13 to 0.08)	0.08 (−0.04 to 0.19)
Obese (≥ 30)	−0.28 (−1.93 to 1.36)	0.33 (−0.64 to 1.31)	−1.28 (−2.95 to 0.39)	0.75 (−0.31 to 1.80)	0.41 (−1.35 to 2.17)	−0.23 (−1.30 to 0.85)	−0.59 (−2.34 to 1.17)	0.42 (−0.53 to 1.37)	0.11 (−0.12 to 0.33)	0.22 (0.11–0.34)**
Smoking										
Never	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Previous	−0.40 (−1.24 to 0.43)	0.19 (−0.65 to 1.02)	−0.10 (−0.94 to 0.75)	1.53 (0.62–2.43)*	0.06) (−0.83 to 0.95)	1.09 (0.16–2.02)*	−0.26 (−1.15 to 0.63)	0.78 (−0.03 to 1.60)	0.07 (−0.04 to 0.19)	0.06 (−0.04 to 0.16)
Current	0.58 (−0.43 to 1.59)	1.36 (0.19–2.53)*	−0.47 (−1.49 to 0.55)	0.86 (−0.40 to 2.12)	0.58 (−0.50 to 1.65)	1.22 (−0.07 to 2.50)	0.20 (−0.88 to 1.27)	0.43 (−0.71 to 1.57)	0.07 (−0.07 to 0.21)	−0.06 (−0.20 to 0.08)
Alcohol (units/week)										
None	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Missing	−0.57 (−1.81 to 0.68)	−0.13 (−1.13 to 0.86)	−0.19 (−1.44 to 1.06)	−0.12 (−1.19 to 0.94)	0.57 (−0.75 to 1.88)	0.45 (−0.65 to 1.54)	−0.45 (−1.76 to 0.86)	−0.15 (−1.12 to 0.82)	0.06 (−0.10 to 0.23)	−0.06 (−0.18 to 0.06)
Lowest (0.1–2)	0.03 (−1.19 to 1.24)	−0.10 (−0.96 to 0.77)	0.01 (−1.20 to 1.22)	−0.15 (−1.09 to 0.78)	−0.14 (−1.41 to 1.13)	0.36 (−0.59 to 1.32)	−0.57 (−1.85 to 0.70)	0.14 (−0.70 to 0.99)	−0.01 (−0.18 to 0.15)	−0.01 (−0.12 to 0.09)
Middle (3–5)	−1.07 (−2.40 to 0.26)	−1.03 (−2.32 to 0.27)	−1.00 (−2.33 to 0.33)	−1.44 (−2.82 to −0.06)*	0.15 (−1.25 to 1.55)	0.85 (−0.57 to 2.28)	−1.21 (−2.61 to 0.19)	−0.93 (−2.18 to 0.31)	0.11 (−0.07 to 0.29)	−0.16 (−0.32 to −0.01)*
Highest (≥ 6)	−0.89 (−2.03 to 0.26)	−1.88 (−3.40 to −0.37)*	−1.16 (−2.31 to −0.02)*	−2.27 (−3.90 to −0.63)*	0.03 (−1.18 to 1.23)	−0.42 (−2.07 to 1.24)	−0.65 (−1.85 to 0.55)	−1.40 (−2.87 to 0.06)	0.03 (−0.12 to 0.19)	0.004 (−0.17 to 0.18)

Values are expressed as β (95% CI). N exposed is the number of patients included in each model. Random coefficient analysis by linear mixed models was used for the estimates. All models include random intercept. β reflects the estimated mean difference in disease activity measurements over the first year. [a] BMI, smoking, and alcohol consumption were adjusted for each other and further adjusted for age, education level at baseline, and treatment with NSAIDs, csDMARDs, and bDMARDs as time-varying covariates. [b] The logarithm of CRP (mg/L) + 1 is the outcome of the present analysis. * P <0.05. ** *P* < 0.001. ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; bDMARD: biologic disease-modifying antirheumatic drug; CRP: C-reactive protein; csDMARD: conventional synthetic disease-modifying antirheumatic drug; DA: disease activity; NSAID: nonsteroidal antiinflammatory drug; PtGA: patient global assessment of disease activity; Q: question.

cross-sectional studies.[12] In our study, this association was significant only in female patients. In females, this effect of moderate AC was seen both on spinal pain and peripheral symptoms over time. These findings are supported by a number of previous studies which demonstrated that low to moderate AC in the general population may be associated with decreased likelihood of developing chronic widespread pain and back pain,[38,39,40,41] as well as more favorable pain outcomes in patients already in a painful condition.[42,43,44,45] Potential underlying mechanisms include the stress reduction, fear avoidance, and social integration associated with low-moderate AC, resulting in better pain outcomes.[46]

Limitations of the present study relate firstly to the reliability of self-reported smoking status and AC. The retrospective character of the questions used to gather this information might introduce recall bias.[37] Social desirability and selective recall of unhealthy behaviors may contribute to underestimates.[37,47,48] On the other hand, the use of self-administered questionnaires in the present study, compared to interview-administered questionnaires, may alleviate this issue.[49] Moreover, former drinkers may be mixed with lifetime or long-term abstainers.[50] However, it is not clear how such misclassifications would bias analyses of the association between AC and DA over time. Further, there may be residual confounding. We were not able to adjust for known confounders such as physical activity and psychological status, or for other unknown factors that may strongly correlate with modifiable lifestyle factors and partly explain these associations. Physical exercise might have an effect on DA through effects on the investigated lifestyle factors, or through direct effects on muscle strength and mobility, but data on exercise habits were not available for the present analyses. Finally, the higher ASDAS scores at baseline and over time in females may have affected the observations described above, as it may facilitate detection of modest effects in women.

The main strengths of the present study are the use of a cohort of patients with early axSpA and symptom duration of < 2 years, the analysis of data over 1 year, and the relatively large number of patients. At this early disease stage, the effect of the disease experience is expected to have less effect on the patient's lifestyle choices, compared to r-axSpA, where a vicious circle between disease severity and lifestyle is more plausible. In the era of tailored targeted treatment decisions and new efficacious therapies, early identification of modifiable lifestyle factors that may affect the natural course of DA over time is crucial.

This is the first study, to our knowledge, demonstrating that modifiable lifestyle factors such as BMI, cigarette smoking, and AC may be associated with DA over the first year after diagnosis in patients with early axSpA, with different patterns in males and females. Obesity may be associated with a modest elevation of DA over 1 year in women. In both sexes, AC may be associated with lower DA, and smoking with higher DA over 1 year. The results suggest that modification of these lifestyle factors could potentially improve disease activity over time in patients with early axSpA. However, further longitudinal studies with longer follow-up to assess the true predictive role of these factors, as well as intervention studies to assess the effect of lifestyle modification on DA and other outcomes are needed.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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